Original Article

Micafungin for Candida infections in Slovenia and Romania: A multicenter, observational, prospective study

Samo Zver1,2, Simona Avcin2,3, Ovidiu Bedreag4, Sanja Bizilj5, Vanja Erculj6, Janez Jazbec2,3, Nina Puconja5, Rade Stanic7, Matjaž Jereb2,8

1 Department of Hematology, University Medical Center, Ljubljana, Slovenia
2 Medical Faculty, University of Ljubljana, Ljubljana, Slovenia
3 Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, Division of 4 Pediatrics, University Medical Center, Ljubljana, Slovenia
4 Faculty of Medicine, “Victor Babes” University of Medicine and Pharmacy, Timisoara, Romania
5 Astellas Pharma d.o.o., Ljubljana, Slovenia
6 Rho Sigma Research and Statistics, Ljubljana, Slovenia
7 Center for Intensive Therapy, Department for Anaesthesiology and Surgical Intensive Therapy, University Medical Center, Ljubljana, Slovenia
8 Department of Infectious Diseases, University Medical Center, Ljubljana, Slovenia

Abstract

Introduction: An echinocandin, such as micafungin, is recommended as first-line treatment for invasive Candida infections in immunocompromised patients. This multicenter, observational, prospective, non-interventional study evaluated the real-world use of micafungin in clinical practice in Slovenia and Romania, as this remains unexplored.

Methodology: The primary endpoint was evaluation of micafungin use, including rationale for prescription, treatment duration, and daily dose. Secondary endpoints included recordings of patient baseline characteristics and evaluations of efficacy and safety. Across 11 centers in two countries, 118 patients (18 children [< 16 years] and 100 adults [≥ 16 years]) received micafungin for the first time according to their clinic’s standard practice.

Results: Micafungin was prescribed for treatment in 57.6% of patients and for prophylaxis in 40.7% of patients. The median (range) treatment duration was 9.0 (0 – 54) days and 13.0 (2 – 6) days, respectively. The median dose of micafungin was higher than recommended for children receiving prophylaxis or treatment for invasive candidiasis and for adults receiving prophylaxis. Fever was the most commonly observed clinical sign at baseline (16 children [88.9%] and 31 adults [31%]) and hematologic malignancy was the most frequent primary diagnosis at admission (11 children [61.1%] and 40 adults [40%]). Candida species were the most commonly identified causal agents of invasive fungal infections (2 children [11.1%] and 48 adults [48%]).

Conclusions: The efficacy and safety profiles of micafungin use in Slovenia and Romania based on clinician’s own experiences in local clinical practice were consistent with those reported in other real-world studies.

Key words: Antifungal agents; Candida spp.; candidemia; micafungin; prophylaxis; treatment.

J Infect Dev Ctries 2021; 15(6):877-888. doi:10.3855/jidc.12755

(Received 03 April 2020 – Accepted 11 November 2020)

Copyright © 2021 Zver et al. This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

In recent years, the incidence of invasive fungal infections (IFIs) has increased worldwide. Immunosuppressed individuals are at an increased risk of IFIs, including those undergoing autologous and allogeneic hematopoietic stem cell transplantation (HSCT), solid organ transplantation, chemotherapy, and major surgical procedures [1]. Candida species are the most common cause of IFIs, with Candida albicans being the most dominant strain globally (44 – 70% of cases) [2,3], although regional variations exist [2-7]. Invasive candidiasis (IC) remains a leading cause of opportunistic fungal infection in hospitals and is associated with substantial morbidity and mortality [2,8], with an estimated ~700,000 cases occurring globally each year [9]. In 2016, there were an estimated 984 cases of candidemia in Romania [10]. Additionally, epidemiological data from Slovenia showed that the incidence of candidemia increased from 4.23 to 7.02/100,000 inhabitants between 2013 and 2017, with C. albicans (51.7%) and Candida glabrata (27.7%) identified as the most prevalent species among isolates [11].

Echinocandins, such as micafungin, induce fungal cell lysis by inhibiting the synthesis of 1,3-β-glucan synthase [12]. Guidelines recommend an echinocandin
as first-line treatment for IC and esophageal candidiasis, and for prophylaxis in patients at high-risk for Candida infection, including those who are immunocompromised and undergoing HSCT [13-16]. Micafungin has broad-spectrum anti-fungal activity against Candida species and some Aspergillus species [17], and is approved for the treatment of adults and children (< 16 years) with IC, for the treatment of esophageal candidiasis in adults, and for prophylaxis in patients undergoing allogeneic HSCT and those expected to have neutropenia (absolute neutrophil count < 500 cells/µL) for ≥ 10 days [18] when other antifungals are not appropriate. Micafungin has demonstrated non-inferiority to caspofungin, amphotericin B, fluconazole, and itraconazole in the treatment of IFIs [19, 20], and is the only echinocandin approved for antifungal prophylaxis; in clinical trials, micafungin has shown superiority to fluconazole and non-inferiority to itraconazole for fungal prophylaxis [20-22].

Micafungin exhibits broad spectrum fungicidal activity against Candida spp., including those with reduced fluconazole susceptibility (C. glabrata), and intrinsic resistance to fluconazole (C. krusei) and amphotericin B (C. lusitaniae). Micafungin has also demonstrated efficacy in vitro against all common Aspergillus spp. [18,23], including some that are resistant to azoles [24-30]. In some cases, echinocandins may be used as salvage therapy either alone or in combination with another antifungal agent [29,31].

Following the launch of micafungin for clinical use in Slovenia and Romania in October 2012, this study aimed to collect and evaluate data on its use in daily hospital practice, assessed separately for prophylactic and treatment use, and focused on the rationale for prescription, and dose and treatment duration in both children and adults.

**Methodology**

**Study design**

M-TREAT (Micafungin® in Routine Clinical Practice for the Treatment of IC, esophageal candidiasis or Prophylaxis of Candida Infections: A Multicenter, Observational, Prospective, Non-interventional Study; ISN/protocol number: SEE-MYC-01) was performed to evaluate the use of micafungin in routine clinical practice in Slovenia and Romania. The study included an initiation visit (Visit one), during which micafungin was prescribed, and a follow-up visit at the end of micafungin treatment or treatment withdrawal (Visit two). The therapeutic approach was not decided in advance or influenced by the protocol; each patient was treated and followed up at the investigator’s discretion and according to their clinic’s standard practice. Treatment decisions were made based on the patient’s clinical condition and the identification of causative fungal species.

**Ethics**

Before the start of the study, written approval was obtained from the Independent National Ethics Committee (IEC). The study was conducted in adherence to the ethical principles of the Declaration of Helsinki, International Conference of Harmonisation Good Clinical Practice Guidelines, the European Union Clinical Trials Directive 2001/20/EC, and applicable local laws and regulations. Written informed consent was obtained from each patient or their legal representative before study enrolment. The authors confirm that the ethical policies of the journal, as noted on the journal’s author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received.

**Patients**

Between December 2013 and March 2017, patients were prospectively assessed across 11 centres in Slovenia (n = 1) and Romania (n = 10). Patients prescribed micafungin for the first time in accordance with the label were included in the study. There were no exclusion criteria.

**Endpoints and assessments**

The primary endpoints were reasons for micafungin prescription (treatment or prophylaxis) in the overall population; duration of micafungin treatment (defined as the time from treatment initiation to discontinuation or switching to another antifungal treatment); and micafungin daily dose (measured at Visits one and two). The secondary endpoints included efficacy assessments of micafungin when used for treatment and prophylaxis (changes in clinical signs and symptoms, and microbiological and radiographic tests at Visits one and two); safety (assessed via changes in laboratory parameters at Visits one and two, and by recording adverse events [AEs] and severity [at Visit one and two]); identification of the possible causative agents of fungal infections at Visit one; prior antifungal treatments and concomitant medication use at Visit one; and treatment switching after micafungin discontinuation at Visit two. Visits one and two occurred while the patient was hospitalized.
Table 1. Baseline characteristics and disease status.

|                                | Children (N = 18) | Adults (N = 100) | Total (N = 118) |
|--------------------------------|-------------------|------------------|----------------|
| **Number of patients by country, n (%)** |                   |                  |                |
| Slovenia                        | 16 (88.9)         | 63 (63.0)        | 79 (66.9)      |
| Romania                         | 2 (11.1)          | 37 (37.0)        | 39 (33.1)      |
| Male, n (%)                     | 11 (61.1)         | 52 (52.0)        | 63 (53.4)      |
| **Age in years, median (range)** | 5 (0.3 – 15.0)    | 56.5 (16.0 – 88.0) | –              |
| **Vital signs at baseline, mean (SD)** |                   |                  |                |
| SBP (mmHg)                      | 96.2 (16.2)       | 124.2 (21.3)     | –              |
| DBP (mmHg)                      | 56.2 (11.7)       | 68.3 (21.1)      | –              |
| Pulse rate (beats/min)          | 109.1 (27.3)      | 90.4 (21.5)      | –              |
| **Primary diagnosis at admission, n (%)**† |                   |                  |                |
| Hematologic malignancy          | 11 (61.1)         | 40 (40.0)        | 51 (43.2)      |
| Other malignancies/tumors       | 5 (27.8)          | 13 (13.0)        | 18 (15.3)      |
| Sepsis                          | 1 (5.6)           | 14 (14.0)        | 15 (12.7)      |
| Abdominal disease               | 0 (0)             | 12 (12.0)        | 12 (10.2)      |
| Hematologic malignancy, sepsis  | 0 (0)             | 1 (1.0)          | 1 (0.8)        |
| Infectious disease              | 0 (0)             | 4 (4.0)          | 4 (3.4)        |
| Infectious disease, respiratory disease | 0 (0)             | 1 (1.0)          | 1 (0.8)        |
| Liver transplantation           | 0 (0)             | 3 (3.0)          | 3 (2.5)        |
| Respiratory disease             | 0 (0)             | 4 (4.0)          | 4 (3.4)        |
| Trauma                          | 0 (0)             | 3 (3.0)          | 3 (2.5)        |
| Other                           | 1 (5.6)           | 5 (5.0)          | 6 (5.1)        |
| **Clinical signs and symptoms or diagnoses, n (%)**† |                   |                  |                |
| Fever                           | 16 (88.9)         | 31 (31.0)        | 47 (39.8)      |
| Cough                           | 7 (38.9)          | 16 (16.0)        | 23 (19.5)      |
| Pneumonia                       | 4 (22.2)          | 22 (22.0)        | 26 (22.0)      |
| Pleuritic pain                  | 2 (11.1)          | 4 (4.0)          | 6 (5.1)        |
| **Underlying conditions, concomitant diseases, n (%)** |                   |                  |                |
| **Tumors**                      |                   |                  |                |
| Hematologic                     | 9 (50.0)          | 39 (39.0)        | 48 (40.7)      |
| Solid                           | 5 (27.8)          | 14 (14.0)        | 19 (16.1)      |
| Bone marrow transplantation      | 6 (33.3)          | 14 (14.0)        | 20 (16.9)      |
| **Surgery**                     |                   |                  |                |
| Intra-abdominal surgery/intestinal perforation | 1 (5.6)          | 23 (23.0)        | 24 (20.3)      |
| Transplantation of organs       | 0 (0)             | 5 (5.0)          | 5 (4.2)        |
| **Specific support**            |                   |                  |                |
| Central venous catheter         | 16 (88.9)         | 57 (57.0)        | 73 (61.9)      |
| Parenteral nutrition            | 13 (72.2)         | 44 (44.0)        | 57 (48.3)      |
| Respiration support             | 3 (16.7)          | 33 (33.0)        | 36 (30.5)      |
| Hemodialysis                    | 0 (0)             | 3 (3.0)          | 3 (2.5)        |
| **Therapy**                     |                   |                  |                |
| Broad spectrum antibiotics      | 15 (83.3)         | 63 (63.0)        | 78 (66.1)      |
| Anticancer therapy              | 15 (83.3)         | 39 (39.0)        | 54 (45.8)      |
| Immunosuppressors               | 3 (16.7)          | 28 (28.0)        | 31 (26.3)      |
| High-dosage long-term corticotherapy | 3 (16.7)          | 8 (8.0)          | 11 (9.3)       |
| Immune deficiency               | 15 (83.3)         | 42 (42.0)        | 57 (48.3)      |
| **Systemic diseases**           |                   |                  |                |
| Bacterial infections            | 5 (27.8)          | 18 (18.0)        | 23 (19.5)      |
| Diabetes                        | 0 (0)             | 10 (10.0)        | 10 (8.5)       |
| Pancreatitis                    | 0 (0)             | 2 (2.0)          | 2 (1.7)        |

DBP: diastolic blood pressure; mmHg: millimeter of mercury; SBP: systolic blood pressure; SD: standard deviation. † Data was missing for the following patients: fever (adults, n = 1); cough (adults, n = 14); pneumonia (adults, n = 14); pleuritic pain (children, n = 1; adults, n = 17).
IFIs were classified as “proven”, “probable” or “possible” based on criteria outlined in De Pauw et al. [32]. AEs were recorded from the moment the patient signed the informed consent form until the end of the study. An AE was defined as any untoward medical occurrence that did not necessarily have a causal relationship with the treatment. A treatment emergent AE (TEAE) was defined as an AE observed after starting administration of the study drug. A serious adverse event (SAE) was defined as a life-threatening; resulted in death; was life-threatening; resulted in prolongation of hospitalization; or other medically important events. ADRs were those listed in the summary of product characteristics for micafungin [18].

**Diagnostic tests**

Investigators recorded whether culture-based microbiological diagnostic tests, non-culture microbiological diagnostic tests (fungal biomarkers and metabolites), and radiographic diagnostic tests were performed at Visits one and two, together with their results. Microbiological culture tests were performed using samples obtained from both sterile and non-sterile sites, and included blood culture (venipuncture, central venous catheter), cerebrospinal fluid, peritoneal fluid, bronchoalveolar lavage, tracheal aspirate, and other (specified by the investigator according to practice at each participating center). Matrix assisted laser desorption ionisation time of flight (Bruker Daltonics, Coventry, UK) and antifungigrams were used to identify causative fungal agents isolated from these sites. Non-culture tests for fungal biomarkers and metabolites included galactomannan test, 1,3-β-D-glucan test, and other (specified by the investigator). Radiographic tests included chest x-ray, thoracic computed tomography (CT), cerebral CT, ultrasonography, and other (specified by the investigator). All tests were performed according to standard practice at each participating center.

**Statistical analyses**

Data were analyzed using SPSS version 23.0. Mean (standard deviation [SD]) is reported for continuous variables where the distribution is approximately normal. Median (range) is reported for continuous variables where the distribution is highly skewed (Shapiro–Wilk test). Frequencies and percentages were recorded for categorical variables. No imputation method was applied to account for missing data. The safety analysis set (SAF) included all patients who were prescribed micafungin and was used for assessment of all safety-related variables. The full analysis set (FAS) included all patients who received any medication during the study and was used for all other analyses. The relationship between micafungin treatment duration and change in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values from baseline to end of micafungin treatment was evaluated by Spearman correlation coefficient. Spearman correlation coefficient between treatment duration and AST/ALT change was calculated per each daily dose group (50 mg; ≥ 100 mg). Statistical significance was considered when \( p < 0.05 \).

**Results**

**Patient demographics and baseline characteristics**

Patient characteristics at baseline are presented in Table 1. Between December 2013 and March 2017, 118 patients, including 18 (15.3%) children (<16 years) and 100 (84.7%) adults (≥16 years), were enrolled in 11 centers across Slovenia (79 [66.9%] patients, including 16 children) and Romania (39 [33.1%] patients, including two children). A patient flow diagram is shown in Supplementary Figure 1. Approximately half of all patients were male (63 [53.4%] of 118 patients) and the median (range) age was 5.0 (0.3–15) years for children and 56.5 (16–88) years for adults. Fever was the most frequently observed clinical sign at baseline (16 [88.9%] of 18 children; 31 [31%] of 100 adults) and hematologic malignancy was the most common primary diagnosis at admission (11 [61.1%] of 18 children; 40 [40%] of 100 adults). Further primary diagnoses common at admission included other malignancies/tumors (five [27.8%] of 18 children; 13 [13%] of 100 adults), sepsis (one [5.6%] of 18 children; 14 [14%] of 100 adults), and abdominal disease (12 [12%] of 100 adults). Fluconazole was the most common prior antifungal treatment for patients who received micafungin for treatment (22 patients) and secondary prophylactic (15 patients) purposes (Supplementary Table 1), and the median (range) duration of prior fluconazole treatment was 8 (0–54) days and 4 (0–92) days, respectively. Systemic antibacterial agents were the most common concomitant medications, with use reported in 114 (96.6%) patients (Supplementary Table 2).

**Reasons for micafungin prescription**

Reasons for micafungin prescription were available for 116 patients (Table 2). Investigators prescribed
micafungin for treatment reasons in 68 (57.6%) patients (38 in Slovenia and 30 in Romania). Of these 68 patients, 12 (17.6%) were children and 56 (82.3%) were adults. The most common reason for micafungin treatment was IC (39/68 patients [57.4%]), followed by esophageal candidiasis (14/68 patients [20.6%]). Treatment patterns differed in Slovenia and Romania. Overall, 26/38 patients (68.4%) prescribed micafungin for treatment reasons in Slovenia were adults; all the patients prescribed micafungin for treatment reasons in Romania were adults. A total of 13/38 patients (34.8%) in Slovenia and 26/30 patients (86.7%) in Romania were treated for IC.

Micafungin was prescribed for prophylactic use in 48 (40.7%) patients (41 in Slovenia and 7 in Romania). Most of the 48 patients were adults (42 [87.5%]) and the most common conditions for which prophylactic micafungin was prescribed were neutropenia (28/48

| Table 2. Number of patients who received micafungin for treatment or prophylaxis. |
|-------------------------------|-----------------|-----------------|--------------|
|                               | Slovenia (n = 79) | Romania (n = 39) | Total (N = 118) |
| Treatment, n (%)              |                 |                 |               |
| Children                      | 38 (48.1)       | 30 (76.9)       | 68 (57.6)     |
| Adults                        | 12 (31.6)       | 0 (0)           | 12 (17.6)     |
| Esophageal candidiasis, n (%) | 26 (68.4)       | 30 (100)        | 56 (82.4)     |
| Invasive candidiasis, n (%)   | 13 (34.2)       | 1 (3.3)         | 14 (20.6)     |
| Other, n (%)                  | 13 (34.2)       | 26 (86.7)       | 39 (57.4)     |
| NA†                           | 12 (31.6)       | 3 (10.0)        | 15 (22.1)     |
| Empiric treatment             | 9 (23.7)        | 1 (3.3)         | 10 (14.9)     |
| Empiric treatment (suspected Aspergillosis) | 1 (2.6) | 0 (0) | 1 (1.5) |
| Pre-emptive treatment         | 1 (2.6)         | 2 (6.7)         | 3 (4.4)       |
| Probable invasive fungal infection† | 1 (2.6) | 0 (0) | 1 (1.5) |
| Prophylaxis, n (%)            | 41 (51.9)       | 7 (17.9)        | 48 (40.7)     |
| Children                      | 4 (9.8)         | 2 (28.6)        | 6 (12.5)      |
| Adults                        | 37 (90.2)       | 5 (71.4)        | 42 (87.5)     |
| Allogeneic HSCT patient, n (%)| 9 (22.0)        | 0 (0)           | 9 (18.8)      |
| Neutropenic patient, n (%)    | 25 (61.0)       | 3 (42.9)        | 28 (58.3)     |
| Other, n (%)                  | 7 (17.1)        | 4 (57.1)        | 11 (22.9)     |
| Liver transplant patient      | 4 (9.8)         | 0 (0)           | 4 (8.3)       |
| Pre-emptive treatment         | 1 (2.4)         | 0 (0)           | 1 (2.1)       |
| Suspected infection           | 1 (2.4)         | 0 (0)           | 1 (2.1)       |
| NA†                           | 1 (2.4)         | 4 (57.1)        | 5 (10.4)      |
| **NA§, n (%)**                | 0 (0)           | 2 (5.1)         | 2 (1.7)       |

| HSCT: hematopoietic stem cell transplant; NA: not applicable. † NA: missing data, poor investigator compliance. ‡ Probable invasive fungal infection was defined according to de Pauw et al. [32]. § For two patients in Romania, no treatment indication was recorded; these patients were prophylactic cases. |

| Table 3. Micafungin therapy dose and duration. |
|-------------------------------|-----------------|-----------------|--------------|
|                               | Slovenia (n = 79) | Romania (n = 37) | Total (n = 116) |
| **Median (range) duration of therapy, days** |                 |                 |               |
| Treatment                     | 10.5 (1 – 54)    | 8.0 (0 – 26)    | 9.0 (0 – 54)  |
| Prophylaxis                   | 13.0 (3 – 69)    | 5.0 (2 – 14)    | 13.0 (2 – 69) |
| **Median (range) therapeutic dose, mg day^-1** |                 |                 |               |
| **Treatment**                 |                 |                 |               |
| **Starting daily dose**       |                 |                 |               |
| Children                      | 3.1 (1.6 – 4.4)  | NA†             | 3.1 (1.6 – 4.4) |
| Adults                        | 100 (100 – 200)  | 100 (50 – 200)  | 100 (50 – 200) |
| **End daily dose**            |                 |                 |               |
| Children                      | 3.3 (1.7 – 4.5)  | NA†             | 3.3 (1.7 – 4.5) |
| Adults                        | 100 (100 – 200)  | 100 (50 – 200)  | 100 (50 – 200) |
| **Prophylaxis**               |                 |                 |               |
| **Starting daily dose**       |                 |                 |               |
| Children                      | 2.4 (0.8 – 4.8)  | 2.4 (2.3 – 2.4) | 2.4 (0.8 – 4.8) |
| Adults                        | 100 (50 – 150)   | 100 (50 – 100)  | 100 (50 – 150) |
| **End daily dose**            |                 |                 |               |
| Children                      | 2.4 (0.7 – 5.1)  | NA‡             | 2.3 (0.7 – 5.1) |
| Adults                        | 100 (50 – 150)   | 100 (50 – 100)  | 100 (50 – 150) |

| NA: not applicable; † No children received treatment with micafungin in Romania; ‡ Dose was recorded at end of prophylaxis for only one child in Romania, therefore median and range could not be measured. |
patients [58.3%]) and allogenic HSCT (9/48 patients [18.8%]).

**Micafungin dose and treatment duration**

The median micafungin dose and treatment duration are presented in Table 3. Patients received micafungin for a median (range) duration of 9 (0 – 54) days for treatment and 13 (2 – 69) days for prophylaxis. In Slovenia, the median (range) duration of treatment was 10.5 (1 – 54) days and was 13 (3 – 69) days for prophylaxis, whilst in Romania, it was 8 (0 – 26) days and 5 (2 – 14) days, respectively. The median (range) dose of micafungin prescribed for treatment reasons in children was 3.1 (1.6 – 4.4) mg kg\(^{-1}\) day\(^{-1}\) and 3.3 (1.7 – 4.5) mg kg\(^{-1}\) day\(^{-1}\) at the start and end of the study, respectively, and was 100 (50 – 200) mg day\(^{-1}\) at both time points in adults. The median (range) dose of micafungin prescribed for prophylaxis in children was 2.4 (0.8 – 4.8) mg kg\(^{-1}\) day\(^{-1}\) and 2.3 (0.7 – 5.1) mg day\(^{-1}\) at the start and end of the study, respectively, and for adults was 100 (50 – 150) mg day\(^{-1}\) at both time points. Most adult patients received 100 mg day\(^{-1}\) micafungin both at Visit one (treatment, 49 [87.5%] patients; prophylaxis, 28 [66.7%] patients) and Visit two (treatment, 49 [87.5%] patients; prophylaxis, 27 [64.3%] patients).

**Causative agents of fungal infections**

*Candida* spp. were recorded in two (11.1%) children and 48 (48%) adult patients in the overall population (Table 4). *Candida albicans* was the most frequently isolated *Candida* spp.; this was the causative agent in all children who had *Candida* spp. recorded (two children), and in 27 adults. Other species were identified in two (11.1%) children (both *Saccharomyces cerevisiae*) and two (2%) adults (one case of *S. cerevisiae* and one case of *Cryptococcus neoformans*). Missing data (due to poor investigator compliance in recording data or failure to perform a diagnostic test) or no causative fungal agent (due to a negative test result) was recorded for 14 (77.8%) children and 50 (50%) adults. Ten (55.6%) children and 11 (11%) adults had possible IFI, two (11.1%) children and 22 (22%) adults had probable IFI, and no (0%) children and 29 (29%) adults had proven IFI.

**Antifungal treatment switching**

There were 17 switches to another antifungal agent in 13 of the 68 patients who received micafungin for treatment, and a total of 12 switches in 11 of the 48 patients who received micafungin for prophylaxis (Table 5). Reasons for treatment switching included identification of the causative fungal species, prolonged febrile neutropenia, and deteriorating condition of the patient. Patients were switched to fluconazole as de-

| Causative agent, n (%)\(^*\) | Children (N = 18) | Adults (N = 100) |
|-------------------------------|-------------------|------------------|
| *Candida* spp.                | 2 (11.1)          | 48 (48.0)        |
| *C. albicans*                 | 2 (100.0)         | 33 (68.8)        |
| *C. glabrata*                 | 0 (0)             | 9 (18.8)         |
| *C. krusei*                   | 0 (0)             | 3 (6.3)          |
| Other *Candida* spp.          | 0 (0)             | 10 (20.8)        |
| Other (non-*Candida* spp.)\(^\d\) | 2 (11.1)         | 2 (2.0)          |
| NA\(^$\)                      | 14 (77.8)         | 50 (50.0)        |

**Classification of latest systemic fungal infection, n (%)\(^*\)**

|                          | Children (N = 18) | Adults (N = 100) |
|--------------------------|-------------------|------------------|
| Possible                 | 10 (55.6)         | 11 (11)          |
| Probable                 | 2 (11.1)          | 22 (22)          |
| Proven                   | 0 (0)             | 29 (29)          |
| Prophylaxis              | 6 (33.3)          | 38 (38)          |

\(^*\)Some adults are included more than once as they had more than one type of infection; \(^\d\) Other specified causative agents were *Saccharomyces cerevisiae* (n = 2) in children and *Cryptococcus neoformans* (n = 1) and *Saccharomyces cerevisiae* (n = 1) in adults; \(^$\) Missing data (due to poor investigator compliance in recording data or no diagnostic test performed) or no causative fungal agent (due to negative test result) was recorded for 14 (77.8%) children and 50 (50%) adults; \(^*\) Probable invasive fungal infection was defined according to de Pauw et al. [32].
escalation therapy in cases of *C. albicans* identification, and switched to amphotericin B, posaconazole, or voriconazole as protection against *Aspergillus* and infection by other moulds.

### Efficacy

Changes in diagnoses or clinical signs and symptoms of an IFI (fever, cough, pneumonia, and pleuritic pain) in patients receiving micafungin are shown in Table 6. Fewer patients had fever at Visit two (16 [13.6%]) compared with Visit one (47 [39.8%]). Similarly, fewer patients presented the other diagnoses or clinical signs and symptoms of IFI (cough, pneumonia and pleuritic pain) at the end of the study compared with the beginning.

Microbiological culture tests were recorded for 38 of 48 patients who received micafungin prophylactically (Supplementary Table 3). Ten of 38 patients had a positive culture test at Visit one, of whom five had a negative culture test at Visit two. Two patients had no culture tests recorded at Visit two. One patient with a negative culture test at Visit one had a positive culture test at Visit two.

Positive culture tests at Visit one included bronchoalveolar lavage (one positive test), tracheal aspirate (two positive tests) and other (four positive tests), including stool culture and rectal swab. At Visit two, positive culture tests were obtained from sputum culture + throat culture (one positive test) and throat swab + rectal swab (one positive test).

Among patients prescribed micafungin for treatment reasons, 58 of 68 had microbiological culture tests at Visit one, and 41 had culture tests at Visit two.

### Table 7. Summary of TEAEs.

| Clinical sign/symptom/diagnosis | Number of cases |
|---------------------------------|----------------|
| Total, n                        | 22             |
| Anemia                          | 1              |
| Critical illness myopathy and polyneuropathy | 1          |
| Deteriorating pneumonia with evolving respiratory insufficiency | 1          |
| Evolving ARDS and SIRS          | 1              |
| Fever                           | 1              |
| Paroxysmal atrial fibrillation   | 1              |
| Increased inflammatory biomarkers and lesions on chest X-ray | 1          |
| Subarachnoid hemorrhage         | 1              |
| Suspected pulmonary candidiasis | 1              |
| Thrombocytopenia                | 1              |
| Vomiting and nausea             | 1              |

### Table 6. Changes in diagnosis or clinical signs and symptoms from baseline.

| Clinical sign/symptom/diagnosis | Visit 1 N = 118 | Visit 2 N = 118 |
|---------------------------------|-----------------|-----------------|
| **Fever, n (%)**                |                 |                 |
| No                              | 70 (59.3)       | 100 (84.7)      |
| Yes                             | 47 (39.8)       | 16 (13.6)       |
| NA†                             | 1 (0.85)        | 2 (1.7)         |
| **Cough, n (%)**                |                 |                 |
| No                              | 81 (68.6)       | 91 (77.1)       |
| Yes                             | 23 (19.5)       | 14 (11.9)       |
| NA†                             | 14 (11.9)       | 13 (11.0)       |
| **Pleuritic pain, n (%)**       |                 |                 |
| No                              | 94 (79.7)       | 102 (86.4)      |
| Yes                             | 6 (5.1)         | 2 (1.7)         |
| NA†                             | 18 (15.3)       | 14 (11.9)       |
| **Pneumonia, n (%)**            |                 |                 |
| No                              | 78 (66.1)       | 90 (76.3)       |
| Yes                             | 26 (22.0)       | 18 (15.3)       |
| NA†                             | 14 (11.9)       | 10 (8.5)        |

† NA: missing data.
A positive test was recorded at Visit one in 36 of 58 patients, including blood culture (12 positive tests), peritoneal fluid (five positive tests), bronchoalveolar lavage (two positive tests), tracheal aspirate (16 positive tests) and other (16 positive tests), including buccal/oral swab, tongue swab, pharyngeal swab, sputum cultures, urine culture and urine culture + sputum culture + stool culture. Of these, at Visit two, no test was performed for 11 patients, 12 patients had a negative test, and 13 patients had a positive test (including blood culture [four positive tests], peritoneal fluid [four positive tests], bronchoalveolar lavage [one positive test], tracheal aspirate [one positive test] and other [seven positive tests], including stool culture, urine culture, sputum swab, wound swab, thoracic fluid culture and corpus vitreous culture).

Safety
Overall, 22 TEAEs were reported in 19 (16.1%) patients. One TEAE (fever) was assessed by the investigator as possibly drug related. Three TEAEs were mild, seven moderate, and 12 severe. There were 21 serious TEAEs reported in 19 patients; 13 of these were considered unrelated to micafungin; causality was not recorded in eight cases (Table 7). Eleven patients died during the study; 10 deaths were assessed as not related to micafungin. One event was assessed as unassessable (cause of death unknown). Changes in laboratory parameters and vital signs are presented in Supplementary Table 4. There were no unexpected safety issues relating to liver or kidney function, as assessed by changes in laboratory parameters. For adult patients receiving a daily dose of 50 mg or ≥ 100 mg micafungin who had AST/ALT data available (n = 9 and 61 patients, respectively), there were no statistically significant correlations between micafungin treatment duration and change in AST (50 mg: r = 0.243, p = 0.529; ≥ 100 mg: r = 0.123, p = 0.348) or ALT levels (50 mg: r = 0.226, p = 0.559; ≥ 100 mg: r = -0.043, p = 0.740). For children, there were no statistically significant correlations between micafungin treatment duration and change in AST (r = -0.08, p = 0.845) or ALT levels (r = 0.375, p = 0.321), or between micafungin daily dose and change in AST (r = 0.311, p = 0.415) or ALT levels (r = 0.05, p = 0.897) from baseline to the end of the study (n = 9 children).

Discussion
The aim of this non-interventional, multicenter, prospective study was to collect and evaluate data on the use of micafungin in daily clinical practice in Slovenia and Romania, focusing on the reasons for prescription, dose, and treatment duration. Overall, the duration of treatment and dose of micafungin in this study deviated from the instructions supplied in the labelling from the pharmaceutical laboratory, and in some cases, the recommended treatment guidelines [13-16,18]. These findings add to the body of evidence supporting the efficacy and safety of micafungin when used in real-world settings for prophylactic and treatment purposes against Candida infections in hospitalized patients. In this study, fewer patients were enrolled in Romania than in Slovenia (39 and 79 patients, respectively) and considerably fewer patients received prophylaxis in Romania compared with Slovenia (nine and 41 patients, respectively). These differences in recruitment and treatment patterns may be reflective of differences in the real-world use of micafungin between Slovenia and Romania. The data reported here are consistent with data from previous real-world studies. For example, in the present study, micafungin was most commonly used for the treatment of Candida infections (57.6%), whilst in an observational study in France, antifungal prophylaxis with an azole, amphotericin B, or an echinocandin was recorded as the leading antifungal strategy, accounting for 76% of prescriptions in French hematological units, regardless of underlying disease [33]. However, in the observational study in France, antifungal treatment was only prescribed by hematologists, while in Slovenia, hematologists as well as other specialists, such as ICU doctors, infectologists and pediatricians, who more frequently encounter IC, were involved. Consequently, the population of patients included in M-TREAT from Slovenia and Romania was more consistent with those in other observational studies of micafungin use [17,34].

Overall, the duration of micafungin treatment was shorter than the recommended minimum duration of 14 days in both countries [18] and was shorter in Romania than in Slovenia (5 – 8 vs. 11 – 13 days, respectively). This may be explained by the high number of patients who received prior antifungal treatment (65 patients overall), the high number of patients who switched to another antifungal treatment after receiving micafungin (24 patients overall) and the clinical condition of the patients in addition to real-world differences in clinical practice between these two countries. Whilst guidelines recommend antifungal treatment for ≥14 days after the end of candidemia in non-neutropenic patients, this can be simplified by stepping down from an echinocandin to oral fluconazole after 5 – 10 days if the patient is stable and isolated strains are susceptible to fluconazole [13-16]. It is possible that the shorter duration of
treatment in both countries is representative of real-world clinical practice; however, other factors, such as the financial burden of treatment on the healthcare systems, cannot be discounted. Studies have reported variation in the duration of micafungin treatment in real-world settings; in a retrospective, observational study of Chinese patients treated for IFIs in a hospital setting, micafungin was administered for a mean treatment duration of 10.2 days [17]. In a real-world study of prophylactic micafungin use in patients with hematological malignancies, the duration of micafungin treatment was consistent with the label from the pharmaceutical laboratory [35], whilst a longer treatment duration has been observed in some studies (25–36 days) [36,37].

In the present study, children receiving prophylaxis and treatment for IC, and adults receiving prophylaxis, were administered micafungin at doses higher than recommended by the label from the pharmaceutical laboratory [18]. More than half of patients with a recorded indication of esophageal candidiasis received a lower daily dose of micafungin than recommended in the product information and treatment guidelines [15,18]. Prophylaxis with 100 mg day<sup>−1</sup> for some patients in Slovenia was selected based on data from a previous study in which this dose was well-tolerated [38]. In addition, guidelines from the Infectious Diseases Society of America recommend 100 mg day<sup>−1</sup> for prophylaxis of IC in the ICU setting; however, this is a weak recommendation with low-quality evidence [15].

Another reason for the high daily doses in prophylactic patients could be that a significant proportion of patients were recorded as having immune deficiency (57 patients, including 15 children and 42 adults) and had a diagnosis of hematologic malignancy (48 patients, including 9 children and 39 adults). In case of breakthrough fever, a micafungin dose of 50 mg in severely neutropenic hematological patients may not be a consequence of non-effectiveness, but the result of micafungin underdosing. A higher dose of micafungin might lead to the resolution of fever, re-establishing the efficacy of micafungin. In previous studies, micafungin has been administered for prophylaxis at 50 mg day<sup>−1</sup>, which is consistent with the approved use but lower than that administered in the present study [37,39-41]. Higher doses of 100 mg day<sup>−1</sup> and 150 mg day<sup>−1</sup> have been used in other studies, including for prophylaxis in neutropenic patients and high-risk liver transplant recipients [42,43]. For treatment, doses administered to adult patients in other hospital-based studies are consistent with the approved and recommended doses and are comparable to those administered here [17,41]. The deviation in treatment duration and dose from the label and associated treatment guidelines in this study reflect the real-world use of micafungin in Slovenia and Romania and may be a consequence of socio-economic factors and clinicians’ experience of the treatment of invasive fungal infections in these two countries. Furthermore, in Slovenia, different clinical wards have differing prescription policies, which may be influenced by patient age and clinical condition and could also influence treatment decisions.

In this study, C. albicans was the most frequently isolated fungal species, consistent with the findings of other observational studies (57–60% of patients) [6,34], a study conducted using data from a North American registry (46% patients) [5] and a multicenter, retrospective study where C. albicans accounted for 37% of blood isolates [44]. However, no causative agent was identified in a considerable number of patients due to poor investigator compliance or failure to perform a diagnostic test, which reflects real-life clinical practice in the participating hospital centers.

IC is associated with high morbidity and mortality, with mortality rates of around 40% reported [2,8]. However, studies have shown that early anti-fungal treatment can improve outcomes, meaning that the prompt and accurate diagnosis of IFI is crucial [45-47]. Conventional diagnostic procedures such as microscopic examinations, culture and identification of micro-organisms are essential investigations; however, their performance is dependent on the possibility of obtaining samples from deep tissues, whether the samples collected are from sterile sites, the expertise of laboratory personnel and the availability of the diagnostic method in the hospital center. Furthermore, owing to the low sensitivity of blood culture, a negative result does not exclude IFIs. To overcome this, nonculture-based diagnostic tests have been developed for the diagnosis of IC that detect fungal biomarkers and metabolites [48].

The results of M-TREAT support the well-established safety and efficacy profile of micafungin observed in other real-world studies [17,40,41]; there was an overall reduction in the number of patients with signs and symptoms of an IFI at the end of the study and a considerable number of patients with a positive microbiological or radiographic test at visit one had a negative result by visit two. There were no grade 3/4 effects of micafungin on renal or hepatic function in this study, which is in line with previous observations [43,49,50]. The results showing a lack of correlation between micafungin daily dose, treatment duration and
changes in AST/ALT levels should be interpreted with caution due to the low number of patients assessed. The label from the pharmaceutical laboratory indicates that micafungin should be used on a careful risk/benefit basis in patients with impaired liver function due to adverse hepatic events observed in rats [18]; because it is not metabolized by the liver, anidulafungin is often favoured in patients with hepatic impairment, and is the only echinocandin indicated for patients with severe liver impairment [12,51,52]. However, the results of this study suggest that micafungin is well-tolerated in patients with hepatic impairment and may be suitable as an alternative to anidulafungin. The results from the present real-life study support the favourable safety profile of micafungin observed in previous studies [17,35-43].

The main strength of this observational study was that it provided the opportunity to study a wider patient group than possible in randomized-controlled trials due to a lack of strict selection criteria, i.e., all patients, with and without comorbidities, treated with micafungin for the first time were included according to local clinical practice. In addition, it allowed responses to treatment to be evaluated in a real-world setting, representative of everyday clinical practice. One limitation of this study was the risk of selection bias; no measures to reduce bias were taken as this reflected real-world situations.

The study was open-label and therefore there was no removal of bias through blinding. In addition, missing observations might have distorted study results. In this study, test samples were selected based on the availability/accessibility of patients and at the discretion of the investigator. The results were also influenced by the heterogeneity of the healthcare systems and treatment patterns in Slovenia and Romania, as well as the heterogeneity of the studied population. No standard protocol relating to treatment decisions could be implemented across the study centers. Finally, the number of patients enrolled in Romania was lower than the number enrolled in Slovenia and fewer patients received prophylaxis in Romania compared with Slovenia, providing an unbalanced dataset. Nevertheless, these data reflect the real-world use of micafungin in these countries. Additionally, as this was an observational study performed to document micafungin use in a real-world setting, there was no formal assessment of the clinical response to treatment, other than the presence of symptoms, and the results of culture and radiological tests.

Conclusions
In conclusion, this study, in which treatment decisions were based on clinicians’ own experience in local clinical practice, provides information about the use of micafungin in daily clinical practice in Slovenia and Romania for the first time. The safety and tolerability of micafungin in this study were consistent with previous real-world clinical studies.

Acknowledgements
The study was funded by Astellas Pharma Europe S.V. Medical writing assistance, funded by Astellas Pharma Inc., was provided by Jilly Hope, PhD, Bioscript Medical, Macclesfield, UK.

Data sharing statement
Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

References
1. De la Torre P, Reboli AC (2014) Micafungin: an evidence-based review of its place in therapy. Core Evid 9: 27-39.
2. Schmiedel Y, Zimmerli S (2016) Common invasive fungal diseases: an overview of invasive candidiasis, aspergillosis, cryptococcosis, and Pneumocystis pneumonia. Swiss Med Wkly 146: w14281.
3. Colombo AL, de Almeida Júnior JN, Slavin MA, Chen SCA, Sorrell TC (2017) Candida and invasive mould diseases in non-neutropenic critically ill patients and patients with haematological cancer. Lancet Infect Dis 17: e344-e356.
4. Almirante B, Rodriguez D, Cuenca-Estrella M, Almela M, Sanchez F, Ayats J, Alonso-Torres C, Rodriguez-Tudela JL, Païssa A (2006) Epidemiology, risk factors, and prognosis of Candida parapsilosis bloodstream infections: case-control population-based surveillance study of patients in Barcelona, Spain, from 2002 to 2003. J Clin Microbiol 44: 1681-1685.
5. Horn DL, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, Marr KA, Pfaller MA, Chang CH, Webster KM (2009) Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis 48: 1695-1703.
6. Leroy O, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP, Carlet J, Reyines J, Rosenberg M, Regnier B, Lortholary O (2009) Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: a multicenter, prospective, observational study in France (2005-2006). Crit Care Med 37: 1612-1618.
7. Bassetti M, Merelli M, Righi E, Diaz-Martín A, Rosello EM, Luzzati R, Parra A, Trecarichi EM, Sanguinetti M, Posteraro B, Garnacho-Montero J, Sartor A, Rello J, Tumbarello M (2013) Epidemiology, species distribution, antifungal susceptibility, and outcome of candidemia across five sites in Italy and Spain. J Clin Microbiol 51: 4167-4172.
8. Kullberg BJ, Arendrup MC (2015) Invasive Candidiasis. N Engl J Med 373: 1445-1456.
9. Bongomin F, Gago S, Oladele RO, and Denning DW (2017) Global and multi-national prevalence of fungal diseases—estimate precision. J Fungi (Basel) 3: 57.
10. Mares M, Moroti-Constantinescu VR, Denning DW (2018) The burden of fungal diseases in Romania. J Fungi (Basel) 4: 31.
11. Golle A, Pirs M, Matos T (2018) Candidaemia: the national epidemiologic study. Med Razgl 57: 3-16.
12. Kofla G, Ruhnke M (2011) Pharmacology and metabolism of anidulafungin, caspofungin and micafungin in the treatment of invasive candidiasis: review of the literature. Eur J Med Res 16: 159-166.
13. Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Akdagli S, Bille J, Donnelly JP, Jensen HE, Lass-Florl C, Richardson MD, Akova M, Bassetti M, Calandra T, Castagnola E, Conley OA, Garbino J, Groll AH, Herbrecht R, Hope WW, Kullberg BJ, Lortholary O, Meersseman W, Petrulkovs G, Rolíides E, Viscoli C, Ullmann AJ (2012) ESCMID* guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures. Clin Microbiol Infect 18 Suppl 7: 9-18.
14. Conley OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, Meersseman W, Akova M, Arendrup MC, Arikan-Akdagli S, Bille J, Castagnola E, Cuenca-Estrella M, Donnelly JP, Groll AH, Herbrecht R, Hope WW, Jensen HE, Lass-Florl C, Petrulkovs G, Richardson MD, Rolíides E, Verweij PE, Viscoli C, Ullmann AJ (2012) ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 18 Suppl 7: 19-37.
15. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Rebolci AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD (2016) Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Microbiol Infect 62: e1-50.
16. Groll AH, Castagnola E, Cesaro S, Dalle JH, Engelhard D, Hope W, Rolíides E, Styczynski J, Warris A, Lehrnbecher T (2014) Fourth European Conference on Infections in Leukaemia (ECIL- 4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. Lancet Oncol 15: e327-e340.
17. Zheng X, Huang X, Luo J, Li J, Li W, Liu Q, Niu T, Wang X, Zhou J, Zhang X, Hu J, Liu K (2018) Effectiveness and tolerability of micafungin in Chinese patients with invasive fungal infections: a retrospective, multicenter study. Adv Ther 35: 1400-1410.
18. European Medicines Agency (2018) Micafungin summary of product characteristics. Available: https://www.ema.europa.eu/en/documents/product-information/micafungin-epar-product-information_en.pdf. Accessed: 2 April 2019.
19. Pappas PG, Rotstein CM, Betts RF, Nucci M, Talwar D, De Waele JJ, Vazquez JA, Dupont BF, Horn DL, Ostrosky-Zeichner L, Rebolci AC, Suh B, Digumarti R, Wu C, Kovanda LL, Arnold LJ, Buell DN (2007) Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 45: 883-893.
20. Scott LJ (2012) Micafungin: a review of its use in the prophylaxis and treatment of invasive candida infections. Drugs 72: 2141-2165.
21. Datapharm Electronic Medicines Compendium (2017) Caspofungin summary of product characteristics. Available: https://www.medicines.org.uk/emc/product/8956/smpc. Accessed: 3 June 2021.
22. Datapharm Electronic Medicines Compendium (2017) Anidulafungin summary of product characteristics. Available: https://www.medicines.org.uk/emc/product/10698/smpc. Accessed: 3 June 2021.
23. Fritz JM, Brielmaier BD, Dubberke ER (2008) Micafungin for the prophylaxis and treatment of Candida infections. Expert Rev Anti Infect Ther 6: 153-162.
24. Denning DW, Vankateswara L, Oakley KL, Anderson MJ, Manning NJ, Stevens DA, Warnock DW, Kelly SL (1997) Itraconazole resistance in Aspergillus fumigatus. Antimicrob Agents Chemother 41: 1364-1368.
25. Verweij PE, Te Dorsthorst DT, Rijs AJ, De Vries-Hospers HG, Meis JF (2002) Nationwide survey of in vitro activities of itraconazole and voriconazole against clinical Aspergillus fumigatus isolates cultured between 1945 and 1998. J Clin Microbiol 40: 2648-2650.
26. Kontoyiannis DP, Lionakis MS, Lewis RE, Chamilos G, Healy M, Peregó C, Safdar A, Kantarjian H, Champlin R, Walsh TJ, Raad II (2005) Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis 191: 1350-1360.
27. Verweij PE, Mellingo E, Melchers WJ (2007) Multiple-triazole-resistant aspergillosis. N Engl J Med 356: 1481-1483.
28. van der Linden JW, Arendrup MC, Warris A, Lagrou K, Pelloux H, Hauser PM, Chrysanthou E, Mellingo E, Kidd SE, Tororton AM, Dannaoui E, Gausp B, Paddy JJ, Ueketter A, Lass-Florl C, Klimgo N, Moore CR, Denning DW, Pasqualotto AC, Kibbler C, Arikan-Akdagli S, Andes D, Meletiadis J, Naumakt M, Nuoci M, Melchers WJ, Verweij PE (2015) Prospective multicenter international surveillance of azole resistance in Aspergillus fumigatus. Emerg Infect Dis 21: 1041-1044.
29. Meis JF, Chowdhary A, Rhodes JL, Fisher MC, Verweij PE (2016) Clinical implications of globally emerging azole resistance in Aspergillus fumigatus. Philos Trans R Soc Lond B Biol Sci 371: 20150460.
30. Perlin DS, Rautemaa-Richardson R, Alastrew-Izuquierdo A (2017) The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis 17: e383-e392.
31. Conerny OA, Meens L, Herbret R, Viscoli C, van Amsterdam RG, Ruhnke M (2015) Randomised, multicentre trial of micafungin vs. an institutional standard regimen for salvage treatment of invasive aspergillosis. Mycososes 58: 58-64.
32. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Billie J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Munoz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, Zaoutis T, Bennett JE (2008) Revised definitions of invasive fungal disease from 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) Consensus Group. Clin Infect Dis 46: 1813-1821.
33. Gangneux JP, El Cheikh J, Herbret R, Yakoub-Agha I, Quiniou JB, Caillot D, Michallet M (2018) Systemic antifungal prophylaxis in patients hospitalized in hematologic units in France: the AFHEM Cross-Sectional Observational Study. Infect Dis Ther 7: 309-325.
34. Viscoli C, Bassetti M, Castagnola E, Cesaro S, Menichetti F, Ratto S, Tascini C, Giacobbe DR (2014) Micafungin for the treatment of proven and suspected invasive candidiasis in children and adults: findings from a multicenter prospective observational study. BMC Infect Dis 14: 725.

35. Nachbaur D, Angelova O, Orth-Holler D, Ditlbacher A, Lackner M, Aubberger J, Lass-Florl C (2015) Primary antifungal prophylaxis with micafungin in patients with haematological malignancies: real-life data from a retrospective single-centre observational study. Eur J Haematol 94: 258-264.

36. Hashino S, Morita L, Takahata M, Onozawa M, Nakagawa M, Kawamura T, Fujisawa F, Kahata K, Izumiyama K, Yonezu M, Chiba K, Kondo T, Asaka M (2008) Administration of micafungin as prophylactic antifungal therapy in patients undergoing allogeneic stem cell transplantation. Int J Haematol 87: 91-97.

37. Huang X, Chen H, Han M, Zou P, Wu D, Lai Y, Huang H, Chen X, Liu T, Zhu H, Wang J, Hu J (2012) Multicenter, randomized, open-label study comparing the efficacy and safety of micafungin versus itraconazole for prophylaxis of invasive fungal infections in patients undergoing hematopoietic stem cell transplant. Biology Blood Marrow Transplant 18: 1509-1516.

38. Racil Z, Toskova M, Kocmanova I, Buresova L, Kouba M, Drgona L, Masaraov L, Guman T, Tothova E, Gazdivilova J, Forsterova K, Haber J, Ziaikova B, Bojarova E, Rolencova M, Timilisina S, Cetkovsky P, Mayer J (2012) Micafungin as empirical antifungal therapy in hematological patients: a retrospective, multicenter study in the Czech and Slovak Republics. Leukemia & Lymphoma 54: 1042-1047.

39. van Burik JA, Ratanatharathorn V, Stepán DE, Miller CB, Lipton JH, Vesole DH, Bunin N, Wall DA, Hiemenz JW, Satoi Y, Lee JM, Walsh TJ (2004) Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 39: 1407-1416.

40. El Cheikh J, Celballos P, Dalle JH, Duchastelle-Lepretre S, Dulon E, Herbrecht R (2019) Micafungin prophylaxis in routine medical practice in adult and pediatric patients with hematological malignancy: a prospective, observational study in France. Diag Microbiol Infect Dis 94: 268-273.

41. Kotsopoulos M, Papadaki C, Anargyrou K, Spyridonidis A, Baltadakis I, Papadaki HA, Angelopoulou M, Pappa V, Liakou K, Tzanetakou M, Moustaka M, Vassilopoulos G (2019) Effectiveness and safety of micafungin in managing invasive fungal infections among patients in Greece with hematologic disorders: the ASPIRE study. Infect Dis Ther 8: 255-264.

42. Hiramatsu Y, Maeda Y, Fujiwara N, Saito T, Nawa Y, Hara M, Yano T, Asakura S, Sunami K, Tabayashi T, Miyata A, Matsuoka KI, Shinagawa K, Ikeda K, Matsu K, Tanizoto M (2008) Use of micafungin versus fluconazole for antifungal prophylaxis in neutropenic patients receiving hematopoietic stem cell transplantation. Int J Haematol 88: 588-595.

43. Saliba F, Pascher A, Cointault O, Laterre PF, Cervera C, De Waele JJ, Cillo U, Langer RM, Lugano M, Goran-Ericzon B, Phillips S, Tweddle D, Karas A, Brown M, Fischer L (2015) Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients. Clin Infect Dis 60: 997-1006.

44. Eschenauer GA, Nguyen MH, Shoahm S, Vazquez JA, Morris AJ, Pascullle WA, Kubin CJ, Klinker KP, Carver PL, Hanson KE, Chen S, Lam SW, Potoski BA, Clarke LG, Shields RK, Clancy CJ (2014) Real-world experience with echinocandin MICs against Candida species in a multicenter study of patients with invasive candidiasis. Antimicrob Agents Chemother 58: 1897-1906.

45. Darouiche RO (2009) Candida in the ICU. Clin Chest Med 30: 287-293, vi-vii.

46. Hsu D, Nguyen M, Nguyen L, Law A, Wong-Beringer A (2010) A multicentre study to evaluate the impact of timing of caspofungin administration on outcomes of invasive candidiasis in non-immunocompromised adult patients. J Antimicrob Chemother 65: 1765-1770.

47. Lin S, Chen R, Zhu S, Wang H, Wang L, Zou J, Yan J, Zhang X, Farmakiotis D, Tan X, Mylonakis E (2018) Candidemia in adults at a tertiary hospital in China: clinical characteristics, species distribution, resistance, and outcomes. Mycopathologia 183: 679-689.

48. Clancy CJ, Nguyen MH (2013) Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis 56: 1284-1292.

49. Cornely OA, Pappas PG, Young JA, Maddison P, Ullmann AJ (2011) Accumulated safety data of micafungin in therapy and prophylaxis in fungal diseases. Expert Opin Drug Saf 10: 171-183.

50. Schneeweiß S, Carver PL, Datta K, Galar A, Johnson MD, Johnson MG, Marty FM, Nagel J, Najdizanowicz M, Saul M, Shoham S, Silvera FP, Varughese CA, Wilck M, Weatherby L, Auton T, Walker AM (2016) Short-term risk of liver and renal injury in hospitalized patients using micafungin: a multicentre cohort study. J Antimicrob Chemother 71: 2938-2944.

51. Dowell JA, Stogniew M, Krause D, Damle B (2007) Anidulafungin does not require dosage adjustment in subjects with varying degrees of hepatic or renal impairment. J Clin Pharmacol 47: 461-470.

52. Montesinos P, Rodriguez-Veiga R, Martinez-Cuadron D, Boluda B, Navarro I, Vera B, Alonso CM, Sanz J, Lopez-Chulia F, Martin G, Jannone R, Sanz G, Lanciarro A, Cano I, Palau J, Lorenzo I, Jarque I, Salavert M, Ramirez P, Sanz MA (2015) Treatment of invasive fungal disease using anidulafungin alone or in combination for hematologic patients with concomitant hepatic or renal impairment. Rev Iberoam Micol 32: 185-189.

Corresponding author
Professor. Dr. Samo Zver, MD, PhD
Department of Hematology, University Medical Center Ljubljana, Zalošca cesta 2, 1000 Ljubljana, Slovenia
Phone: +386 (1) 522 50 50
Fax: +386 (1) 522 24 82
Email: samo.zver@klj.si

Conflict of interests: Sanja Bizilj and Tina Puconja are employees of Astellas Pharma S.E.E.; Samo Zver, Simona Avcin, Ovidiu Bedreag, Vanja Erculj, Janez Jazbec, Rade Stanič, and Matjaž Jereb declare no conflicts of interest.
### Annex – Supplementary Items

**Supplementary Table 1.** Summary of therapy duration for prior antifungal treatments.

|                       | N   | Median | Range  |
|-----------------------|-----|--------|--------|
| **Duration of prior therapy in treatment group, days** |     |        |        |
| Amphotericin B        | 3   | 28.0   | 18 – 29|
| Caspofungin           | 3   | 15.0   | 14 – 43|
| Fluconazole           | 22  | 8.0    | 0 – 54 |
| Itraconazole          | 2   | 40.0   | 3 – 77 |
| Posaconazole          | 3   | 30.0   | 12 – 103|
| Voriconazole          | 1   | –      | –      |
| **Duration of prior therapy in prophylaxis group, days** |     |        |        |
| Amphotericin B        | 7   | 8.0    | 0 – 28 |
| Anidulafungin         | 2   | 5.5    | 4 – 7  |
| Caspofungin           | 1   | –      | –      |
| Fluconazole           | 15  | 4.0    | 0 – 92 |
| Posaconazole          | 9   | 2.0    | 0 – 17 |
| Voriconazole          | 3   | 37.0   | 11 – 66|

**Supplementary Table 2.** Concomitant medication use.

| Concomitant medications (therapeutic subgroup) | Number of patients, n (%); N = 118 |
|------------------------------------------------|-----------------------------------|
| Systemic antibacterials                        | 114 (96.6)                        |
| Drugs for acid-related disorders               | 56 (47.5)                         |
| Analgesics                                     | 48 (40.7)                         |
| Systemic antivirals                            | 41 (34.7)                         |
| Psycholeptics                                  | 29 (24.6)                         |
| Systemic corticosteroids                       | 28 (23.7)                         |
| Immunostimulants                               | 26 (22.0)                         |
| Diuretics                                      | 23 (19.5)                         |
| Immunosuppressants                             | 22 (18.6)                         |
| Drugs for functional GI disorders              | 21 (17.8)                         |
| Antigout preparations                          | 20 (16.9)                         |
| Antithrombotic agents                          | 18 (15.3)                         |
| Antihemorrhagics                               | 18 (15.3)                         |
| Antineoplastic agents                          | 18 (15.3)                         |
| Antiemetics and antinauseants                  | 17 (14.4)                         |
| Beta blocking agents                           | 13 (11.0)                         |
| Cough and cold preparations                    | 13 (11.0)                         |
| Antidiarrheals, intestinal anti-inflammatory/anti-infective agents | 12 (10.2) |
| Antiprotozoals                                 | 12 (10.2)                         |
| Calcium channel blockers                       | 11 (9.3)                          |
| Agents acting on the renin-angiotensin system  | 10 (8.5)                          |

GI: gastrointestinal. Only agents used in ≥ 10 patients are shown. Other concomitant medication included: bile and liver therapy, mineral supplements, drugs for constipation, cardiac therapy, thyroid therapy, anesthetics, psychoanaleptics, general nutrients, antianemic preparations, blood substitutes and perfusion solutions, antimiycobacterials, drugs used in diabetes, vitamins, antihypertensives, sex hormones and modulators of the genital system, anti-inflammatory and antirheumatic products, other nervous system drugs, pituitary and hypothalamic hormones and analogues, antiepileptics, vasoprotectives, lipid modifying agents, urological and endocrine therapy.
### Supplementary Table 3. Shift table of change in results from microbiological and radiographic tests at visit one and visit two.

| Baseline (Visit 1) | Treatment, n (%) | Prophylaxis, n (%) |
|--------------------|------------------|-------------------|
|                    | Any positive     | All performed are negative | All negative | None performed | Any positive | All performed are negative | All negative | None performed |
| **Microbiological or radiographic tests (total)** |
| Any positive       | 23 (50.0)        | 9 (19.6)           | –            | 14 (30.4)      | 8 (50.0)     | 5 (31.3)            | –            | 3 (18.8)       |
| All performed are negative | 4 (25.0)       | 4 (25.0)           | –            | 8 (50.0)      | 3 (11.1)     | 8 (29.6)            | –            | 16 (59.3)      |
| All negative       | –                | –                  | –            | –             | –           | –                 | –            | –              |
| None performed     | 1 (16.7)         | 2 (33.3)           | –            | 3 (50.0)      | 0 (0)       | 2 (40.0)            | –            | 3 (60.0)       |
| **Microbiological culture tests** |
| Any positive       | 13 (36.1)        | 12 (33.3)          | 0 (0)        | 11 (30.6)     | 3 (30.0)     | 5 (50.0)            | 0 (0)        | 2 (20.0)       |
| All performed are negative | 7 (31.8)       | 4 (18.2)           | 0 (0)        | 11 (50.0)     | 1 (3.6)      | 10 (35.7)           | 0 (0)        | 17 (60.7)      |
| All negative       | 0 (0)            | 0 (0)              | 0 (0)        | 0 (0)         | 0 (0)       | 0 (0)              | 0 (0)        | 0 (0)          |
| None performed     | 3 (30.0)         | 2 (20.0)           | 0 (0)        | 5 (50.0)      | 0 (0)       | 6 (60.0)            | 0 (0)        | 6 (60.0)       |
| **Microbiological non-culture tests** |
| Any positive       | 1 (20.0)         | 0 (0)              | 1 (20.0)     | 3 (60.0)      | 4 (80.0)     | 0 (0)              | 0 (0)        | 1 (20)         |
| All performed are negative | 0 (0)           | 0 (0)              | 0 (0)        | 0 (0)         | 0 (0)       | 0 (0)              | 0 (0)        | 0 (0)          |
| All negative       | 1 (20.0)         | 0 (0)              | 0 (0)        | 4 (80.0)      | 0 (0)       | 0 (0)              | 0 (0)        | 12 (100.0)     |
| None performed     | 2 (3.4)          | 0 (0)              | 4 (6.9)      | 52 (89.7)     | 1 (3.2)      | 4 (12.9)            | 0 (0)        | 26 (83.9)      |
| **Radiographic examination** |
| Any positive       | 11 (42.3)        | 6 (23.1)           | 0 (0)        | 9 (34.6)      | 1 (14.3)     | 3 (42.9)           | 0 (0)        | 3 (42.9)       |
| All performed are negative | 0 (0)          | 11 (40.7)          | 0 (0)        | 16 (59.3)     | 4 (19.0)     | 5 (23.8)           | 0 (0)        | 12 (57.1)      |
| All negative       | 0 (0)            | 0 (0)              | 0 (0)        | 0 (0)         | 0 (0)       | 0 (0)              | 0 (0)        | 0 (0)          |
| None performed     | 1 (6.7)          | 1 (6.7)            | 0 (0)        | 13 (86.7)     | 0 (0)       | 0 (0)              | 0 (0)        | 20 (100.0)     |

Row percentages are shown for treatment and prophylaxis separately. All negative – all possible tests were performed, and the results were all negative. All performed are negative – not all possible tests were performed, but those that were performed were negative. Microbiological culture tests recorded at start of micafungin treatment: hemoculture (venopunction), hemoculture (blood from CVC), cerebrospinal fluid, peritoneal fluid, bronchoalveolar lavage, tracheal aspirate, coproculture, rectal swab, throat swab, urocultures, CVC tip swab, wound secretion + pleural fluid culture. Microbiological culture tests recorded at the end of micafungin treatment: hemoculture (venopunction), hemoculture (blood from CVC), cerebrospinal fluid, peritoneal fluid, bronchoalveolar lavage, tracheal aspirate, coproculture, ascites culture, CVC tip swab, wound swab, pharyngeal swab, anal swab, axillary swab, sputum culture, throat swab, rectal swab. Microbiological non-culture tests recorded at the start and end of micafungin treatment: galactomannan test, 1,3-β-D-glucan test, mannan, anti-mannan antibodies. Radiographic tests recorded at the start and end of micafungin treatment: chest x-ray, thoracic CT, cerebral CT, ultrasonography (CT: computerized tomography; CVC: central venous catheter).
### Supplementary Table 4. Changes in laboratory parameters and vital signs from visit 1 to visit 2.

| Parameter                  | Children | Adults |
|----------------------------|----------|--------|
| **Neutrophils change (×109/L)** |          |        |
| n                          | 16       | 85     |
| Median (range)             | 0 (−5.6, 99.9) | 0.7 (−13.0, 12.7) |
| **AST change (μkat/L)**    |          |        |
| n                          | 9        | 69     |
| Median (range)             | 0.2 (−1.9, 0.9) | −0.1 (−153.3, 2.9) |
| **ALT change (μkat/L)**    |          |        |
| n                          | 9        | 70     |
| Median (range)             | −0.2 (−1.5, 2.2) | −0.1 (−38.5, 3.2) |
| **GGT change (μkat/L)**    |          |        |
| n                          | 8        | 43     |
| Median (range)             | 0 (−3.3, 1.1) | −0.2 (−5.4, 14.5) |
| **Alkaline phosphatase (μkat/L)** | 1      | 50    |
| Median (range)             | −3.8 (−3.8, −3.8) † | 0.3 (−5.6, 4.7) |
| **Creatinine change (μ/mol)** |        |        |
| n                          | 13       | 92     |
| Median (range)             | 1.9 (−94.0, 50) | −8.0 (−316.0, 146.0) |
| **Bilirubin change (μ/mol)** | 7      | 76    |
| Median (range)             | 0.3 (−14.0, 32.2) | −2.2 (−79.2, 132.0) |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; SD: standard deviation; † Alkaline phosphatase change was recorded for only one child in Romania.

### Supplementary Figure 1. Patient flow diagram.

[Diagram showing patient flow with categories such as 'Assessed for eligibility, N = 118', 'Excluded, n = 0', 'Allocated to intervention, N = 118', 'Analysed, n = 118 (100.0%)', 'Premature study discontinuation, n = 15 (12.7%)', etc.]