Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Micafungin (as sodium)

Proprietary Product Name: Mycamine

Sponsor: Astellas Pharma Australia Pty Ltd

Date of CER: 28 June 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. List of abbreviations

Abbreviation	Meaning
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AGIHO	Infectious Disease Working Party
AIDS	Acquired immunodeficiency syndrome
ALT (SGPT)	Alanine transaminase (Serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
APACHE	Acute Physiology And Chronic Health Evaluation II
ASBMT	American Society for Blood and Marrow Transplantation
AST (SGOT)	Aspartate transaminase (Serum glutamic oxaloacetic transaminase)
AUC	Area under the plasma concentration – time curve
BMT	Bone marrow transplant
BUN	Blood urea nitrogen
CDC	Center for Disease Control
CHMP	Committee for Medicinal Products for Human Use
CLSI	Clinical and Laboratory Standards Institute, 2002, including modifications
CMH	Cochran-Mantel-Haenszel test
CI	Confidence interval
C/IC	Candidaemia/invasive candidiasis
CIOMS	Council for International Organization of Medical Sciences
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CRF	Case report form
CYP	Cytochrome
DGHO	German Society of Haematology and Oncology

Abbreviation	Meaning
EC	Oesophageal candidiasis
EMEA	European Agency for the Evaluation of Medicinal Products
EORTC	European Organization for Research and Treatment of Cancer
EUCAST	European Committee on Antibiotic Susceptibility Testing
EOT	End of therapy
FAS	Full analysis set
FK463	Micafungin
GFR	Glomerular filtration rate
GVHD	Graft-versus-host disease
HAART	Highly active antiretroviral therapies
HSCT	Haematopoietic stem cell transplant
HIV	Human immunodeficiency virus
IA	Invasive aspergillosis
IC	Invasive candidiasis
ICU	Intensive care unit
IDRB	Independent Data Review Board
IDSA	Infectious Diseases Society of America
IFI	Invasive fungal infection
LDH	Lactate dehydrogenase
LFT	Liver function tests
MED	Minimum effective dose
mFAS	Modified full analysis set
MICx	Minimum inhibitory concentration of study compound needed to prevent x% of the test organism from growing
MITT	Modified intention to treat population
MMF	Mycophenolate mofetil

Abbreviation	Meaning
NIAID MSG	National Institute of Allergy and Infectious Diseases Mycoses Study Group
OC	Oropharyngeal candidiasis
PK	Pharmacokinetics
PPS	Per protocol set
Qod	Every other day
SAE	Serious adverse event
SOC	System organ class
ULN	Upper limit of normal
VLBW	Very-low-birth-weight

2. Introduction

Micafungin (as sodium) is a water soluble, semi-synthetic derivative of a fermentation product from the environmental mould Coleophoma empetri. Micafungin belongs to a new class of antifungal agents, the echinocandin lipopeptides. These compounds non-competitively inhibit the synthesis of 1,3-b-D-glucan, an essential component of the fungal cell wall, which is not present in mammalian cells.

The proposed indications for Mycamine are:

Adults, adolescents ≥16 years of age and the elderly:

- treatment of invasive candidiasis
- treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate
- prophylaxis of Candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/µL) for 10 or more days.

Children (including neonates) and adolescents <16 years of age:

- treatment of invasive candidiasis
- prophylaxis of Candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/µL) for 10 or more days.

Mycamine is proposed to be administered once daily by intravenous infusion. The proposed dosage depends on the indication and body weight of the patient, as shown below:

Table 1. Proposed dosage for adults, adolescents ≥16 years of age and the elderly

Indication	Body weight >40 kg	Body weight ≤40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Treatment of oesophageal candidiasis	150 mg/day	3 mg/kg/day
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

* If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing >40 kg or 4 mg/kg/day in patients weighing ≤40 kg.

Treatment duration

The proposed treatment duration for *Candida* infection is a minimum of 14 days. The antifungal treatment should continue for at least one week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection.

For the treatment of oesophageal candidiasis, Mycamine is to be administered for at least one week after resolution of clinical signs and symptoms. For prophylaxis of *Candida* infection, Mycamine should be administered for at least one week after neutrophil recovery.

Table 2. Proposed dosage for children (including neonates) and adolescents <16 years of age

Indication	Body weight >40 kg	Body weight ≤40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

***** If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing >40 kg or 4 mg/kg/day in patients weighing ≤ 40 kg.

Treatment duration

The treatment duration for *Candida* infection is for a minimum of 14 days and should continue for at least one week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection. For prophylaxis of *Candida* infection, Mycamine should be administered for at least one week after neutrophil recovery.

2.1. Contents of the clinical dossier

Clinical study information was provided in support of this application. This consisted of information from a total of 63 studies, comprising 35 pharmacokinetic studies, 20 efficacy and safety studies, and 8 post-marketing studies. Of the pharmacokinetic studies, 5 assessed pharmacokinetics in healthy subjects, 12 assessed pharmacokinetics in infected patient groups, 4 assessed pharmacokinetics in special populations, and 14 assessed potential drug interactions.

Of the efficacy/safety studies, 10 assessed efficacy in patients with confirmed candidaemia or invasive candidiasis, 4 assessed efficacy in oesophageal candidiasis and 6 assessed efficacy in prophylaxis of candida infection.

2.2. Good clinical practice

No issues were identified in these aspects of the clinical development program.

3. Pharmacokinetics

3.1. Introduction

Information on pharmacokinetics was provided in both the nonclinical and clinical submissions. In the clinical submission, information was provided by 35 clinical studies, including 5 studies assessing pharmacokinetics in healthy subjects, 12 studies in infected patient groups, 4 studies in special populations and 14 studies involving potential drug interactions. Basic pharmacokinetic parameters were obtained from the 5 clinical studies involving healthy subjects, which are described below.

3.1.1. Study FJ-463-0001

This study was a phase I single-dose intravenous administration study of FK463 (Mycamine), conducted between February and June 1997. The aim of the study was to evaluate safety and pharmacokinetics of FK463 in healthy male adult volunteers given a single intravenous dose of the study drug. Subjects received FK463 in a single intravenous dose of 2.5 mg (Step 1), 5 mg (Step 2), 12.5 mg (Step 3), 25 mg (Step 4) or 50 mg (Step 5) over 2 hours during fasting in the morning and underwent various examinations including clinical laboratory tests, physical examination, ECG examination and medical examination. Plasma and urine drug concentrations

were also determined. A total of 27 healthy adult male volunteers were enrolled. Although some adverse events occurred, there were no particular clinical concerns and FK463 was well tolerated. In pharmacokinetics, the time courses in C_{max} and AUC of unchanged drug were dose-proportional and the β, $t_{1/2}$, Vd_{ss} and CLt values were not significantly different between the dose groups. It is thus concluded that the pharmacokinetics of FK463 are linear at the dose of up to 50 mg.

3.1.2. Study FJ-463-0002

This study was a phase I repeated-dose intravenous administration study of FK463 conducted between October and November 1997. The aim of the study was to investigate safety and pharmacokinetics of FK463 in healthy adult male volunteers given repeated intravenous doses of the study drug. Subjects receive 100 mL of physiological saline solution of 25 mg of FK463 (0.25 mg/mL) or physiological saline alone by one-hour i.v. infusion once daily for seven consecutive days and underwent various examinations including clinical laboratory tests and physical examinations. Plasma and urine drug concentrations were determined. A total of 9 healthy adult male volunteers were enrolled. The plasma concentrations of FK463 during repeated-dose administration were well described by a linear two-compartment model. They reached a steady state by day 4. The maximum plasma drug concentration was attained at the end of one-hour infusion, and it increased from 1.91 ± 0.20 μg/mL on day 1 to 2.39 ± 0.28 μg/mL on day 4 to 2.46 ± 0.27 μg/mL on day 7. The elimination half-life after final dosing, which was determined by model independent analysis, was 14.6 ± 1.5 hours. The area under the plasma concentration-time curve from time zero to 24 hours after the last dose on day 7 was 29.6 ± 4.6 μg.h/mL, and total clearance was 0.222 ± 0.027 mL/min/kg. Unchanged FK463 was scarcely excreted in the urine, showing a urinary recovery of 0.63 ± 0.14% of the administered dose. FK463 was highly bound to the plasma proteins and the percent bound was 99.84 ± 0.03%.

3.1.3. Study 97-0-040

This study was designed to assess pharmacokinetics and disposition of ^{14}C-FK463 in healthy male volunteers following a single IV infusion conducted between April 1998 and January 1999. The aim of the study was to 1) obtain pharmacokinetic profiles of FK463 and total radioactivity, 2) establish elimination routes and elimination/excretion rates of FK463 and total radioactivity, 3) establish the presence or absence of metabolites in plasma and urine and determine the distribution (if any) of radioactivity within these matrices and 4) obtain a mass balance estimate for ^{14}C-FK463. Subjects were 6 healthy male volunteers, 18 years of age or older that were within 15% of ideal weight who received a single one hour infusion dose of ^{14}CFK463 at a single study site. The mean plasma parent FK463 concentration versus time profile declined in a biexponential manner. The mean terminal elimination half-life was 13.6 hours; estimated using plasma concentrations that were detected out through 48 hours. In most cases, maximum plasma FK463 concentration (C_{max}) values were obtained at 1-hour, the end of the infusion period. In two subjects, C_{max} was found to occur at 1.5 hours. In 5 of the 6 subjects, plasma FK463 concentrations were not measurable beyond the 48 hour collection time point; the sixth subject had a measurable plasma concentration of 0.05 μg/mL at 72 hours. Metabolites, M-1 and M-2, were not detected (<0.050 μg/mL) over the entire collection period.

3.1.4. Study FJ-463-0005

This study was a phase I single and repeated-dose intravenous administration study of FK463 conducted between September and October 2000. The aim of the study was to assess the pharmacokinetics of FK463 in healthy male volunteers after a single intravenous dose of 25, 50 75 or 150 mg or after a repeated daily intravenous dose of 75 mg for 7 days. Measurements were made for FK463 and its metabolites M1 and M2 in plasma and urine and for unbound FK463 in plasma. Healthy male volunteers received a single intravenous infusion of 25, 50 75 or 150 mg or repeated daily intravenous infusions of 75 mg for 7 days in the open-label

pharmacokinetic study. A total of 30 healthy male volunteers participated. After a single infusion of FK463, $t_{½}$, CLt, Vd_{ss}, and Vdb were independent of the dose administered, and AUC_{0-inf} increased in proportion to dose (r=0.989, n=23). After repeated daily infusions of 75 mg FK463, systemic exposure slightly increased over time. Estimates for $t_{½}$, CLt, Vd_{ss}, and Vdb were similar after a single dose of FK463 compared with estimates after repeated doses.

3.1.5. Study FG-463-21-14

This study was a phase I single and repeated-dose intravenous administration study of FK463 conducted between September and October 2000. The aim of the study was to study the pharmacokinetics during single and repeated intravenous administration of FK463 to healthy adult male subjects. Healthy male volunteers received a single intravenous infusion of 25, 50, 75 or 150 mg or repeated daily intravenous infusions of 75 mg for 7 days, or infusion with transfusion pump at a rate of 200 mL over period of 30 minutes (or over period of 1 hour for 150 mg dose) in an open-label pharmacokinetic study. A total of 30 healthy male volunteers participated. The plasma concentrations of unchanged drug declined in a bi-exponential way after cessation of infusion during single administration of FK463. The elimination half-life ($t_{1/2}$) was 13.3 to 14.2 hours, and there were no differences between dosage groups. The plasma concentration of unchanged drug increased proportionally to dose, as did the post-dosing plasma concentration-time area under curve to infinity ($AUC_{0-\infty}$). There were no differences between dosage groups in the pharmacokinetic parameters ($t_{1/2}$, Vd_{SS}, and CLt). The mean $t_{1/2}$ for all groups was 13.9 ± 1.0 (mean ± S.D.), the CLt was 0.197 ± 0.018 mL/min/kg, and the distribution volume in steady state (Vd_{SS}) was 0.228 ± 0.016 L/kg. The drug was thus concluded to exhibit linear pharmacokinetics. There were 12 adverse events for which a causal relation to FK463 could not be ruled out occurred in 7 subjects, but all were mild, required no treatment for recovery, and were thus not considered problematic for clinical purposes.

3.2. Absorption

3.2.1. Bioavailability

Micafungin is a sterile, non-pyrogenic lyophilised product for intravenous infusion and is not intended for oral administration.

3.2.2. Bioequivalence

Not applicable.

3.2.3. Influence of food

Not applicable.

3.3. Distribution

In an *in vitro* study in which ^{14}C-micafungin was added to whole human blood, the blood to plasma ratio was approximately 0.85 and was independent of concentration over the range of 0.1 to 10 μg/mL micafungin. The percent transfer into human red blood cells was approximately 35%. Based on *in vitro* studies with human biomaterials, micafungin is highly protein bound (> 99%), primarily to albumin and, to a lesser extent, to alpha1-acid glycoprotein. Micafungin does not displace albumin-bound bilirubin at clinically relevant concentrations (and therefore would not be expected to cause kernicterus) and is not an inhibitor of P-glycoprotein (and therefore would not be expected to alter P-glycoprotein mediated drug transport activity).

3.4. Elimination

3.4.1. Excretion

Elimination route was investigated in study 97-0-040, in which 6 healthy male subjects received a single dose of ^{14}C-micafungin. Between 44.4% to 57.5% of the administered radioactive dose was recovered from subjects upon completion of the study, 168 hours post-dose. Mass balance was not reached. Faecal excretion was the major route of elimination accounting for a mean recovery of 43.8% of administered ^{14}C dose. Urinary excretion played a minor role in the elimination process accounting for a mean recovery of 7.4% of administered ^{14}C dose. At study end, ^{14}C-micafungin derived total radioactivity in plasma (concentration times total body plasma volume) accounted for a mean of 1.8% of the administered dose.

As mass balance was not reached by 168 hours post-infusion, a further study was conducted.

In study FG-463-21-14, a single dose of ^{14}C-micafungin was followed by a 29-day residential period with follow-up assessments on Days 35, 42 and 56. Once-weekly samples were taken until Day 55. By Day 28, approximately 82.5% of the radioactive dose was recovered with a further 4.9% extrapolated as being excreted between Days 29 to 55.

3.4.2. Metabolism

In vitro, the metabolism of micafungin involves multiple CYP isozymes including CYP1A2, 2B6, 2C and 3A4. Concentration–dependant inhibition of CYP3A4 was observed in vitro, with no effect at 5 μM and 80% inhibition at 50 μM, which is equivalent to a C_{max} of 60 μg/mL (observed with a dose of 8 mg/kg in patients).

3.4.2.1. Interconversion

Five metabolites have been detected after administration of micafungin to humans: M-5 (main metabolite in plasma), M-1 and M-2 (minimal to undetectable in plasma), and M-3 and M-11 (faeces/urine). *In vitro*, M-2 has a potency and spectrum of activity similar to that of the parent compound; M-1 is 4- to 16-fold less potent than the parent compound; and M-5 has no activity (<1% of parent compound).

3.4.2.2. Pharmacokinetics of metabolites

After a single dose of ^{14}C-micafungin to healthy subjects, M-5 accounted for 2.8% to 8.3% of the micafungin C_{max} between 4 and 48 hours post-administration, and M-1 and M-2 accounted for ≤ 1% of the micafungin C_{max} in plasma. In patients undergoing HSCT, steady-state concentrations of M-1 and M-2 after 200 mg/day were approximately 4% and 1% of the micafungin C_{max}. Given the minimal concentrations of M-1 and M-2 in plasma and the biological inertness of M-5, it is unlikely that metabolites in plasma contribute to the activity of micafungin. M-1, M-2 and M-5 concentrations from further studies in healthy subjects (studies 03-0-175, 03-0-176, 03-0- 177, 03-0-178 and 04-0-193, FG-463-21-09, FG-463-21-14, FG-463-21-15, FG-463-21-16) and patients (studies 03-7-008 and 03-7-009) confirmed this observation.

During a clinical trial, M5 exposure in neonates and young infants was found to be more than 20% of total drug-related exposure (mean AUC_{24} for M5 was 266.4 μg.h/mL in Study 9463-CL-2104 for patients dosed at 10 mg/kg/day). Additional nonclinical toxicology studies of FR22149, the M5 metabolite of micafungin (9463-TX-0048, TX107003 and TX107004) were conducted. No target organs were identified at exposures up to 5-fold higher than those observed in human neonates and young infants at doses of 10 mg/kg/day. Additionally, no genotoxic potential was indicated for M5. These findings support reinitiation of the Phase 3 study in neonates and young infants at a dose of 10 mg/kg/day (9463-CL-2303).

3.4.2.3. Consequences of possible genetic polymorphism

Not applicable.

3.5. Dose proportionality and time dependency

3.5.1.1. Dose proportionality

In adult patients receiving micafungin as a 1-hour infusion for the prophylaxis of fungal infections, pharmacokinetic parameters were similar to those observed in adult healthy subjects. Following repeated administration of micafungin to patients, dose-linear pharmacokinetics was demonstrated up to doses of 8 mg/kg/day. The $t_{1/2}$ was 10 to 17 hours and a steady-state was reached by day 5. There was no evidence of systemic accumulation of micafungin in humans.

3.5.1.2. Time dependency

Please refer above.

3.6. Intra- and inter-individual variability

The PK of micafungin appears to be consistent across studies. Studies with both healthy subjects and patients have shown: a bi-exponential decline in micafungin concentrations; mean half-life values of approximately 15 hours which remained constant with increases in dose; no evidence of systemic accumulation with repeated administration; increases in systemic exposure (AUC and Cmax) proportional to increases in dose; and steady-state reached by Day 7 after repeated daily administration.

3.7. Pharmacokinetics in the target population

Information on pharmacokinetics in the target population was provided by 12 clinical studies. These are described as below.

3.7.1. Study FG463-21-03

This study was a phase I/II study to determine the safety profile, the maximum tolerated dose and pharmacokinetics of FK463 for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. Thirty-six patients entered the study. Subjects were male or female patients aged between 18 to 60 years, who had undergone a bone marrow or peripheral stem cell transplant. FK463 was administered daily as a 1 h intravenous infusion beginning 2 to 3 days prior to transplantation and continued until either recovery from neutropenia or after a period of at least seven days, whichever was the longer. FK463 administration could have been continued for up to five days following recovery from neutropenia at the Investigator's discretion, but FK463 was only to be administered up to a maximum period of four weeks. FK463 was administered as a 1 hr infusion (100 mL) at dose levels of 3, 4 and 6 mg/kg/day and as a 1 hr infusion (200 mL) at 8 mg/kg/day. The pharmacokinetics of FK463 in bone marrow/peripheral stem cell transplant patients are similar to those seen in previous studies with healthy subjects and in transplant patients, and there was no pharmacokinetic reason to preclude the clinical use of FK463 in the dose range of 3 to 8 mg/kg/day (approximately 230 to 600 mg/day).

3.7.2. Study FJ-463-0003

This study was a phase II study of FK463 on deep mycosis. The primary objectives of this study were to evaluate efficacy, safety and pharmacokinetics of FK463 in adult patients with deep mycosis. Patients received FK463 (12.5, 25, 50, 70, 100 or 150 mg/day) as an infusion (0.5 to 2.08 hours). A total of 71 patients were enrolled and 70 received at least one dose of FK463. Subjects were male and female adult patients with deep-seated mycosis. The elimination half-life of FK463 was estimated to be approximately 13 to 14 hours and was similar with doses of 12.5 to 150 mg. Both C_{min} and C_{max} were proportional to dose. Plasma concentrations of metabolites were low.

3.7.3. Study 97-0-041

This study was a phase I/II study to determine the maximum tolerated dose and pharmacokinetics of FK463 in combination with fluconazole for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. The objectives of this study were to provide a pharmacokinetic evaluation of FK463 when administered in combination with fluconazole to bone marrow and stem cell transplant patients participating in a maximum tolerated dose (MTD) study of FK463, and to provide an apparent steady state pharmacokinetic evaluation of fluconazole when administered in combination with FK463 to bone marrow and stem cell transplant patients at FK463 doses of 12.5 mg per day and higher. FK463 was administered as a 1-hour intravenous infusion beginning at some point between 48 hours prior to initiation of transplant and 24 hours after initiation of transplant. Treated patients received a FK463 infusion and fluconazole (FK463 treatment group) or a normal saline infusion and fluconazole (control group). FK463 was administered as a 1 hour infusion (100 mL) at dosages of 12.5 mg/day, 25 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 150 mg/day, or 200 mg/day. The control group received a 1 hour normal saline infusion (100 mL). Fluconazole (400 mg/day) was administered either orally (whenever clinically feasible) or intravenously.

A total of 74 randomized patients received at least one dose of assigned therapy. Subjects were male or female patients, 18-55 years of age, who underwent a bone marrow or peripheral stem cell transplant. The mean terminal elimination half-life ($t_{1/2}$) was approximately 13 hours over the study and did not vary over time or across doses. On Day 1, both C_{max} and AUC_{24} were relatively proportional to dose. The CL and V estimates ranged from 1.09 to 1.28 L/hr and from 17.7 to 25.6 L, respectively. On Day 7, C_{max} was higher at each respective dose relative to Day 1. AUC_{24} values on Day 7 were relatively similar to Day 1 AUC_{inf} values across the seven dose levels as were CL and V. Levels of metabolites, M1 and M2, were relatively low when compared to parent compound.

On Days 1 and 7, M1, the predominant metabolite was approximately 1% and 5% of C_{max} of parent, respectively, and M2 was approximately 0.4% of C_{max} of the parent. FK463 was extensively bound to plasma proteins in the study patients and ranged from 99.49 to 99.87%; this extent of binding is consistent with what has been found in serum from normal subjects. Concurrent administration of fluconazole did not affect the pharmacokinetics of FK463. Similarly, the pharmacokinetics of fluconazole were not affected by FK463. As expected for a drug with a 10- to 16-hour half-life, AUC and C_{max} showed accumulation with repeated daily dosing. However, a comparison of Day 1 AUC_{inf} to Day 7 AUC_{24} and similar CL and V between Day 1 and Day 7 shows that the pharmacokinetics of FK463 in adult cancer patients did not change following repeated daily administrations.

3.7.4. Study 98-0-043

This study was a phase I study to determine the safety and pharmacokinetics of FK463 in febrile neutropenic paediatric patients. The objectives of this study were to provide a pharmacokinetic evaluation of FK463 from plasma concentration data obtained on Days 1 and 4 in neutropenic paediatric patients treated with FK463 as a one hour infusion at doses up to 4 mg/kg/day; but not greater than 200 mg/day. The clinical study was an open-label, sequential group, dose-escalation, tolerance study to determine the maximum tolerated dose (MTD) of FK463. A total of 78 patients were enrolled in this study, 73 with FK463 plasma concentration data. Subjects were patients 2 to 17 years of age with neutropenia (absolute neutrophil count [ANC] <500 cells/mm^3). FK463 was administered intravenously once daily as a 1-hour infusion. FK463 was initiated within 24 hours of the initiation of antibacterial therapy for febrile neutropenia. Patients received 0.5 mg/kg per day (not to exceed 25 mg per day); 1 mg/kg per day (not to exceed 50 mg per day); 1.5 mg/kg per day (not to exceed 75 mg per day), 2.0 mg/kg per day (not to exceed 100 mg per day), 3.0 mg/kg per day (not to exceed 150 mg per day), or 4.0 mg/kg per day (not to exceed 200 mg per day). The entire data set indicated that the

pharmacokinetics of FK463 in neutropenic paediatric patients appeared to be relatively linear over the 0.5 to 4.0 mg/kg dose range investigated. CL, V_{ss}, and $t_{1/2}$ remain relatively constant across doses and did not change with repeated administration. Furthermore, the pharmacokinetic profile of FK463 in febrile neutropenic paediatric patients with the exception of CL was consistent with that obtained in healthy adult volunteers and adult bone marrow transplant patients.

3.7.5. Study 99-0-063

This study was a phase I study to determine pharmacokinetic, safety, and tolerance of three dose levels of micafungin (FK463) in premature infants. The objective of this study was to evaluate the pharmacokinetics, safety, and tolerance of three dose levels of micafungin (FK463) in premature infants. This was a Phase 1, single dose, multi-centre, open-label, sequential dose trial of intravenous micafungin. Three dose levels (0.75 mg/kg, 1.5 mg/kg, and 3.0 mg/kg) within two weight groups (500 g to 1000g and >1000 g) were to be studied. Each weight group was dose-escalated independently of the other. Subjects were premature infants aged ≤40 weeks postconceptional age with body weight ≥500 g. Patients receiving systemic antifungal therapy or near completion of their systemic antifungal therapy were enrolled. A total of 23 patients were enrolled. Dose levels were 0.75 mg/kg, 1.5 mg/kg, and 3.0 mg/kg of micafungin administered as a single 30-minute intravenous infusion. Patients received a single dose at one of the dose levels. Some patients were concurrently enrolled in ongoing Study 98-0-047 and received additional doses of micafungin on subsequent days. Single doses of micafungin, ranging up to 3.0 mg/kg, were safe and well tolerated by premature infants ≥500 g. Since only 5 infants with body weights between 500 and 1000 g were enrolled, and only 4 of these had evaluable pharmacokinetics, the information about pharmacokinetics in the smaller infants was very limited. In general, pharmacokinetic parameters in the premature infants were comparable to those of other young children (2 to 8 years of age) except for half-life and clearance. The premature infants experienced a shorter half-life and more rapid clearance per kilogram body weight.

3.7.6. Study FG463-21-09

This study was a phase II multicentre, double blind, four parallel group, randomised study to investigate the dose response of micafungin (FK463) compared with fluconazole administered to HIV positive patients with confirmed oesophageal candidiasis (PK sub-study). The objective of this study was to investigate the pharmacokinetics of micafungin in HIV positive patients with confirmed oesophageal candidiasis. Eligible patients were randomised 1:1:1:1 to 50, 100 or 150 mg/day micafungin or 200 mg/day fluconazole. The planned treatment period was 14 days, but was allowed to extend to 21 days for patients who did not achieve endoscopic clearance by Day 14. A total of 101 patients were enrolled of which 74 received micafungin. Subjects were adult HIV positive patients with confirmed oesophageal candidiasis (OEC). Micafungin exhibited linear pharmacokinetics over the dose range investigated (50-150 mg/day). The half-life and clearance remained consistent with increasing dose. Visual examination of trough levels on days 3, 7 and 14 suggested that steady state was reached between day 3 and day 7. There was no accumulation of micafungin following repeated daily dosing for 14 or 21 days.

3.7.7. Study 03-7-009

This study was a phase I study of the safety and pharmacokinetics of repeated-dose micafungin (FK463) in adults (≥ 16 Years) with oesophageal candidiasis. The objective of this study was to characterize the single-dose and steady-state pharmacokinetics of micafungin (150 mg/day for 14 days) in adults with oesophageal candidiasis. This was a prospective, open-label, multi-centre, repeat-dose study. All subjects were to receive 150 mg/day micafungin, administered over 14 successive days as a 1-hour intravenous infusion (100 mL). Subjects were adult subjects, ≥ 16 years old and weighing ≥ 40 kg, with a diagnosis of oesophageal candidiasis.

Thirty subjects were enrolled and completed the study and data from all subjects was analysed. The safety data in this study suggest that micafungin was well tolerated at the 150 mg/day dose level in patients with confirmed oesophageal candidiasis. The adverse event profile observed was consistent with those of previous studies. The pharmacokinetic data in this study suggest that steady state was attained quickly; after four to seven doses. The pharmacokinetic profile after the 14th daily 150 mg dose of micafungin demonstrated that C_{max} was 17.7 µg/mL at a T_{max} of 1 hour (end of infusion), AUC_{0-24} was 196 µg.hr/mL, and $t_{½}$ was 15.4 hours.

3.7.8. Study FJ-463-FP01

This study was a multi-centre open-label non-controlled study to assess safety, pharmacokinetics and efficacy of FK463 in paediatric patients with deep mycosis. The objective of the study was to analyse the pharmacokinetics of FK463 using data on plasma concentration of FK463 and its metabolites obtained in a phase III study of paediatric patients with deep mycosis. In the study, once daily repeated-dose intravenous administration of FK463 was conducted in paediatric patients with deep mycosis probably caused by *Aspergillus* or *Candida* species at an initial dose of 1.0 mg/kg. Subjects were paediatric patients who were considered to have deep mycosis caused by *Aspergillus* or *Candida*. A total of 19 subjects were enrolled. There was an almost linear relationship between pharmacokinetic parameters and doses from 1.0 to 6.0 mg/kg in paediatric patients. $T_{1/2}$ of FK463 appeared not to be affected by differences in age, body weight, height, sex or dose in paediatric patients and not to significantly differ from that of adults.

3.7.9. Study FG-463-21-08

This study was a multi-centre, double blind, comparative, randomised study to evaluate the efficacy and safety of micafungin (FK463) versus liposomal amphotericin B (Ambisome) in the treatment of invasive candidiasis and candidaemia (PK sub-study). The objective of the study was to investigate the pharmacokinetics of micafungin in neutropenic and nonneutropenic patients with confirmed IC or candidaemia caused by *Candida albicans* and nonalbicans *Candida* species. Patients were randomised 1:1 to receive either Micafungin or Amphotericin B. A total of 101 patients were enrolled into the pharmacokinetic sub-study, 45 of whom were treated with Micafungin. Twenty of the micafungin treated patients provided evaluable profiles and were included in the pharmacokinetic analyses. Subjects were patients with confirmed invasive candidiasis or candidaemia. Micafungin (at an initial dose of 100 mg for patients weighing more than 40 kg, 2.0 mg/kg for patients weighing 40 kg or less) or Ambisome (3 mg/kg/day) was administered once daily by a 1-hour infusion in a blinded manner. The minimum duration of therapy was 14 days. The pharmacokinetics observed in this patient population were similar to those obtained in earlier studies in adults. The mean elimination half-life of micafungin was approximately 14 hours and did not vary with time. There was no accumulation of micafungin beyond that expected for a drug with linear pharmacokinetics following repeated daily dosing for 14 or 28 days. Clearance, too, did not vary over the period of the study. Exposure to M-1 and M-2 was low throughout the study with M-2 representing only trace levels relative to micafungin. Relative to micafungin, M-1 and M-2 accounted for 12% and 2% of the systemic exposure at the end of therapy. M-5 was the more abundant metabolite in plasma and accounted for approximately 11% of AUC_{0-24} relative to the parent compound on Day 1 and approximately 17% at end of therapy.

3.7.10. Study 9463-CL-2102

This study was a phase 1, open-label study of the safety and pharmacokinetics of repeated-dose micafungin (FK463) in infants and toddlers (≥ 4 months to < 24 months of age) with oesophageal candidiasis or other invasive candidiasis. The objective of the study was to evaluate the pharmacokinetics and safety of intravenous (IV) micafungin (FK463) after repeated daily dosing at 4.5 mg/kg in infants and toddlers (≥ 4 months to < 24 months of age) with proven or probable oesophageal candidiasis or other invasive candidiasis or suspected *Candida* infection.

Infants and toddlers (≥ 4 months to < 24 months of age) with proven or probable candidiasis were enrolled to receive daily IV infusions of micafungin. Micafungin was administered by infusion over 1 hour, once a day for 10 to 14 days. Subjects were infants and toddlers (≥ 4 months to < 24 months of age) with oesophageal candidiasis or other invasive candidiasis. A total of 9 subjects were enrolled.

The mean plasma micafungin AUC_{tau} was 299.422 hr.µg/mL (median 263.795). The mean plasma micafungin C_{max} was 32.825 µg/mL (median 21.700), with relatively large inter-subject variability (CV=69.19%). The mean CL_{ss}/Wt was16.673 mL/hr/kg (median 16.411). The CV of CL_{ss} was 51.13 %, whilst that of CL_{ss}/Wt was 31.77%, suggesting that weight explains some of the inter-subject variability in clearance. For M1, the mean C_{max} was 1.332 µg/mL and mean AUC_{tau} was 27.898 hr.µg/mL and for M5, the mean C_{max} was 3.265 µg/mL and mean AUC_{tau} was 68.794 hr.µg/mL. The M1 and M5 exposures relative to micafungin (PR_{AUC}) were 8.9% and 22.9 %, respectively. The 4.5 mg/kg dose in these paediatric patients was chosen to target micafungin exposure levels seen in adults (mean 167+/- SD 40 hr.µg/mL) treated with 150 mg daily dose. The micafungin exposure data suggested that a lower dose would be needed to achieve the target exposure levels.

3.7.11. Study 9463-CL-2103

This study was a phase 1, open-label study of the safety and pharmacokinetics of repeated-dose micafungin (FK463) as antifungal prophylaxis in children and adolescents undergoing haematopoietic stem cell transplantation. The objective of the study was to evaluate the pharmacokinetics and safety of intravenous (IV) micafungin (FK463) after repeated daily dosing at either of 2 doses (1 mg/kg and 1.5 mg/kg) as prophylaxis in children and adolescents undergoing autologous, syngeneic, or allogeneic hematopoietic stem cell transplant (HSCT).

Transplantation types may have included cord blood, peripheral stem cell, and bone marrow. Patients were enrolled according to age and stratified by weight to receive either 1 mg/kg micafungin (weight > 25 kg) or 1.5 mg/kg micafungin (weight < 25 kg). Children (4 to < 24 months, 2 to 5 years, and 6 to 11 years) and adolescents (12 to 16 years) undergoing a HSCT were allowed to participate. Micafungin was administered by infusion over 1 hour, once a day for 10 to 14 days. Subjects were children and adolescents (4 months to 16 years of age) scheduled to undergo a HSCT. A total of 40 patients were enrolled. The mean micafungin AUC_{tau} observed in patients 4 months to 5 years of age in the 1.5 mg/kg treatment group was comparable to that observed in patients 6 to 11 years of age in the 1 mg/kg group, but lower than in patients 6 to 11 years of age in the 1.5 mg/kg group. Mean micafungin C_{max} was similar for all age groups within the same dose level. Mean micafungin CL_{ss} increased with age, but this appeared to be fully explained by change in body weight in patients over 6 years of age. However, the higher mean CL_{ss} in patients 4 months to 5 years of age suggested an approximately 50% higher body-weight adjusted micafungin dose is needed to achieve comparable micafungin exposure in this younger patient population.

3.7.12. Study 9463-CL-2104

This study was a phase 1, open-label study of the safety and pharmacokinetics of repeated-dose micafungin (FK463) in neonates. The objective of the study was to evaluate the pharmacokinetics and safety of intravenous (IV) micafungin (FK463) in neonates (greater than 48 hours of age and up to day of life [DOL] 120) with suspected candidaemia or invasive candidiasis. Patients weighing <1000 grams were assigned to receive 10 mg/kg/day and patients weighing ≥1000 grams were assigned to receive 7 mg/kg/day. Each daily dose was administered over a period of one hour. The final micafungin concentration in solution was 0.5 mg/mL to 4.0 mg/mL, dependent on the volume restrictions of the patient. The treatment period was 4 or 5 consecutive days, as appropriate. Subjects were infants with suspected systemic *Candida* infection who were older than 48 hours and up to 120 DOL at the time of initial study drug dose. A total of 13 subjects were enrolled.

Micafungin doses of 7 mg/kg per day and 10 mg/kg per day administered for 4 to 5 days resulted in a lower median AUC value for infants weighing ≥ 1000 grams who received 7 mg/kg per day than that of infants weighing < 1000 grams who received 10 mg/kg per day (258 µg.h/mL vs. 291 µg.h/mL, respectively). Median C_{max} values were similar for each group (23.3 µg/mL for 7 mg/kg/day vs.24.9 µg/mL for 10 mg/kg/day). Median clearance per kg body weight for infants ≥1000 grams was 21% lower than for infants < 1000 grams. A dose of 10 mg/kg per day administered to higher weight patients (≥ 1000 grams) will result in a similar or marginally higher exposure as that of lower weight patients (< 1000 grams). These results suggested that 1 dose would be appropriate for both weight groups. The doses evaluated were safe and well tolerated in this infant population.

3.8. Pharmacokinetics in special populations

Information on pharmacokinetics in special populations was provided by 4 clinical studies. These are described below.

3.8.1. Study FJ-463-0004

This study was a phase 1, open-label study of the pharmacokinetics of FK463 in elderly subjects compared with non-elderly subjects. The objective of the study was to compare the pharmacokinetics during single intravenous administration of FK463 with elderly male and non-elderly male subjects. Subjects were healthy males between 65 and 79 years of age (elderly) and between 20 and 44 years of age (non-elderly control group). A total of 20 subjects were enrolled. The plasma concentrations of unchanged drug of both elderly and non-elderly subjects declined in a biexponential way after administration of continuous infusion. The mean level of C_{max} in elderly and non-elderly subjects was 4.968 µg/mL and 4.949 µg/mL, respectively, the $t_{1/2}$ was 14.9 hours and 15.2 hours, respectively, the Vd_{β} was 0.257 L/kg and 0.243 L/kg, respectively, the Vd_{ss} was 0.239 L/kg and 0.228 L/kg, respectively, and the CL_t was 12.0 mL/h/kg and 11.1 mL/h/kg, respectively. The t_{max} was 1 hour in both groups of subjects. Statistical analysis of the pharmacokinetic parameters for elderly and non-elderly subjects revealed no statistically significant differences in any of the parameters between the two groups. No significant differences were found in pharmacokinetic parameters or protein binding rate in plasma between the elderly and non-elderly subjects.

3.8.2. Study 01-0-110

This study was a phase 1, open-label study of the pharmacokinetics of FK463 in subjects with severe renal dysfunction. The primary objective was to characterize and compare the pharmacokinetics of FK463 in subjects with normal renal function (GFR > 80 mL/min) and severe renal dysfunction (GFR < 30 mL/min). A secondary objective was to determine if severe renal dysfunction alters the extent of FK463 plasma protein binding. All subjects received a 100 mg IV infusion of FK463 over the course of 1 hour. A total of 18 subjects were enrolled. The differences observed in FK463 pharmacokinetics were negligible; however, the 90% confidence intervals for several parameters were not contained within the protocol specified range of 80–125% necessary to conclude an absence of effect. The 90% confidence intervals for the original scale V_{ss}/kg and CL/kg were 94.3-118.1% and 96.5 to 124.9%, respectively. A corresponding reduction in $AUC_{(0–48)}$ and $AUC_{(0–inf)}$ was also observed. The 90% confidence interval for $\ln[AUC_{(0–inf)}]$ was 77.6–112.3%. Since the magnitude of the observed differences in FK463 is extremely small, it is probable that the calculated 90% confidence intervals outside of the desired range reflect a small sample size, rather than an actual alteration by renal failure.

3.8.3. Study 01-0-111

This study was a phase 1, open-label study of the pharmacokinetics of FK463 in subjects with moderate hepatic dysfunction. The primary objective was to characterize and compare the pharmacokinetics of FK463 in subjects with normal liver function and moderate hepatic

impairment (Child-Pugh score 7–9). A secondary objective was to determine if moderate hepatic impairment alters the extent of FK463 plasma protein binding. All subjects received a 100 mg IV of FK463. Hepatic dysfunction resulted in an increase in mean V_{ss}/kg from 0.194 to 0.208 L/kg. Total body clearance of FK463 also increased from 0.161 mL/min/kg to 0.180 mL/min/kg. The 90% confidence intervals for the original scale V_{ss}/kg and CL/kg were 92.7–121.5% and 96.5–127.7%, respectively. A corresponding reduction in C_{max}, $AUC_{(0–48)}$, $AUC_{(0–72)}$, and $AUC_{(0–inf)}$ was also observed. The 90% confidence intervals for the ln(C_{max}) and ln($AUC_{[0–inf]}$) were 62.5–97.8% and 64.7–92.4%, respectively.

3.8.4. Study 9463-CL-1105

This study was a phase 1, open-label study of the pharmacokinetics of FK463 in subjects with severe hepatic dysfunction. The primary objective of the study was to characterize the pharmacokinetics of FK463, and to determine whether severe hepatic dysfunction alters the extent of FK463 exposure, after a single constant rate intravenous (iv) infusion over 1 hour, of 100 mg, in 2 groups of subjects: subjects with severe hepatic dysfunction; and age-, weight-, ethnic- and gender-matched healthy subjects with normal hepatic function (healthy control subjects). The secondary objective of the study was to assess the safety and tolerability of a single iv dose of FK463 in subjects with severe hepatic dysfunction. Subjects with severe hepatic dysfunction were required to have Child-Pugh score of 10-12. A total of 19 subjects (8 with severe hepatic dysfunction and 11 healthy control subjects) were enrolled. The 90% confidence intervals for the mean ratios of the pharmacokinetic variables C_{max}, AUC_{0-24h}, AUC_{last} and AUC_{inf} (as primary characteristics of the extent of exposure of FK463 and of the metabolites), fall outside the acceptance range of 80% to 125%. This acceptance range was used to determine whether hepatic dysfunction alters the extent of FK463 exposure. It cannot be concluded that severe hepatic dysfunction had no effect on the pharmacokinetics of micafungin and M-5. A possible explanation for the differences in pharmacokinetics observed is a difference in protein binding due to a lower concentration of plasma albumin.

3.8.5. Evaluator's overall comments on pharmacokinetics in special populations

Information on pharmacokinetics in special populations was provided by 4 clinical studies, FJ-463-0004, 01-0-110, 01-0-111, and 9463-CL-1105.

From the information provided, subjects with severe renal impairment (GFR [glomerular filtration rate] < 30 mL/min), moderate hepatic dysfunction (Child-Pugh score of 7-9) or severe hepatic dysfunction (Child-Pugh score of 10-12) showed no marked differences in micafungin PK compared with age-, weight-, and sex-matched normal subjects, and elderly male subjects showed no significant differences in micafungin PK parameters compared with young male subjects.

3.9. Pharmacokinetic interactions with medicinal products or substances

3.9.1. *In-vitro* pharmacokinetic interactions

This was assessed in the pre-clinical evaluation. Combination of micafungin with AMPH-B, FLCZ and ITCZ had additive effects against *C. albicans* isolates. In addition, additive interaction was prevalently seen on *A. fumigatus* for the combination with AMPH-B and ITCZ. No antagonism was observed in any combination for *C. albicans* and *A. fumigatus*. While micafungin alone was reported to be inactive against *C. neoformans* strong synergistic or additive interaction was observed when combined with AMPH-B. Combination with ITCZ, however, displayed antagonistic effects on *C. neoformans*. The interaction of micafungin and FLCZ was indifferent for all the isolates of *C. neoformans* tested.

3.9.2. *In-vivo* pharmacokinetic interactions

Fourteen clinical drug-drug interaction studies in healthy volunteers were conducted to evaluate the potential for interaction between micafungin and drugs commonly used in the target patient populations, including CYP3A4 substrates, inhibitors and inducers. MMF,

cyclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, voriconazole, amphotericin B, itraconazole, ritonavir (a potent inhibitor of CYP3A4) and rifampicin (a potent inducer of CYP3A4) were evaluated. These studies are described below.

3.9.2.1. Study 01-0-104

This study was a phase 1, open-label, study to assess concomitant pharmacokinetics of Cyclosporine and FK463 in healthy adult volunteers. The objectives of this study were to evaluate the effects of single dose and steady-state FK463 on the single dose pharmacokinetics of cyclosporine and to evaluate the effects of single dose cyclosporine on single dose and steady-state pharmacokinetics of FK463. Volunteers received a single oral dose of cyclosporine (approximately 5 mg/kg) on Day 1 (alone) and then single oral doses of cyclosporine (approximately 5 mg/kg) concurrent with FK463 on Days 9 and 15. Additionally, volunteers received a single daily 1-hour infusion of FK463 (100 mg/day) on Day 7 (alone) and Day 9 (with cyclosporine), followed by daily infusions of FK463 (100 mg/day) on study Days 11 through 15. The last (steady state) dose of FK463 on Day 15 was administered concurrently with cyclosporine. Twenty eight (28) subjects were enrolled in the study. For cyclosporine, the 90% confidence intervals for the primary PK parameters, i.e., dose-normalized, natural log-transformed C_{max} and AUC_{0-12}, were contained within the 80 to 125% range after both single and multiple FK463 doses. This suggests that there are no interaction effects of single or multiple dose FK463 on the PK of single dose cyclosporine. Similarly, the 90% confidence intervals for carryover-corrected primary PK parameters for FK463, i.e., natural log-transformed C_{max} and AUC_{0-inf} were also contained within the 80 to 125% range. Accordingly, the results suggest that there are no interaction effects of single dose cyclosporine on the PK of single dose FK463.

3.9.2.2. Study FG-463-21-04

This study was a phase 1, open-label, study to investigate the effects of multiple oral doses of Tacrolimus upon the single intravenous dose pharmacokinetics of FK463 in healthy male subjects. The objectives of this study were to determine the effect of steady-state concentrations of tacrolimus on the single dose pharmacokinetics of FK463 in healthy male subjects, and to determine the effect of single doses of FK463 on the steady-state pharmacokinetics of tacrolimus in healthy male subjects. Twenty four subjects entered and completed the study. All subjects received a single IV infusion of FK463 on the morning of Days 1, 7 and 16. Multiple oral doses of tacrolimus were administered twice daily to all subjects on Days 7 to 15 inclusive, with a final dose administered on the morning of Day 16. The doses of FK463 and tacrolimus given on the morning of Days 7 and 16 were co-administered. Co-administering FK463 with tacrolimus resulted in systemic exposure of FK463 varying by no more than 11%, based on $AUC_{(0-\infty)}$ and C_{max}, when compared to FK463 alone. These differences are considered to be of no clinical significance, as the 90% confidence intervals of the ratios of the LS means were fully contained within the FDA-defined limit for bioequivalence of 0.80 to 1.25. Co-administration of single doses of FK463 had no effect on the steady-state systemic exposure of tacrolimus, based on $AUC_{(0-\tau)}$, as statistical analysis revealed no significant difference between the ratios of LS means in the presence and absence of FK463. Overall, there was no evidence for a clinically-relevant pharmacokinetic interaction in healthy male subjects between FK463 (single dose) and steady-state tacrolimus.

3.9.2.3. Study FG-463-21-05

This study was a phase 1, open-label, study to investigate the effects of multiple oral doses of Neoral upon the single intravenous dose pharmacokinetics of FK463 in healthy male subjects. The objectives of this study were to determine the effect of steady-state concentrations of Neoral on the single dose pharmacokinetics of FK463 in healthy male subjects, and to determine the effect of single doses of FK463 on the steady-state pharmacokinetics of Neoral in healthy male subjects. Twenty-four subjects entered and completed the study. All subjects received a single IV infusion of FK463 in the morning of Days 1, 7 and 16. Multiple oral doses of Neoral

were administered twice daily to all subjects on Days 7 to 15 inclusive, with a final dose administered in the morning of Day 16. The doses of FK463 and Neoral given in the morning of Days 7 and 16 were co-administered, with Neoral being administered at the start of the FK463 infusion. Systemic exposure to FK463 following single IV doses differed by no more than 8% when co-administered with Neoral compared to the administration of FK463 alone. This difference was considered to be of no clinical concern as the 90% confidence interval determined during the statistical comparison was fully contained within the FDA-defined bioequivalence limits. Furthermore, the low inter-subject variability in FK463 levels was not affected by co-administration with Neoral. Steady-state systemic exposure to cyclosporin A is not affected by co-administration with FK463. In addition, the moderate inter-subject variability in cyclosporin A exposure is not affected by co-administration with FK463. Overall, there was no clinically important pharmacokinetic interaction between single 200 mg IV doses of FK463 and multiple 50 mg oral doses of Neoral in healthy male subjects.

3.9.2.4. Study 01-0-105

This study was a phase 1, open-label, study to assess concomitant pharmacokinetics of Tacrolimus and FK463 in healthy adult volunteers. The objectives of this study were to evaluate the effects of single dose and steady state FK463 on the single dose pharmacokinetics of tacrolimus and to evaluate the effects of single dose tacrolimus on single dose pharmacokinetics of FK463. Subjects received a single oral dose of FK506 Prograf (tacrolimus) 1 x 5 mg capsule on Day 1 (alone) and on Days 9 and 16 (with FK463). Subjects received an infusion of FK463 (micafungin) 100 mg over 1 hour on Days 7 (alone), 9 (with FK506) and 12–16 (Day 16 with FK506) yielding 7 days of administration. Twenty-six subjects entered and completed the study. Single-dose and steady-state FK463 had no effects on single-dose tacrolimus pharmacokinetics. The 90% confidence intervals of the ratio of the product means for ln(C_{max}), ln(C12), ln[$AUC_{(0\text{-}t)}$], ln[$AUC_{(0\text{-}24)}$], and ln[$AUC_{(0\text{-}inf)}$] were all within the range of 80%–125%. Single-dose tacrolimus exposure did not alter the pharmacokinetics of FK463. The 90% confidence intervals for ln(C_{max}) and ln[$AUC_{(0\text{-}inf)}$] were within the range of 80%–125%.

3.9.2.5. Study FG-463-21-06

This study was a phase 1, open-label, study to investigate the pharmacokinetic interaction between multiple oral doses of prednisolone and single intravenous doses of FK463 in healthy male subjects. The objectives of this study were to assess the effect of prednisolone on the single intravenous dose pharmacokinetics of FK463 in healthy male subjects, and to assess the effect of single doses of FK463 on the steady-state pharmacokinetics of prednisolone in healthy male subjects. Twenty-four subjects entered and completed the study. All subjects received a single IV infusion of FK463 in the morning of Days 1 and 12. Multiple oral doses of prednisolone were administered once daily to all subjects in the morning of Days 5 to 14, inclusive. The doses of FK463 and prednisolone given on Day 12 were co-administered. Doses of FK463 (and prednisolone on Day 12) were administered in the fasted state, and doses of prednisolone on Days 5 to 11, inclusive, and on Days 13 and 14 were administered immediately after a standard breakfast. Exposure to FK463 following a single 200 mg IV dose is not affected by co-administration with 20 mg prednisolone at steady-state, with the 90% confidence interval of the ratio of the LS means for $AUC_{(0\text{-}\infty)}$ and C_{max} being fully contained within the FDA-defined limits for equivalence of 0.80 to 1.25. Total exposure to 20 mg prednisolone at steady-state, based on $AUC_{(0\text{-}\tau)}$, is not affected by co-administration with a single IV dose of 200 mg FK463 with the 90% confidence interval of the ratio of the LS mean being fully contained within the FDA-defined limits for equivalence of 0.80 to 1.25. However, C_{max} for prednisolone occurs earlier and is increased by approximately 19% following co-administration with FK463, and the upper 90% confidence interval for C_{max} lies outside the upper limit for equivalence of 1.25. The apparent effect of FK463 on prednisolone C_{max} and t_{max} may be a result of dietary changes during the study. Overall, there was no clinically important pharmacokinetic interaction between single 200 mg IV doses of FK463 and multiple 20 mg oral doses of prednisolone.

3.9.2.6. Study FG-463-21-15

This study was a phase 1, open-label, study to investigate the pharmacokinetic interaction between multiple oral doses of Ritonavir and single intravenous doses of FK463 in healthy male subjects. The primary objective was to determine the effect of steady-state concentrations of ritonavir on the single intravenous dose pharmacokinetics of FK463 in healthy male subjects.

The secondary objectives were: to further assess the safety and tolerability of single intravenous doses of FK463 in healthy male subjects; and to assess the effect of single intravenous doses of FK463 on QT/QTc intervals both when administered alone and in conjunction with ritonavir in healthy male subjects. Twenty-five subjects entered the study and 24 subjects completed the study. All subjects received a single IV dose of 200 mg FK463 on Day 1, followed by a washout period of 5 days. Subjects received oral doses of 300 mg ritonavir twice-daily on Days 6 to 17, with a second IV dose of 200 mg FK463 co-administered with the morning dose of ritonavir on Day 10. Multiple oral doses of ritonavir, an inhibitor of CYP3A4, had no effect on the pharmacokinetics of single IV doses of 200 mg FK463. Co-administration of both drugs did not change the systemic exposure or disposition of FK463 compared to a single IV dose given alone. In addition, there was no apparent effect on QT/QTc intervals when FK463 was administered with and without ritonavir.

3.9.2.7. Study FG-463-21-16

This study was a phase 1, open-label, study to investigate the pharmacokinetic interaction between multiple oral doses of rifampicin and single intravenous doses of FK463 in healthy male subjects. The primary objective was to assess the effect of multiple oral doses of rifampicin on the single intravenous dose pharmacokinetics of FK463 in healthy male subjects. The secondary objective was to further assess the safety and tolerability of single intravenous doses of FK463 in healthy male subjects. Twenty-four subjects entered and completed the study. All subjects received a single IV dose of 200 mg FK463 on Day 1, followed by a washout period of 4 days. Subjects received oral doses of 600 mg rifampicin once-daily on Days 5 to 15, with a second IV dose of 200 mg FK463 co-administered on Day 12. Multiple oral doses of rifampicin, an inducer of CYP3A4, had no effect on the pharmacokinetics of single IV doses of 200 mg FK463. Co-administration of both drugs did not change the systemic exposure or disposition of FK463 compared to a single IV dose given alone. Single IV doses of FK463, at a dose level of 200 mg, were considered to be safe and well tolerated when administrated alone and in combination with once-daily oral doses of 600 mg rifampicin to healthy male subjects.

3.9.2.8. Study 03-0-175

This study was a phase 1, open-label, study to investigate the safety and pharmacokinetics of repeated-dose Micafungin (FK463) and single-dose Sirolimus after separate and concomitant administration to healthy adult volunteers. The objectives of this study were to characterize the pharmacokinetic effect of micafungin as a 150 mg daily infusion for 15 days on the single-dose pharmacokinetics of sirolimus; to characterize the pharmacokinetic effect of a single dose of sirolimus on the steady-state pharmacokinetics of micafungin; and to characterize the safety of repeated-dose micafungin, administered daily as 150 mg infusions, alone and in combination with a single dose of sirolimus, in healthy female and male volunteers. A total of 30 subjects who met the inclusion criteria were enrolled in the study on Day 1. A single oral dose of sirolimus (6 mg as three 2 mg tablets) was administered on day 1, followed by a 1-week washout period. Micafungin (150 mg/day) was administered on 15 successive days (days 8 through 22) as a 1-hour intravenous infusion. A second single dose of sirolimus (6 mg as three 2 mg tablets) was administered concomitantly with the fifteenth dose of micafungin on day 22. Steady-state micafungin affected the single-dose pharmacokinetics of sirolimus as follows: While the C_{max} of single-dose sirolimus was not affected by steady-state micafungin, the total sirolimus exposure (AUC_{0-72}) was increased by 21%. Single-dose sirolimus did not affect the pharmacokinetic parameters of steady-state micafungin or its metabolites (M-1, M-2, and M-5).

The proportion of each micafungin metabolite (M-1, M-2, and M-5) measured in the plasma samples was small (1% to 4%) relative to the parent drug, regardless of concomitant administration of sirolimus. Micafungin, at 150 mg/day over 15 days, was well tolerated, whether given alone or in combination with a single dose of sirolimus, in this group of subjects. No serious or life-threatening adverse events occurred during this study.

3.9.2.9. Study 03-0-176

This study was a phase 1, open-label, study to investigate the safety and pharmacokinetics of repeated-dose Micafungin (FK463) and single-dose Mycophenolate Mofetil (MMF) after separate and concomitant administration to healthy adult volunteers. The objectives of this study were: to characterize the pharmacokinetic effect of micafungin as a 150 mg daily infusion for 15 days on the single-dose pharmacokinetics of mycophenolate mofetil (MMF); to characterize the pharmacokinetic effect of a single dose of MMF on the steady-state pharmacokinetics of micafungin; and to characterize the safety of repeated-dose micafungin, administered daily as 150 mg infusions, alone and in combination with a single dose of MMF, in healthy female and male volunteers. A total of 30 subjects who met the inclusion criteria were enrolled in the study on day 1. A single oral dose of MMF (1500 mg as three 500 mg tablets) was administered on day 1, followed by a 1-week washout period. Micafungin (150 mg/day) was administered on 15 successive days (days 8 through 22) as a 1-hour intravenous infusion. A second single oral dose of MMF (1500 mg as three 500 mg tablets) was administered concomitantly with the fifteenth dose of micafungin on day 22. The extent of MMF absorption (assessed by MPA C_{max}) and total exposure to MPA (AUC_{0-72}) were not affected by coadministration with micafungin at steady state. Single-dose MMF did not affect the pharmacokinetic parameters of steady-state micafungin or its metabolites. The proportion of each micafungin metabolite (M-1, M-2, and M-5) measured in the plasma samples was small (1% to 4%) relative to the parent drug, regardless of concomitant administration of MMF. Repeated-dose micafungin, at 150 mg/day for up to 15 days, was found to be safe and well tolerated when administered alone and in combination with a single dose of MMF, for this group of subjects.

3.9.2.10. Study 03-0-177

This study was a phase 1, open-label, study to investigate the safety and pharmacokinetics of repeated-dose Micafungin (FK463) and single-dose Fluconazole after separate and concomitant administration to healthy adult volunteers. The objectives of this study were: to characterize the pharmacokinetic effect of micafungin as a 150 mg daily infusion for 15 days on the single-dose pharmacokinetics of fluconazole; to characterize the pharmacokinetic effect of a single dose of fluconazole on the steady-state pharmacokinetics of micafungin; and to characterize the safety of repeated-dose micafungin, administered daily as 150 mg infusions, alone and in combination with a single dose of fluconazole, in healthy female and male volunteers. A total of 30 subjects who met the inclusion criteria were enrolled in the study on day 1. A single oral dose of fluconazole (200 mg as one 200 mg tablet) was administered on day 1, followed by a 1-week washout period. Micafungin (150 mg/day) was to be administered on 15 successive days (days 8 through 22) as a 1-hour intravenous infusion. A second single dose of fluconazole (200 mg as one 200 mg tablet) was to be administered concomitantly with the fifteenth dose of micafungin on day 22. No interaction between steady-state micafungin and single-dose fluconazole was observed in healthy volunteers with regard to fluconazole pharmacokinetics.

A single dose of fluconazole did not affect the steady-state pharmacokinetics of micafungin or its metabolites. The proportion of each micafungin metabolite (M-1, M-2, and M-5) measured in the plasma samples was small (1% to 3%) relative to the parent drug, regardless of concomitant administration of fluconazole. Repeated-dose micafungin, at 150 mg/day for up to 15 days, was found to be safe and well tolerated when administered alone and in combination with a single dose of fluconazole for this group of subjects.

3.9.2.11. Study 03-0-178

This study was a phase 1, open-label, study to investigate the safety and pharmacokinetics of repeated-dose Micafungin (FK463) and single-dose Nifedipine after separate and concomitant administration to healthy adult volunteers. The objectives of this study were: to characterize the pharmacokinetic effect of micafungin as a 150 mg daily infusion for 15 days on the single-dose pharmacokinetics of nifedipine; to characterize the pharmacokinetic effect of a single dose of nifedipine on the steady-state pharmacokinetics of micafungin; and to characterize the safety of repeated-dose micafungin, administered daily as 150 mg infusions, alone and in combination with a single dose of nifedipine, in healthy female and male volunteers. A total of 30 subjects who met the inclusion criteria were enrolled in the study on day 1. A single oral dose of nifedipine (10 mg as one 10 mg capsule) was administered on day 1, followed by a 1-week washout period. Micafungin (150 mg/day) was administered on 15 successive days (days 8 through 22) as a 1-hour intravenous infusion. A second single dose of nifedipine (10 mg as one 10 mg capsule) was administered concomitantly with the fifteenth dose of micafungin on day 22.

Single-dose nifedipine did not affect the pharmacokinetic parameters of steady-state micafungin or its metabolites (M-1, M-2, and M-5). Steady-state micafungin affected the single-dose pharmacokinetics of nifedipine as follows: the total nifedipine exposure ($AUC_{0\text{-}inf}$) and maximum concentration (C_{max}) were increased (18% and 42%, respectively) in the presence of steady state micafungin. The increase in C_{max} (54.94 ng/mL vs. 84.57 ng/mL) appears to have occurred in conjunction with a decrease in T_{max} (1.5 hours vs. 0.67 hours). The elimination profile for nifedipine was similar with and without micafungin. The proportion of each micafungin metabolite (M-1, M-2, and M-5) measured in the plasma samples was small (1% to 3%) relative to the parent drug, regardless of concomitant administration of nifedipine.

Repeated-dose micafungin, at 150 mg/day for up to 15 days, was found to be safe and well tolerated when administered alone or in combination with a single dose of nifedipine for this group of subjects.

3.9.2.12. Study 04-0-193

This study was a phase 1, open-label, study to investigate the safety and pharmacokinetics of repeated-dose Micafungin (FK463) and steady state Voriconazole after separate and concomitant administration to healthy adult volunteers. The objectives of this study were to (1) characterize the pharmacokinetic effect of steady state micafungin on the steady state pharmacokinetics of voriconazole; (2) characterize the pharmacokinetic effect of steady state voriconazole on the steady state pharmacokinetics of micafungin; and, (3) characterize the safety of micafungin and voriconazole when given concomitantly at clinically relevant doses. The total duration of the study was approximately 28 days. All subjects received oral voriconazole on days 1 to 4 and days 21 to 24 and were randomized 2:1 to receive intravenous micafungin or placebo once daily in a blinded manner on days 11 to 24. Thirty five subjects were enrolled in the study. Daily coadministration of voriconazole at a clinically relevant dose did not significantly affect the pharmacokinetics of micafungin. Micafungin steady state was attained quickly, after 3 to 6 doses. Likewise, coadministration of micafungin at 150 mg/day did not alter the pharmacokinetics of voriconazole. Both drugs were well tolerated during the study.

3.9.2.13. Study FG-463-21-22

This study was a phase 1, open-label, study to investigate the safety and pharmacokinetics of repeated-dose Micafungin (FK463) and Amphotericin B in healthy adult volunteers. The objectives of this study were to determine the pharmacokinetic interaction of intravenous FK463 and amphotericin B following repeated administration to healthy male subjects, and to further assess the safety and tolerability of multiple intravenous doses of FK463. Subjects received a daily i.v. infusion of FK463 (200 mg), administered over 1 hour, for 5 days. After a 3-day washout subjects received an initial test dose of 1 mg amphotericin B administered as an i.v.

infusion over 0.5 hours. Following a 0.5-hour observation period, subjects were to receive an i.v. infusion of amphotericin B (500 µg/kg) administered over a 4-hour period. Daily i.v. dosing with amphotericin B (500 µg/kg) was to be continued for 5 days. The dose of 500 µg/kg amphotericin B was not well tolerated and dosing was stopped after the first 8 subjects. Following approval of protocol amendment 1, the study restarted with a further 26 healthy male subjects. The subjects followed the same dosing schedule as the initial 8 subjects, with the exception of a reduction of the daily dose of amphotericin B to 250 µg/kg. Subjects then received concurrent daily administration of FK463 (200 mg) and amphotericin B (250 µg/kg) for a further 5 days. A total of 34 subjects were enrolled. The pharmacokinetic profile of FK463, at steady state, was considered similar when FK463 was administered in the presence of amphotericin B compared to FK463 administered alone. Systemic exposure ($AUC_{0-\tau}$) to amphotericin B was approximately 30% higher following co-administration of FK463 with amphotericin B compared to amphotericin B administered alone. This difference is considered to be related to accumulation of the drug to steady state. Repeat IV doses of FK463, at a dose level of 200 mg, were considered to be safe and well tolerated in healthy male subjects.

3.9.2.14. Study FG-463-21-23

This study was a phase 1, open-label, study to investigate the safety and pharmacokinetics of repeated-dose Micafungin (FK463) and Itraconazole in healthy male adult volunteers. The objectives of this study were to determine the pharmacokinetic interaction of intravenous (IV) FK463 and oral itraconazole following repeated administration to healthy male subjects, and to further assess the safety and tolerability of multiple IV doses of FK463. Single IV doses of FK463 were administered as a 1 hour constant rate infusion on Days 1 to 5 and on Days 31 to 35. Itraconazole was administered twice daily (bid) on Days 19 and 20 (at 12-hourly intervals) and once daily (od) on Days 21 to 35. On Days 31 to 35, the itraconazole dose was administered at the time corresponding to the start of the FK463 infusion on Day 1. A total of twenty-four subjects entered and completed the study in accordance with the protocol. The pharmacokinetic profile of FK463, at steady state, was considered similar when FK463 was administered in the presence of itraconazole compared to FK463 administered alone. Any small but statistically significant differences in systemic exposure determined (≤5%), were of no clinical significance. Systemic exposure (based on $AUC_{(0-\tau)}$) to the FK463 metabolites M-1 and M-5, showed a 16% decrease and a 9% increase, respectively, following co-administration of FK463 with itraconazole compared to FK463 administered alone. The FK463 metabolite M-2 was barely quantifiable in plasma. Systemic exposure (based on $AUC_{(0-\tau)}$) to itraconazole and hydroxyitraconazole, at steady state, showed a 22% and 20% increase, respectively, following co-administration of FK463 with itraconazole compared to itraconazole administered alone.

3.9.3. Evaluator's overall comments on pharmacokinetic interactions

A total of 14 clinical drug-drug interaction studies in healthy volunteers were conducted to evaluate the potential for interaction between micafungin and drugs commonly used in the target patient populations, including CYP3A substrates, inhibitors and inducers. Mycophenolate mofetil (MMF), cyclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, voriconazole, ritonavir (a potent inhibitor of CYP3A4), rifampicin (a potent inducer of CYP3A4), amphotericin B and itraconazole were evaluated in studies 01-0-104, 01-0-105, FG-463-21-04, FG-463-21-05, FG-463-21-06, FG-463-21-15, FG-463-21-16, 03-0-175, 03-0-176, 03-0-177, 03-0-178, 04-0-193, FG-463-21-22, FG-463-21-23.

From the information provided, no interaction that altered the PK of micafungin was observed. There was no effect of single-dose or steady-state micafungin on the PK of MMF, cyclosporin, tacrolimus, prednisolone, fluconazole, voriconazole, ritonavir or rifampicin. Increases in exposure (AUC) for sirolimus (by 21%), nifedipine (by 18%) amphotericin B (by 30%) and itraconazole (by 22%) in the presence of steady-state micafungin were noted. However, these were small, and dose adjustment is not anticipated.

3.10. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics (PK) of micafungin administered by intravenous infusion have been extensively characterised. Information was available from 5 PK studies in healthy subjects, 12 PK studies in infected patient groups, 4 PK studies in special populations and 14 PK studies assessing possible drug interactions. The pharmacokinetics of micafungin was evaluated in healthy subjects, haematopoietic stem cell transplant recipients and patients with invasive and oesophageal candidiasis up to a maximum dose of 8mg/kg.

There is no evidence of systemic accumulation with repeated administration and increases in systemic exposure (AUC and C_{max}) are proportional to increases in dose. Steady-state is generally reached by Day 4. Following intravenous administration, concentrations of micafungin show a bi-exponential decline as the drug is rapidly distributed into tissues. Micafungin is highly protein bound (> 99%), primarily to albumin and to a lesser extent to alpha-1-acid glycoprotein. Binding to albumin is independent of micafungin concentration (10 to 100 µg/mL). Micafungin does not displace albumin-bound bilirubin at clinically relevant concentrations and is therefore not expected to cause kernicterus. From information provided in the application, the blood to plasma ratio was approximately 0.85 and was independent of concentration over the range of 0.1 to 10 µg/mL micafungin. The percent transfer into human red blood cells was approximately 35%. The volume of distribution of micafungin at terminal phase was 0.24 to 0.41 L/kg body weight. Unchanged micafungin is the principal circulating compound in the systemic circulation.

Metabolism takes place in the liver where micafungin is metabolised to M1 (catechol form) by arylsulfatase, with further metabolism to M2 (methoxy form) by catechol-Omethyltransferase. M5 is formed by hydroxylation at the side chain (ω-1 position) of micafungin catalysed by cytochrome P450 (CYP) isoenzymes. Exposure to these metabolites is low and they do not contribute to the overall efficacy of micafungin. Although micafungin is a substrate for CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for metabolism *in vivo*. The mean half-life of micafungin is approximately 10 to 17 hours and stays consistent across doses up to 8mg/kg after single and repeated administration in patients and healthy volunteers. Faecal excretion is the major route of elimination. In 97-0-040, following a single intravenous dose of ^{14}C-micafungin (25 mg) to healthy volunteers, 11.6% of the radioactivity was recovered in the urine and 71.0% in the faeces over 28 days.

With regard to pharmacokinetics in special populations, subjects with severe renal impairment (GFR [glomerular filtration rate] < 30 mL/min), moderate hepatic dysfunction (Child-Pugh score of 7-9) or severe hepatic dysfunction (Child-Pugh score of 10-12) showed no marked differences in micafungin PK compared with age-, weight-, and sex-matched normal subjects, and elderly male subjects showed no significant differences in micafungin PK parameters compared with young male subjects.

With regard to pharmacokinetic interactions, no interaction that altered the PK of micafungin was observed. There was no effect of single-dose or steady-state micafungin on the PK of MMF, cyclosporin, tacrolimus, prednisolone, fluconazole, voriconazole, ritonavir or rifampicin. Increases in exposure (AUC) for sirolimus (by 21%), nifedipine (by 18%) amphotericin B (by 30%) and itraconazole (by 22%) in the presence of steady-state micafungin were noted.

4. Pharmacodynamics

4.1. Introduction

Information on pharmacodynamics was provided in the application, and was supported by a description of the mechanism of action, information on microbiology (including both

susceptibility and resistance considerations), and information from clinical studies, which are described in the *Efficacy* section of this report.

4.2. Mechanism of action

Micafungin, a water-soluble semisynthetic derivative of a fermentation product from the environmental mould *Coleophoma empetri*, is a member of the echinocandin lipopeptide family. In contrast to other classes of antifungal agents such as azoles, polyenes or nucleosides, which act on targets also present in the mammalian cell, echinocandin lipopeptides possess a fungal specificity of action. They non-competitively inhibit the synthesis of 1,3-b-D-glucan polymers, major structural fungal cell wall components that do not have their counterpart in mammalian cells. Together with chitins or mannoproteins, glucan polymers are found in the cell wall of most pathogenic fungi, although composition of polysaccharides between species and/or growth phases of individual fungi may vary. Rope-like glucan fibrils together with chitin are responsible for the cell wall strength and shape. Since constant reconstruction is required to form cell buds of yeast or growing hyphal tips of mycelia, inhibition of 1,3-b-D-glucan formation will result in osmotic fragility and cell lysis of susceptible fungi. The exact mechanism of action of echinocandin lipopeptides upon glucan synthase activity remains to be elucidated. Direct interactions with membrane bound catalytic components were suggested in studies using mutant strains with point mutations in the FKS genes encoding the respective proteins. Interaction with a GTPase-activating protein, namely interaction with the regulatory component of the enzyme complex, was another proposed mechanism of action.

4.3. Primary pharmacology

The primary pharmacology of micafungin has been extensively characterised, and is consistent with the other members of the same pharmacological class as shown below.

Table 3. *In vitro* activities of the echinocandins Micafungin, Caspofungin and Anidulafungin

	MIC90 (MIC range when MIC90 not available)					
	n	Micafungin	n	Caspofungin	n	Anidulafungin
C. albicans	966	0.01-0.25	4265	0.12-1.0	2394	0.01-0.5
C. glabrata	524	0.01-0.5	1289	0.25-1.0	993	0.03-8
C. parapsilosis	439	1.0->8	1034	1-4	231	2->8
C. tropicalis	364	0.03-2	811	0.12-1.0	548	0.06-2
C. krusei	82	0.12-0.25	221	0.5-2	207	0.03-1.0
C.dubliniensis	40	0.03-0.5	177	0.5	92	0.06-4
C.guilliermondii	24	2	158	1.0->8	27	(0.06-4)
C. lusitaniae	23	2	114	0.5-2	81	0.12->8
A. fumigatus	35	≤ 0.01	480	0.12-0.5	94	0.06
A. flavus	18	0.01	127	0.12-0.5	53	≤ 0.03
A. niger	20	< 0.01	68	0.5	21	≤ 0.03
A. terreus	12	< 0.01	42	0.5	10	(<0.03)

MIC_{90}: Minimum inhibitory concentration of study compound needed to prevent 90% of the test organism from growing. Data were obtained in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) guidelines for antifungal susceptibility testing of yeasts or by modified versions. MIC_{90} values are from the review article by A Espinel-Ingroff [2003], which takes into account MIC_{90} values from several studies.

n: number of isolates.

From the pre-clinical information provided, in vitro susceptibility testing has shown activity against the *Candida* species *C.albicans*, *C. tropicalis*, *C. glabrata*, *C. kefyr*, *C. krusei*, *C. parapsilosis*, *C. stellatoidea*, *C. guilliermondii*, *C. dubliniensis* and *C. lusitaniae*; and the *Aspergillus* species *A. fumigatus*, *A. niger*, *A. nidulans*, *A. flavus*, *A. terreus* and *A. versicolor* — with generally lower MIC values compared with fluconazole, itraconazole, amphotericin B and caspofungin. Micafungin has virtually no activity against *Cryptococcus neoformans*, *Trichosporon cutaneum*, *Trichosporon asahii*, *Fusarium solani*, *Pseudallescheria boydii*, *Absidia corymbifera*, *Cunninghamella elegans* or *Rhizopus oryzae*.

Further pharmacodynamic information was then available from the clinical studies conducted. In study FG-463-21-08, baseline micafungin MIC90 values were ≤ 0.125 μg/mL for *C. albicans* (N = 103), *C tropicalis* (N = 63), *C. glabrata* (N = 30), *C. krusei* (N = 8), *C. lusitaniae* (N = 3) and *C. kefyr* (N = 1), ≤ 2 μg/mL for *C. parapsilosis* (N = 39), *C. guilliermondii* (N = 7), and *C. rugosa* (N = 2). Similar baseline micafungin MIC90 values were observed for *Candida* isolates from the Ambisome group. For patients who had mycological persistence at end of therapy (EOT), micafungin MIC values were similar to those observed at baseline in the micafungin group. In study FG-463-21-09, micafungin MIC values at baseline for *C. albicans* (N = 58) and *C. glabrata* (N = 3) ranged from 0.004 to 0.015 μg/mL. In study 03-7-005, baseline MIC90 values were ≤ 0.030 μg/mL for *C. albicans* (N = 457), ≤ 0.030 μg/mL for *C glabrata* (N = 13) and 0.125 μg/mL for *C. krusei* (N = 5); there was no change in susceptibility of the clinical isolates that would suggest development of resistance for the 6 patients in the micafungin group who did not respond to therapy. In study 03-7-008, baseline MIC90 values were ≤ 0.030 μg/mL for *C. albicans* (N = 389), ≤ 0.030 μg/mL for *C. glabrata* (N = 19), 0.125 μg/mL for *C. tropicalis* (N = 5), 0.50 μg/mL for *C. parapsilosis* (N = 3), 0.060 μg/mL for *C. catenulata* (N = 2), 0.50 μg/mL for *C. guilliermondii* (N = 2) and 0.25 μg/mL for *C. krusei* (N = 2).

With regard to resistance, some pre-clinical information was provided. Micafungin was compared with amphotericin B, fluconazole and flucytosine to assess possible changes in the MIC after repeated passages through *C. albicans* cultures. The MIC of micafungin was 0.0156 μg/mL during the first cycle compared with 0.0313 μg/mL after 15 serial transfers. The MIC values for amphotericin B and fluconazole also showed minimal changes in MIC during 15 serial transfers through *C. albicans* cultures. In contrast, the MIC of flucytosine changed from 1 μg/mL to >128 μg/mL after only 3 passages. Only limited data was available from clinical trials to support this information. The application noted the post-marketing surveillance had demonstrated minimal resistance.

4.4. Secondary pharmacology

This was assessed in the nonclinical evaluation.

4.5. Relationship between plasma concentration and effect

The PK of micafungin has been characterised in 54 adult patients with EC who received 50, 100 or 150 mg micafungin in a dose-response study FG-463-21-09. This study also included an assessment of a concentration-response relationship. The EC study 03-7-008 included an assessment of PK for 150 mg/day micafungin (N = 23) and 300 mg every other day (N = 20). The PK of single-dose and steady state micafungin 150 mg/day) was further characterised in 21 adult EC patients in study 03- 7-009. The PK of micafungin has been characterised in 59 HSCT patients who received micafungin at a daily dose of 12.5, 25, 50, 75, 100, 150 or 200 mg in combination with 400 mg fluconazole in study 97-0-041; 34 adult HSCT patients who received micafungin at a daily dose of 3, 4, 6 or 8 mg/kg in study FG-463-21-03 ; 66 adult patients who received micafungin for therapy of deep mycosis in study FJ-463-0003; 71 febrile, neutropenic paediatric patients who received micafungin for prophylaxis of systemic fungal infections in

study 98-0-043; 19 paediatric patients with deep mycosis in study FJ-463-FP01; and 21 premature infants who had been receiving systemic antifungal therapy in study 99-0-063.

4.6. Pharmacodynamic interactions with other medicines or substances

Please refer above.

4.7. Genetic differences in pharmacodynamic response

No information was provided with regard to possible genetic differences in pharmacodynamic response.

4.8. Evaluator's overall conclusions on pharmacodynamics

Information on pharmacodynamics was largely provided from pre-clinical data, although it was supported by information from the clinical development program.

Micafungin is a member of the echinocandin lipopeptide family and inhibits non-competitively the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls which is not present in mammalian cells. Micafungin displayed potent activity against clinically relevant *Candida* species. The Minimum Inhibitory Concentration (MIC) rank order was: *C. albicans* (including azole resistant strains) < *C. tropicalis*, *C. glabrata* < *C. krusei* << *C. parapsilosis*, *C. guilliermondii.* With the exception of *C. parapsilosis* and *C. guilliermondii*, micafungin was generally more potent against the tested *Candida* species than amphotericin B, fluconazole and itraconazole. MIC values for micafungin were lower compared to caspofungin. Micafungin has virtually no activity against *Cryptococcus neoformans*, *Trichosporon cutaneum*, *Trichosporon asahii*, *Fusarium solani*, *Pseudallescheria boydii*, *Absidia corymbifera*, *Cunninghamella elegans, Rhizopus oryzae or Rhizopus microspores.*

5. Clinical efficacy

5.1. Introduction

Information on clinical efficacy of micafungin was provided for each of the three indications: Invasive Candidiasis (IC), Oesophageal Candidiasis (OC), and Prophylaxis of Invasive Fungal Infection (IFI).

The efficacy and safety of micafungin in IC was assessed in the pivotal Phase III reference therapy controlled non-inferiority trials FG-463-21-08 and 03-0-192. Supportive data for the efficacy and safety of micafungin in IC was provided by a further 8 studies, 98-0-047, FJ-463-0003, 98-0-046, FJ-463-0006, FJ-463-FP01, 01-0-125, 9463-CL-1302 and MCFGCAN-03.

Clinical studies that assessed the efficacy and safety of micafungin in the treatment of EC include the pivotal phase III studies 03-7-005 and 03-7-008. Supportive data for the efficacy and safety of micafungin in EC was provided by a further 2 studies, 97-7-003 and FG463-21-09.

A pivotal phase III, reference therapy controlled trial was also conducted for prophylaxis of IFI, study 98-0-050. Supportive data for the efficacy and safety of micafungin in prophylaxis of IFI was provided by a further 5 studies, 01-0-124, 97-0-041, 98-0-043, FG-463-21-03, and MCFGCN02-0.

In addition, a total of 5 ongoing studies were noted in the application. These included 9463-EC-0001 (Phase IIIb, high risk liver transplant recipients), 9463-EC-0002 (Phase III, high risk surgical subjects), 9463-CL-2101 (Phase I, children and adolescents with oesophageal

candidiasis or other invasive candidiasis), 9463-CL-2303 (Phase III, treatment of neonatal candidiasis) and 9463-CL-1401 (observational study, safety).

5.2. Dose response studies

5.2.1. Invasive candidiasis

Selection of the optimal dose for the pivotal FG-463-21-08 study depended on data from the open-label IC study 98-0-047/FG-463-21-02 and the EC dose response study FG-463-21- 09. These studies are described below in the supporting studies section. In study 98-0-047/FG-463-21-02, a mean ± SD daily dose of 74.9 ± 34.1 mg for adults and 1.5 ± 0.9 mg/kg for children were associated with high success rates in candidaemia and IC patients who received micafungin monotherapy. The treatment success rate for these patients was 79.5% (105/132) of patients, with 79/98 (80.6%) newly diagnosed patients and 26/34 (76.5%) efficacy failure patients having experienced treatment success (PPS). In study FG-463-21-09, dose-response data and correlations of efficacy and systemic exposure data indicated that doses of at least 100 mg/day were required to obtain optimal efficacy in the treatment of EC. Based on these findings, the daily dose selected for the pivotal FG-463-21-08 IC study was 100 mg (2.0 mg/kg for patients weighing ≤ 40 kg). Criteria for an increase in dose (to 200 mg [4 mg/kg for patients weighing ≤40 kg]) were mycological persistence and clinical signs and symptoms of the *Candida* infection in combination with radiographic abnormalities.

5.2.2. Oesophageal candidiasis

Selection of the optimal dose for the oesophageal candidiasis indication was based on findings from 2 studies, 97-7-003 and FG-463-21-09. These studies are described below in the supporting studies section. Study 97-7-003 was undertaken to determine the MED of micafungin required for a positive clinical response in adult HIV positive patients with EC. The MED was defined as the lowest dose required to produce a clinical cure or an improvement in at least 65% of patients after 10 or more days of therapy. A clinical cure or an improvement was observed for 67% to 100% of patients across dosage groups; thus, the MED (≥ 65% of patients) could be considered to be 12.5 mg. At doses of 50 mg/day and higher, a substantially higher proportion of patients experienced clinical clearance compared with patients who received lower doses (88.7% [47/53] versus 41.9% [13/31]). Exposure-response data from study FG-463-21-09 suggested that a daily dose of at least 100 mg was necessary to achieve the optimal exposure associated with a therapeutic response for EC. On Day 1, the mean AUC_{0-24} was significantly higher for patients who experienced treatment success (74 µg.hr/mL) than for patients who experienced treatment failure (38 µg.hr/mL) (P = 0.003, Student's t-test, 2-sample assuming equal variances). The mean AUC_{0-24} for patients who experienced treatment failure (38 µg.hr/mL) on Day 1 was similar to that observed in the 50 mg treatment group (36 µg.hr/mL). Compared with the mean AUC_{0-24} of patients who experienced treatment success (74 µg.hr/mL), the mean AUC_{0-24} for the 100 mg treatment group (75 µg.hr/mL) was similar and that of the 150 mg group (104 µg.hr/mL) was higher. Based on these findings, a micafungin daily dose of 150 mg was selected for the comparative Phase III EC clinical studies.

5.2.3. Prophylaxis of invasive fungal infection

The dose used in the pivotal study 98-0-050 was selected taking into consideration non-clinical and clinical findings. A mouse model was used to define the minimum effective concentration (MEC) of micafungin for the treatment of disseminated candidiasis and pulmonary aspergillosis. The MEC was determined to be in the range 0.16-0.26 µg/mL for disseminated candidiasis and 0.55-0.80 µg/mL for pulmonary aspergillosis. Extrapolating from pre-clinical models of infections to humans on a 1:1 basis suggested that the dose of micafungin required in a clinical setting should maintain the minimum plasma concentration (C_{min}) above the MEC of 0.80 µg/mL determined in the mouse model. In the clinical study 98-0-041 with adult BMT patients, a daily micafungin dose of 50 mg resulted in a steady-state C_{min} of 1.05 µg/mL on Day 5. This C_{min} (1.05

μg/mL) was consistent with the MEC of 8 μg/mL found in the mouse model. Based on this, a daily dose of 50 mg was selected for study 98-0-050.

5.3. Main (pivotal) studies

5.3.1. Invasive candidiasis

5.3.1.1. Study FG-463-21-08

This study was a multicentre, double blind, comparative, randomised study to evaluate the efficacy and safety of Micafungin (FK463) versus liposomal Amphotericin B (Ambisome) in the treatment of invasive candidiasis and candidaemia. The objective of the study was to determine the efficacy and safety of micafungin versus liposomal amphotericin B (Ambisome) in treating neutropenic and non-neutropenic patients with confirmed IC or candidaemia caused by *Candida albicans* and non-*albicans Candida* species. Patients were randomised 1:1 to receive either micafungin or Ambisome. Subjects were non-neutropenic and neutropenic (absolute neutrophil count: < 500 cells /μL) adult and paediatric patients who had confirmed candidaemia or IC were eligible for enrolment. A total of 264 patients received Micafungin, and 267 received Ambisome. Micafungin was administered at a daily dose of 100 mg for patients weighing > 40 kg (dose increase to 200 mg permitted) and 2.0 mg/kg for patients ≤ 40 kg (dose increase to 4.0 mg/kg). No decrease in the micafungin dose was allowed. Ambisome was administered at a daily dose of 3 mg/kg (dose increase to 5 mg/kg permitted). A dose decrease of 50% for Ambisome was indicated in the protocol for drug-related nephrotoxicity. The minimum duration of therapy was 14 days. The maximum treatment period was 4 weeks, except for patients with chronic disseminated (hepatosplenic) candidiasis, *Candida* osteomyelitis or *Candida* endocarditis, for whom administration of study drug could be prolonged up to a maximum of 8 weeks.

The primary endpoint was the response rate based on the investigator's assessment of overall treatment success, which was defined as a clinical response (complete or partial) and a mycological response (eradication or presumed eradication) at EOT. Secondary efficacy endpoints included clinical response, mycological response, emergent fungal infections, recurrence of fungal infections and the independent data review board (IDRB) assessment of overall success. The primary endpoint (investigator's assessment of overall treatment success) was analysed using a 1-sided 97.5% confidence interval (CI) (based on normal approximation) for the difference in the proportions (micafungin *minus* fluconazole) adjusted for neutropenia (yes/no) based on the PPS. The CI lying above the pre-defined non-inferiority margin of -0.15 would indicate non-inferiority of the micafungin compared with Ambisome. For the sample size calculation, it was assumed that the response rate based on the investigators assessment of overall treatment success at EOT, the primary endpoint, would be experienced by 65% of patients in the Ambisome treatment group. With a non-inferiority limit of 15% and a significance level α of 0.025 (one-sided), 160 patients per treatment group were determined to be needed for the per protocol set (PPS) to conclude noninferiority with a power of 80%. Results from this study are included below.

Table 4. Overall treatment success including stratification by neutropenic status, adult patients.

	Micafungin		Ambisome		% Difference [97.5% CI]
	n	No. (%)	n	No. (%)	
Overall Treatment Success	202	181 (89.6)	190	170 (89.5)	0.1 [-5.9, 100]
Complete Response		159 (78.7)		148 (77.9)	
Partial Response		22 (10.9)		22 (11.6)	
Treatment Failure		21 (10.4)		20 (10.5)	
Stabilization		12 (5.9)		11 (5.8)	
Progression		9 (4.5)		9 (4.7)	
Overall Treatment Success by Neutropenic Status					
Neutropenia at baseline	24	18 (75.0)	15	12 (80.0)	0.7 [-5.3, 100] †
No neutropenia at baseline	178	163 (91.6)	175	158 (90.3)	

Patient base (Per protocol set): patients with confirmed candidaemia or invasive candidiasis, for whom the assessment of overall treatment success at the end of therapy was available, who received ≥ 5 doses of study drug and did not have any further major protocol violations.

Overall treatment success: a clinical response (complete or partial) and mycological response (eradication or presumed eradication) at the end of therapy:

† Adjusted for neutropenic status.

CI: confidence interval.

Table 5. Overall treatment success by *Candida* species at primary site of infection, adult patients.

	Micafungin (N = 202)		Ambisome (N = 190)	
	n	No. (%)	n	No. (%)
Any *Candida* species	202	181 (89.6)	190	170 (89.5)
Candida albicans	86	76 (88.4)	84	75 (89.3)
Non- *albicans Candida* species	126	113 (89.7)	112	100 (89.3)
C. tropicalis	52	48 (92.3)	43	41 (95.3)
C. parapsilosis	37	33 (89.2)	30	26 (86.7)
C. glabrata	23	19 (82.6)	15	12 (80.0)
C. krusei	6	5 (83.3)	7	6 (85.7)
C. guilliermondii	4	4 (100)	4	4 (100)
C. famata	3	3 (100)	1	1 (100)
C. lusitaniae	1	1 (100)	2	2 (100)
C. rugosa	1	0	1	1 (100)
C. utilis	1	1 (100)	0	---
C. inconspicua	1	1 (100)	0	---
C. dubliniensis	1	1 (100)	1	1 (100)
Other	0	---	13	11 (84.6)
***Candida* species not identified**	4	4 (100)	5	4 (80.0)
Patients with > 1 *Candida* species	17	15 (88.2)	16	14 (87.5)

Patient base (per protocol set, PPS): patients with confirmed candidaemia or invasive candidiasis, for whom the assessment of overall treatment success at the end of therapy was available, who received ≥ 5 doses of study drug and did not have any further major protocol violations.

Overall treatment success: a clinical response (complete or partial) and mycological response (eradication or presumed eradication) at the end of therapy.

Table 6. Overall treatment success by primary site of infection, adult patients.

	Micafungin (N = 202)		Ambisome (N = 190)	
	n	No. (%) [95% CI]	n	No. (%) [95% CI]
Candidaemia	170	154 (90.6) [85.2, 94.5]	163	148 (90.8) [85.3, 94.8]
Invasive candidiasis	32	27 (84.4) [67.2, 94.7]	27	22 (81.5) [61.9, 93.7]

Patient base (per protocol set, PPS): patients with confirmed candidaemia or invasive candidiasis, for whom the assessment of overall treatment success at the end of therapy was available, who received ≥ 5 doses of study drug and did not have any further major protocol violations.

Overall treatment success: a clinical response (complete or partial) and mycological response (eradication or presumed eradication) at the end of therapy.

CI: confidence interval.

Table 7. Mycological success (eradication or presumed eradication) at end of therapy, adult patients.

	Micafungin (N = 202)	Ambisome (N = 190)	P value †
	No. Patients (%)	No. Patients (%)	
Success	182 (90.1)	171 (90.0)	>0.999
Eradication	169 (83.7)	163 (85.8)	
Presumed eradication	13 (6.4)	8 (4.2)	
Failure	20 (9.9)	19 (10.0)	
Persistence	18 (8.9)	18 (9.5)	
Not recorded	2 (1.0)	1 (0.5)	

Patient base (per protocol set, PPS): patients with confirmed candidaemia or invasive candidiasis, for whom the assessment of overall treatment success at the end of therapy was available, who received ≥ 5 doses of study drug and did not have any further major protocol violations.

† Fisher's exact test.

A last-observation-carried forward method was used; missing values were counted as treatment failures.

Table 8. Clinical response (complete or partial response) by time, adult patients – No. Patients (%)

	Micafungin		Ambisome		P Value †
	n	No. Patients (%)	n	No. Patients (%)	
Week 1	202	151 (74.8)	189	142 (75.1)	
Week 2	169	154 (91.1)	168	151 (89.9)	
Week 3	55	48 (87.3)	51	45 (88.2)	
Week 4	23	18 (78.3)	19	17 (89.5)	
EOT	202	185 (91.6)	190	174 (91.6)	> 0.999

Patient base (per protocol set, PPS): patients with confirmed candidaemia or invasive candidiasis, for whom the assessment of overall treatment success at the end of therapy was available, who received ≥ 5 doses of study drug and did not have any further major protocol violations.

† Fisher's exact test; EOT: end of therapy.

At EOT, a last-observation-carried forward method was used; missing values counted as treatment failures.

Treatment success was experienced by 89.6% (181/202) and 89.5% (170/190) of patients in the micafungin and Ambisome groups, respectively (PPS). The difference in proportions of micafungin minus Ambisome adjusted for neutropenic status was 0.7%. Noninferiority of micafungin compared with Ambisome was demonstrated; the lower bound of the 1-sided 97.5% CI adjusted for neutropenic status at baseline of [-5.3%, 100%] was above the pre-defined non-inferiority margin of -15%. The safety data from this study reflected medical complications from a population of patients with severe and very morbid underlying conditions. Overall, more than 90% of adult patients (92.8% and 94.4% in the micafungin [N = 264] and Ambisome [N = 267] groups, respectively) experienced at least 1 AE and more than 40% (42.8% and 47.6%) were

serious. The mortality rates during the study (including a 12-week follow-up) were 40.2% and 40.4%, respectively.

5.3.1.2. Study 03-0-192

This study was a multicentre, double blind, comparative, randomised study to evaluate the efficacy and safety of Micafungin (FK463) versus Caspofungin in the treatment of invasive candidiasis and candidaemia. The objective of this study was to determine the efficacy and safety of two dose levels (100 mg/day and 150 mg/day) of intravenous micafungin versus intravenous caspofungin in the treatment of patients with confirmed invasive candidiasis or candidaemia. Subjects were randomised (1:1:1) to receive micafungin 100 mg once daily [qd], micafungin 150 mg qd, or caspofungin 70 mg qd on day 1 and 50 mg qd thereafter. The minimum length of antifungal treatment (intravenous therapy alone or intravenous therapy followed by oral fluconazole) was 14 days. The maximum length of treatment was 4 weeks, except for pre-defined patients with chronic disseminated candidiasis (including hepatosplenic involvement) or *Candida* endophthalmitis, for whom the administration of intravenous study medication could have been prolonged to a maximum of 8 weeks. A total of 611 patients were enrolled. Subjects were adult patients (≥18 years old) with candidaemia or invasive candidiasis, as documented by at least one typical clinical sign or symptom and confirmed by fungal culture and/or histology.

The primary efficacy endpoint was treatment success at the end of blinded intravenous therapy (based on investigator assessments). Success was defined as a positive clinical response (complete or partial) and a positive mycological response (eradication or presumed eradication) as assessed by the investigator at the end of blinded intravenous therapy. Patients who died during blinded intravenous therapy (last dose day plus one day) were counted as treatment failures. Additionally, if a clinical or mycological response was not assessed at the end of blinded intravenous therapy, the patient was counted as a treatment failure.

Secondary efficacy endpoints included: treatment success at the end of blinded intravenous therapy as assessed by the Data Review Panel (DRP); clinical response at the end of blinded intravenous therapy, based on the investigator's assessment at the end of blinded intravenous therapy; mycological response at the end of blinded intravenous therapy, based on the investigator's assessment at the end of blinded intravenous therapy; incidence of emergent invasive fungal infections during the study, based on the investigator's final baseline diagnosis of fungal infection and subsequent diagnoses of fungal infections; and, incidence of recurrent invasive fungal infections (relapse) during the post-treatment period, based on the investigator's evaluation of relapse at the post-treatment visits at 2 weeks and 6 weeks. Two-sided 95% and 97.5% confidence intervals (CIs) were constructed for each of the two treatment differences adjusting for region and APACHE II score (≤ 20 and > 20) using Cochran-Mantel-Haenszel (CMH) weights. To control for the overall level of significance, the following Hochberg procedure was used: 1) the least significant CI (i.e., 95% CI) with the smallest lower bound was considered; if this lower bound was greater than the margin (i.e., -15%), then both micafungin regimens were considered to be non-inferior to caspofungin and superiority of micafungin treatments was further evaluated using the Hochberg method. 2) If the least significant CI failed to demonstrate non-inferiority (or superiority), then the other treatment comparison was considered using a 97.5% CI. Again, if the lower bound was greater than -15%, then that micafungin regimen was considered to be non-inferior to caspofungin (or superior, if the lower bound was greater than zero). The sample size for the study was estimated based on a non-inferiority hypothesis using the primary efficacy endpoint of treatment success. An estimate of 73% success in patients with invasive candidiasis was achieved for caspofungin based on a Merck comparative trial. Using a 0.05 (two-sided) level of significance and a 73% success rate for both micafungin and caspofungin, 180 patients per treatment arm were to be enrolled to provide approximately 89% power in demonstrating the non-inferiority of micafungin compared to caspofungin over a difference of 15%. Results from this study are included below.

Table 9. Treatment success at end of blinded therapy (Investigator assessment)

Parameter Variable	Micafungin 100 mg (n = 199)	Micafungin 150 mg (n = 202)	Caspofungin (n = 192)
Success	147 (73.9%)	142 (70.3%)	137 (71.4%)
Failure	52 (26.1%)	60 (29.7%)	55 (28.6%)
Died During Blinded Therapy	28 (14.1%)	30 (14.9%)	27 (14.1%)
Unsuccessful	18 (9.0%)	29 (14.4%)	24 (12.5%)
Not Evaluable	6 (3.0%)	1 (0.5%)	4 (2.1%)
Comparison of Success Rates			
Treatment difference†	2.5%	-1.1%	
[95.0% CI]‡	[-5.9%, 11.0%]	[-9.3%, 7.8%]	
[97.5% CI]‡	[-7.1%, 12.2%]	[-10.6%, 9.0%]	

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

Success was defined as a positive clinical response (complete or partial) and a positive mycological response (eradication or presumed eradication) at the end of blinded therapy. Patients who died during blinded therapy (first dose day through last dose day + 1 day) were considered a failure.

CI: Confidence interval.

† Micafungin minus caspofungin.

‡ Based on Cochran-Mantel-Haenszel method, controlling for region and APACHE II score.

Table 10. Clinical response at end of blinded therapy (Investigator assessment)

Parameter Variable	Micafungin 100 mg (n = 199)	Micafungin 150 mg (n = 202)	Caspofungin (n = 192)
Success	168 (84.4%)	174 (86.1%)	165 (85.9%)
Complete	143 (71.9%)	153 (75.7%)	139 (72.4%)
Partial	25 (12.6%)	21 (10.4%)	26 (13.5%)
Failure	31 (15.6%)	28 (13.9%)	27 (14.1%)
Stable	18 (9.0%)	17 (8.4%)	16 (8.3%)
Progression	6 (3.0%)	8 (4.0%)	7 (3.6%)
Not Done	7 (3.5%)	3 (1.5%)	4 (2.1%)
Comparison of Success Rates			
Treatment difference†	-1.5%	0.2%	
[95.0% CI]‡	[-8.2%, 5.4%]	[-6.3%, 6.7%]	

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

CI: Confidence interval.

† Micafungin minus caspofungin.

‡ Based on Cochran-Mantel-Haenszel method, controlling for region and APACHE II score.

Table 11. Mycological response at end of blinded therapy (Investigatory assessment).

Parameter Variable	Micafungin 100 mg (n = 199)	Micafungin 150 mg (n = 202)	Caspofungin (n = 192)
Success	170 (85.4%)	166 (82.2%)	159 (82.8%)
Eradication	160 (80.4%)	151 (74.8%)	151 (78.6%)
Presumed Eradication	10 (5.0%)	15 (7.4%)	8 (4.2%)
Failure	29 (14.6%)	36 (17.8%)	33 (17.2%)
Persistence	23 (11.6%)	32 (15.8%)	30 (15.6%)
Not Done	6 (3.0%)	4 (2.0%)	3 (1.6%)
Comparison of Success Rates			
Treatment difference†	2.6%	-0.6%	
[95.0% CI]‡	[-4.3%, 9.9%]	[-7.8%, 6.9%]	

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

CI: Confidence interval.

† Micafungin minus caspofungin.

‡ Based on Cochran-Mantel-Haenszel method, controlling for region and APACHE II score.

Table 12. Treatment success at end of blinded therapy by type of fungal infection

Type of Infection Class	Micafungin 100 mg (n = 199)	Micafungin 150 mg (n = 202)	Caspofungin (n = 192)
Candidemia (Fungemia)	125/164 (76.2%)	125/169 (74.0%)	119/162 (73.5%)
Invasive *Candida* Infection	22/29 (75.9%)	16/30 (53.3%)	17/26 (65.4%)
Acute Disseminated	6/7 (85.7%)	3/11 (27.3%)	5/8 (62.5%)
Abscess	5/5 (100.0%)	5/6 (83.3%)	6/9 (66.7%)
Peritonitis	4/6 (66.7%)	4/7 (57.1%)	2/5 (40.0%)
Endophthalmitis	4/5 (80.0%)	1/3 (33.3%)	1/1 (100.0%)
Chorioretinitis	0/2	1/1 (100.0%)	0/0
Chronic Disseminated	0/1	0/0	0/0
Organ†	0/0	1/1 (100.0%)	0/0
Other‡	3/3 (100.0%)	1/1 (100.0%)	3/3 (100.0%)
Non-*Candida* Infection	0/3	1/3 (33.3%)	1/3 (33.3%)
Fungemia	0/2	1/2 (50.0%)	1/3 (33.3%)
Acute Disseminated	0/1	0/0	0/0
Peritonitis	0/0	0/1	0/0
No Fungal Infection	0/3	0/0	0/1

Patient base: Full analysis set; all patients in the safety set who did not have a final baseline diagnosis of *Candida* endocarditis, *Candida* osteomyelitis, or *Candida* meningitis.

† Patient Number 13334095; thoracic aorta.

‡ Other, as described by the investigator: pleural infection/empyema (three patients); intraabdominal infection (two patients); cholangitis (one patient); and, pyelonephritis and blood (one patient).

A total of 147/199 (73.9%), 142/202 (70.3%), and 137/192 (71.4%) patients in the micafungin 100 mg, micafungin 150 mg, and caspofungin treatment groups, respectively, were assessed by the investigator as treatment successes at the end of blinded therapy. The 95% CI for the comparison of micafungin 100 mg to caspofungin was [-5.9%, 11.0%]. The 95% CI for the comparison of micafungin 150 mg to caspofungin was [-9.3%, 7.8%]. The 95.0% CIs constructed around the treatment differences (experimental regimen – caspofungin) for the investigator's assessment of treatment success at the end of blinded therapy had lower bounds > -15%, indicating both micafungin regimens were non-inferior to caspofungin for the primary endpoint. Greater than 88% of the patients in each treatment group experienced a treatment-

emergent adverse event. More than 25% of the patients in each treatment group experienced a treatment-emergent adverse event coded under the following system organ classes: gastrointestinal disorders, metabolism and nutrition disorders, infections and infestations, and general disorders and administration site conditions. The majority of treatment-emergent adverse events were mild to moderate in intensity.

5.3.2. Oesophageal candidiasis

5.3.2.1. Study 03-7-005

This study was a phase III, randomized, double-blind, comparative trial of Micafungin (FK463) versus Fluconazole for the treatment of oesophageal candidiasis. The objective of the study was to determine the efficacy and safety of intravenous micafungin versus intravenous fluconazole in the treatment of patients with oesophageal candidiasis. Patients were randomly assigned to receive micafungin or fluconazole using a 1:1 randomization schedule that was stratified by study centre. Subjects were patients ≥16 years of age with a diagnosis of oesophageal candidiasis confirmed by endoscopy and documented by typical clinical symptoms. A total of 518 patients were enrolled. Micafungin 150 mg was administered once daily in 100 mL of 0.9% Sodium Chloride for Injection, USP, as a 1-hour intravenous (IV) infusion. Fluconazole 200 mg was administered once daily in 100 mL of 0.9% Sodium Chloride for Injection, USP, as a 1-hour IV infusion. Duration was once daily for a minimum of 14 days or for 7 days after resolution of all clinical symptoms of oesophageal candidiasis. The maximum permitted duration of study drug treatment was 42 days.

The primary efficacy endpoint was treatment success (endoscopic cure rate), which was defined as an oesophageal mucosal grade of 0 (zero) at the end of therapy. The secondary endpoints included: (1) clinical response at the end of therapy; (2) mucosal response at the end of therapy; (3) overall therapeutic response at the end of therapy; (4) incidence of relapse at 2 weeks and 4 weeks post-treatment; (5) changes in mucosal grade at the end of therapy compared to baseline; (6) changes in clinical symptoms of esophageal candidiasis at the end of therapy compared to baseline; (7) changes in clinical signs and symptoms of oropharyngeal candidiasis at the end of therapy compared to baseline; and (8) mycological response at the end of therapy. A two-sided 95% confidence interval (95% CI) was constructed for the difference in the success rates of micafungin and fluconazole (micafungin minus fluconazole) using the normal approximation method. If the lower bound of the 95% CI exceeded -0.10, micafungin was considered non-inferior to fluconazole. If the lower bound of the 95% CI exceeded 0, micafungin was considered superior to fluconazole. For sample size estimation, a rate of 85% of patients with endoscopic cure was anticipated. A one-sided, large sample normal approximation, non-inferiority test at a 2.5% level of significance, with 201 patients per treatment group, would provide a power of 80% in demonstrating that micafungin is non-inferior to fluconazole over a difference of 10%. Results from this study are included below.

Table 13. Summary of endoscopic cure rate at the end of therapy

	Treatment			
Treatment Outcome	**Micafungin**	**Fluconazole**	**Treatment Difference**	**95% CI for the Difference**
Full Analysis Set	n=260	n=258		
Success	228 (87.7%)	227 (88.0%)	-0.3%	[-5.9%, 5.3%]
Failure	32 (12.3%)	31 (12.0%)		
Mucosal Grade >0	7 (2.7%)	10 (3.9%)		
Not Evaluable	25 (9.6%)	21 (8.1%)		
Modified Full Analysis Set	n=220	n=215		
Success	191 (86.8%)	188 (87.4%)	-0.6%	[-6.9%, 5.7%]
Failure	29 (13.2%)	27 (12.6%)		
Mucosal Grade >0	6 (2.7%)	10 (4.7%)		
Not Evaluable	23 (10.5%)	17 (7.9%)		
Per Protocol Set	n=189	n=192		
Success	183 (96.8%)	182 (94.8%)	2.0%	[-2.0%, 6.0%]
Failure	6 (3.2%)	10 (5.2%)		
Mucosal Grade >0	6 (3.2%)	10 (5.2%)		

Patient base:
Full Analysis Set: all randomized patients who received at least one dose of study drug.
Modified Full Analysis Set: all randomized patients who received at least one dose of study drug and had a positive histology or cytology at baseline.
Per Protocol Set: all randomized patients who received at least 10 doses of study drug, who had confirmed esophageal candidiasis at baseline, who had a baseline and end of therapy endoscopy performed, and who did not have major protocol deviations.
Endoscopic cure: mucosal grade=0 at end of therapy.
n=total number of patients in each treatment group in each analysis set.
95% Confidence Interval: the 95% CI for the difference in success is based on the large sample normal approximation.

Table 14. Summary of clinical response at the end of therapy

	Treatment			
Clinical Response	Micafungin	Fluconazole	Treatment Difference	95% CI for the Difference
Full Analysis Set	n=260	n=258		
Success	245 (94.2%)	244 (94.6%)	-0.3%	[-4.3%, 3.6%]
Cleared	239 (91.9%)	237 (91.9%)		
Improved	6 (2.3%)	7 (2.7%)		
Failure	15 (5.8%)	14 (5.4%)		
Unchanged	2 (0.8%)	3 (1.2%)		
Worse	0 (0.0%)	1 (0.4%)		
Not Evaluable	13 (5.0%)	10 (3.9%)		
Modified Full Analysis Set	n=220	n=215		
Success	206 (93.6%)	206 (95.8%)	-2.2%	[-6.4%, 2.0%]
Cleared	200 (90.9%)	199 (92.6%)		
Improved	6 (2.7%)	7 (3.3%)		
Failure	14 (6.4%)	9 (4.2%)		
Unchanged	1 (0.5%)	1 (0.5%)		
Worse	0 (0.0%)	1 (0.5%)		
Not Evaluable	13 (5.9%)	7 (3.3%)		
Per Protocol Set	n=189	n=192		
Success	187 (98.9%)	189 (98.4%)	0.5%	[-1.8%, 2.8%]
Cleared	184 (97.4%)	183 (95.3%)		
Improved	3 (1.6%)	6 (3.1%)		
Failure	2 (1.1%)	3 (1.6%)		
Unchanged	1 (0.5%)	1 (0.5%)		
Worse	0 (0.0%	1 (0.5%)		
Not Evaluable	1 (0.5%)	1 (0.5%)		

Patient base:
Full Analysis Set: all randomized patients who received at least one dose of study drug.
Modified Full Analysis Set: all randomized patients who received at least one dose of study drug and had a positive histology or cytology at baseline.
Per Protocol Set: all randomized patients who received at least 10 doses of study drug, who had confirmed esophageal candidiasis at baseline, who had a baseline and end of therapy endoscopy performed, and who did not have major protocol deviations.
Success: clinical response of Cleared (total clinical symptom score=0) or Improved (reduction in total symptom score from baseline by 2 or more grades and no increase in grade for any individual symptom) at the end of therapy.
Failure: clinical response of Unchanged (not cleared or improved and no grade increase in any clinical symptom from baseline), Worse (grade increase from baseline in one or more clinical symptoms), or Not Evaluable at end of therapy.
n=total number of patients in each treatment group in each analysis set.
95% Confidence Interval: the 95% CI for the difference in success is based on the large sample normal approximation. Source: Tables 13.4.3.1.1, 13.4.3.1.2, and 13.4.3.1.3 and Appendix 14.4.3.2.

Table 15. Mycological response at the end of therapy.

	Treatment Group	
Mycological Response	**Micafungin**	**Fluconazole**
Full Analysis Set		
n	260	258
Eradication	179 (68.8%)	189 (73.3%)
Persistence (Colonization)	42 (16.2%)	31 (12.0%)
Persistence (Presumed Colonization)	7 (2.7%)	8 (3.1%)
Persistence (Invasive)	8 (3.1%)	10 (3.9%)
Not Evaluable	24 (9.2%)	20 (7.8%)
Modified Full Analysis Set		
n	220	215
Eradication	148 (67.3%)	155 (72.1%)
Persistence (Colonization)	40 (18.2%)	26 (12.1%)
Persistence (Presumed Colonization)	4 (1.8%)	8 (3.7%)
Persistence (Invasive)	6 (2.7%)	10 (4.7%)
Not Evaluable	22 (10.0%)	16 (7.4%)
Per Protocol Set		
n	189	192
Eradication	141 (74.6%)	149 (77.6%)
Persistence (Colonization)	38 (20.1%)	25 (13.0%)
Persistence (Presumed Colonization)	4 (2.1%)	8 (4.2%)
Persistence (Invasive)	6 (3.2%)	10 (5.2%)

Patient base:
Full Analysis Set: all randomized patients who received at least one dose of study drug.
Modified Full Analysis Set: all randomized patients who received at least one dose of study drug and had a positive histology or cytology at baseline.
Per Protocol Set: all randomized patients who received at least 10 doses of study drug, who had confirmed esophageal candidiasis at baseline, who had a baseline and end of therapy endoscopy performed, and who did not have major protocol deviations.
n=total number of patients in each treatment group in each analysis set.

The majority of patients in both treatment groups, 245/260 (94.2%) patients in the micafungin group and 241/258 (93.4%) patients in the fluconazole group, had HIV, either suspected or confirmed, as their primary underlying condition. The endoscopic cure rate was 87.7% for micafungin patients as compared to 88.0% for fluconazole patients. The -0.3% treatment difference had a 95% CI of [-5.9%, 5.3%]. Since the -5.9% lower bound was greater than -10%, micafungin was considered non-inferior to fluconazole. In both treatment groups, most treatment failures were due to non-evaluable patients. Only 2.7% of micafungin patients and 3.9% of fluconazole patients had persistent lesions. Although the endoscopic cure rate for patients with HIV as a primary underlying disease was similar between micafungin patients (216/245, 88.2%) and fluconazole patients (217/241, 90.0%), the endoscopic cure rate for patients without HIV as a primary underlying disease was numerically higher in patients that received micafungin (12/15, 80.0%) compared to those that received fluconazole (10/17, 58.8%). In addition, although the endoscopic cure rate for patients with *C. albicans* infections was similar between the two treatment groups, the endoscopic cure rate for patients with infections due to non-*C. albicans* was numerically higher for patients that received micafungin (10/12, 83.3%) compared to those that received fluconazole (8/13, 61.5%). In HIV patients with a baseline CD4 count ≥100, the odds of endoscopic cure was approximately 2.6 times higher than the odds in HIV patients with a baseline CD4 count <100. A total of 202/260 (77.7%) patients in the micafungin group and 186/258 (72.1%) patients in the fluconazole group experienced one or more treatment emergent adverse events.

5.3.2.2. Study 03-7-008

This study was a phase III, randomized, double-blind, comparative trial of two dosing regimens of Micafungin (FK463) versus Caspofungin for the treatment of oesophageal candidiasis. The

primary objective of the study was to determine the efficacy and safety of daily doses of intravenous micafungin versus intravenous caspofungin for the treatment of patients with oesophageal candidiasis. The secondary objective of this study was to determine if alternate day dosing of micafungin is as effective as daily dosing of micafungin and/or caspofungin. Study drug, either 150 mg micafungin once daily (qd), 50 mg caspofungin qd, or 300 mg micafungin every other day (qod) alternating with placebo, was administered intravenously in a blinded manner. Study drug was administered for a minimum of 14 days or for 7 days after the resolution of clinical symptoms of esophageal candidiasis, whichever was longer. The maximum length of study drug therapy was 28 days. Subjects were adult male and female subjects (patients) with oesophageal candidiasis confirmed by endoscopy and culture and documented by typical clinical signs and symptoms. A total of 454 patients were enrolled.

The primary efficacy endpoint for this study was endoscopic cure (mucosal grade of 0) at the end of therapy. The primary comparison was micafungin 150 mg qd versus caspofungin qd. A secondary comparison of micafungin 300 mg qod versus caspofungin qd was performed. An additional analysis of micafungin 300 mg qod versus micafungin 150 mg qd was also performed. The following parameters were considered secondary efficacy parameters: clinical response at end of therapy; mucosal response at the end of therapy; overall therapeutic response; incidence of relapse at 2 weeks post treatment; incidence of relapse at 4 weeks post treatment; changes in endoscopic assessment of oesophageal candidiasis at the end of therapy compared to baseline; changes in clinical symptoms of oesophageal candidiasis at the end of therapy compared to baseline; changes in clinical signs and symptoms of oropharyngeal candidiasis at the end of therapy compared to baseline; mycological response at the end of therapy; time to complete resolution of clinical symptoms of esophageal candidiasis; and, oropharyngeal response at the end of therapy. Using the full analysis set, a 95% two-sided confidence interval (CI) was constructed for the difference in success rates between micafungin 150 mg qd and caspofungin 50 mg qd using normal approximation. If the lower bound of the confidence interval was greater than -0.15, the micafungin 150 mg qd was considered non-inferior to caspofungin 50 mg qd. If the lower bound of the confidence interval exceeds 0, then micafungin 150 mg qd was considered superior to caspofungin 50 mg qd. The difference in success rates between micafungin 300 mg qod and caspofungin 50 mg qd was compared similarly as a secondary analysis. An additional analysis of the success rates between micafungin 300 mg qod and micafungin 150 mg qd was also performed. For sample size estimation, a rate of 80% of patients with endoscopic cure was anticipated, based on the Merck comparative EC trial. Using a 1-sided, large sample, normal approximation, non-inferiority test at a 2.5% level of significance, enrolment of 150 patients per treatment group would provide a power of at least 90%. Results from this study are included below.

Table 16. Summary of treatment success (mucosal Grade = 0) at end of therapy – Full Analysis Set

	Micafungin 150 mg qd (n = 151)	Caspofungin 50 mg qd (n = 152)	Treatment Difference†	95% CI for Difference‡
Success	139 (92.1%)	139 (91.4%)	0.6%	(-5.6%, 6.8%)
Failure	12 (7.9%)	13 (8.6%)		
Mucosal Grade > 0	2 (1.3%)	5 (3.3%)		
Not Evaluable	10 (6.6%)	8 (5.3%)		

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
†Treatment difference: Micafungin 150 mg qd – Caspofungin 50 mg qd.
‡95% confidence interval for the difference in success based on large sample normal approximation.
Not evaluable: No end-of-therapy endoscopy performed or samples were not obtained from end-of-therapy endoscopy.
CI: Confidence interval.
qd: Once daily.

Table 17. Summary of treatment success (mucosal Grade = 0) at end of therapy – mFAS and PPS

Analysis Set	Outcome	Micafungin 150 mg qd	Caspofungin 50 mg qd	Treatment Difference†	95% CI for Difference‡
mFAS	Success Failure	138 (92.6%) 11 (7.4%)	139 (91.4%) 13 (8.6%)	1.2%	(-4.9%, 7.3%)
PPS	Success Failure	136 (98.6%) 2 (1.4%)	133 (96.4%) 5 (3.6%)	2.2%	(-1.5%, 5.9%)

Patient base: Modified full analysis set (mFAS); all randomized patients who received at least one dose of study drug and had a positive histology or cytology result at baseline. Per protocol set (PPS); all randomized patients who received at least ten doses of study drug, had confirmed esophageal candidiasis at baseline, had baseline and end-of-therapy endoscopies performed, and did not have major protocol deviations.
†Treatment difference: Micafungin 150 mg qd – Caspofungin 50 mg qd.
‡95% confidence interval for the difference in success based on large sample normal approximation.
Success: Mucosal grade = 0.
Failure: Mucosal grade > 0 or not evaluable at end of therapy.
CI: Confidence interval.
qd: Once daily.

Table 18. Summary of treatment success (mucosal Grade = 0) at end of therapy – Micafungin 300 mg qod versus Micafungin 150 mg qd and Caspofungin 50 mg qd.

	Micafungin 300 mg qod (n = 149)	Micafungin 150 mg qd (n = 151)	Caspofungin 50 mg qd (n = 152)
Success	141 (94.6%)	139 (92.1%)	139 (91.4%)
Failure	8 (5.4%)	12 (7.9%)	13 (8.6%)
Mucosal Grade > 0	0	2 (1.3%)	5 (3.3%)
Not Evaluable	8 (5.4%)	10 (6.6%)	8 (5.3%)
Comparison of Success Rates			
Treatment Difference†		2.6%	3.2%
95% CI for the Difference‡		(-3.1%, 8.2%)	(-2.5%, 8.9%)

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug.
†Treatment difference: Micafungin 300 mg qod –Micafungin 150 mg qd or Micafungin 300 mg qod – Caspofungin 50 mg qd.
‡95% confidence interval for the difference in success based on large sample normal approximation.
Not evaluable: No end-of-therapy endoscopy performed or samples were not obtained from end-of-therapy endoscopy.
CI: Confidence interval.
qd: Once daily.
qod: Once every other day.

Table 19. Summary of mycological response at end of therapy

Mycological Response	Micafungin 300 mg qod	Micafungin 150 mg qd	Caspofungin 50 mg qd
Full Analysis Set			
Eradication	124/149 (83.2%)	120/151 (79.5%)	119/152 (78.3%)
Persistence (Colonization)	13/149 (8.7%)	12/151 (7.9%)	16/152 (10.5%)
Persistence (Presumed Colonization)	3/149 (2.0%)	6/151 (4.0%)	8/152 (5.3%)
Persistence (Invasive)	1/149 (0.7%)	3/151 (2.0%)	1/152 (0.7%)
Not Evaluable	8/149 (5.4%)	10/151 (6.6%)	8/152 (5.3%)
Modified Full Analysis Set			
Eradication	119/144 (82.6%)	119/149 (79.9%)	119/152 (78.3%)
Persistence (Colonization)	13/144 (9.0%)	12/149 (8.1%)	16/152 (10.5%)
Persistence (Presumed Colonization)	3/144 (2.1%)	6/149 (4.0%)	8/152 (5.3%)
Persistence (Invasive)	1/144 (0.7%)	3/149 (2.0%)	1/152 (0.7%)
Not Evaluable	8/144 (5.6%)	9/149 (6.0%)	8/152 (5.3%)
Per Protocol Set			
Eradication	115/132 (87.1%)	119/138 (86.2%)	113/138 (81.9%)
Persistence (Colonization)	13/132 (9.8%)	11/138 (8.0%)	16/138 (11.6%)
Persistence (Presumed Colonization)	3/132 (2.3%)	6/138 (4.3%)	8/138 (5.8%)
Persistence (Invasive)	1/132 (0.8%)	2/138 (1.4%)	1/138 (0.7%)
Not Evaluable	0	0	0

Patient base: Full analysis set; all randomized patients who received at least one dose of study drug. Modified full analysis set; all randomized patients who received at least one dose of study drug and had a positive histology or cytology result at baseline. Per protocol set; all randomized patients who received at least ten doses of study drug, had confirmed esophageal candidiasis at baseline, had baseline and end-of-therapy endoscopies performed, and did not have major protocol deviations.
Eradication: A negative fungal culture and a negative histology result.
Persistence (Colonization): A positive *Candida* culture and a negative histology result.
Persistence (Presumed Colonization): A biopsy was not performed. Available results and/or assessments led to the presumption that there was colonization.
Persistence (Invasive): A positive histology result.
Not Evaluable: No mucosal grade and no histology result.

The vast majority of patients in the full analysis set (> 90%) had HIV as their primary underlying disease and, of patients with HIV, > 60% had CD4 counts of < 100 cells/mcL. The treatment difference for success (mucosal grade = 0) at end of therapy between the micafungin 150 mg qd and caspofungin 50 mg qd treatment groups was 0.6%, with a 95% CI of (-5.6%, 6.8%). These data indicate micafungin 150 mg qd was non-inferior to caspofungin 50 mg qd based on the pre-defined non-inferiority limit of 15%. It was noted, however, that the majority of patients that were considered efficacy failures for the primary analysis were classified as not evaluable (patient did not have an end-of- therapy endoscopy performed or no samples were obtained from end-of-therapy endoscopy). The treatment differences and 95% CIs in treatment success for the modified full analysis set and per protocol set supported the conclusion that micafungin 150 mg qd was non-inferior to caspofungin 50 mg qd. The 95% CI for the difference in treatment success (mucosal grade = 0) at the end of therapy was (-2.5%, 8.9%) for micafungin 300 mg qod versus caspofungin 50 mg qd and (-3.1%, 8.2%) for micafungin 300 mg qod versus micafungin 150 mg qd. These results indicate that micafungin 300 mg qod was non-inferior to caspofungin 50 mg qd and comparable to micafungin 150 mg qd. A total of 31 patients experienced a treatment-emergent serious adverse event that did not result in death during the study: 12/151 (7.9%) in the micafungin 150 mg qd treatment group; 9/149 (6.0%) in the micafungin 300 mg qod treatment group; and, 10/152 (6.6%) in the caspofungin 50 mg qd treatment group.

5.3.3. Prophylaxis of invasive fungal infection

5.3.3.1. Study 98-0-050

This study was a phase III, randomized, double-blind, comparative trial of Micafungin (FK463) versus Fluconazole for prophylaxis of fungal infections in patients undergoing a haematopoietic stem cell transplant. The objective of the study was to determine the efficacy and safety of FK463 versus fluconazole in preventing fungal infections in patients undergoing a haematopoietic stem cell transplant. Subjects were adult and paediatric patients (≥6 months old) scheduled to undergo an autologous or syngeneic (for haematologic malignancies) or allogeneic haematopoietic stem cell transplant. A total of 889 patients were randomized (426 FK463, 463 fluconazole); 882 patients were in the full analysis set (425 FK463, 457 fluconazole); 830 patients were in the per protocol set (397 FK463, 433 fluconazole). Patients received either FK463 or fluconazole, 400 mg/day (8 mg/kg/day for patients weighing <50 kg), once daily as a 1-hour infusion. Randomized treatment was initiated at the time the transplant-conditioning regimen was initiated or within 48 hours post-initiation. Treatment was to continue until one of following occurred: the patient experienced neutrophil recovery to a post nadir ANC of ≥500 cells/mm^3 (study drug could be continued for up to 5 days post-neutrophil recovery at the investigator's discretion); the patient developed a proven, probable, or suspected fungal infection; the patient developed unacceptable toxicity; the investigator decided that it was in the best interest of the patient to discontinue; the patient declined further study participation; death occurred; or the patient received prophylactic treatment to a maximum of 42 days after transplant (day +42 after transplant).

The primary efficacy endpoint was treatment success, defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy, AND the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period. The secondary efficacy endpoints included the incidence of proven or probable systemic fungal infections during the study (treatment through 4 weeks post-treatment); the incidence of proven, probable or suspected systemic fungal infections through the end of therapy; the incidence of proven or probable systemic fungal infections during the post-treatment period for patients who did not have a systemic fungal infection through the end of therapy; the incidence of proven or probable systemic fungal infections during the study by organism; the incidence of the use of systemic antifungal agents during the post-treatment period; the time to treatment failure during the study; the time to suspected fungal infection; the incidence of superficial fungal infections through the end of therapy; and the incidence of fungal colonization at baseline and at the end of therapy. A 2-sided 95% confidence interval (CI) for the difference in the true success rates was constructed using a large sample normal approximation of the binomial distribution. FK463 was considered not statistically inferior to fluconazole if the lower confidence bound was ≥ -10%, and statistically superior if the lower confidence bound was >0%. The sample size estimation was based on the primary endpoint, treatment success at the end of the study. Based on prior multicenter, randomized prophylactic trials with fluconazole in adult bone marrow transplant patients [1, 2], the rate of treatment success for fluconazole was estimated to be 40%. Therefore, 400 patients per treatment group would provide at least 80% power at a one-sided 2.5% significance level to demonstrate that FK463 is not inferior to fluconazole over a difference of 10%. Results from this study are included below.

Table 20. Overall treatment success and treatment success by type of transplant at end of study

	FK463 (n=425)	Fluconazole (n=457)	Treatment Difference††	95% CI†
Overall	340 (80.0%)	336 (73.5%)	+ 6.5%	(0.9%, 12.0%)
Type of Transplant				
Allogeneic	157/220 (71.4%)	175/256 (68.4%)	+ 3.0%	
Autologous or Syngeneic	181/203 (89.2%)	161/201 (80.1%)	+ 9.1%	
None	2/2 (100.0%)	0 (0.0%)	N/A	

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).
Treatment success: absence of proven, probable, or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study.
† 95% confidence interval for the difference in overall success rate is based on the large sample normal approximation test.
†† FK463 rate – fluconazole rate
N/A: not applicable

Table 21. Proven or probable fungal infections during the study by organism based on protocol-specified diagnostic criteria

Organism	FK463 (n=425)	Fluconazole (n=457)
Proven	6 (1.4%)	8 (1.8%)
***Aspergillus* species**	0 (0.0%)	4 (0.9%)
***Candida* species**	4 (0.9%)	2 (0.4%)
***Fusarium* species**	1 (0.2%)	2 (0.4%)
***Zygomyces* species**	1 (0.2%)	0 (0.0%)
Probable	1 (0.2%)	3 (0.7%)
***Aspergillus* species**	1 (0.2%)	3 (0.7%)

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).
Proven: includes biopsy-proven (with or without culture) invasive or disseminated fungal infection
Probable: includes patients with the characteristic clinical or radiologic (chest x-ray, CT scan, other) picture of pulmonary aspergillosis plus a positive BAL specimen.

In the full analysis set, the overall success rate for FK463 was significantly higher than the rate for fluconazole patients (80.0% versus 73.5%). The treatment difference was +6.5% (95% CI: 0.9%, 12.0%). The Kaplan-Meier estimate of treatment success was significantly different between the two treatment arms (p=0.025). This treatment difference was consistent in patients who underwent an allogeneic (+3.0%) or autologous (+9.1%) transplant. The treatment benefit of FK463 was consistent across all subgroups analyzed, including the per protocol set which required an ANC <200 cells/mm3. A Cox regression analysis showed that FK463 and the use of haematopoietic growth factors were associated with treatment success. The overall incidence of proven or probable systemic fungal infections was 1.6% in the FK463 treatment arm and 2.4% in the fluconazole treatment arm based on a blinded review of the cases using the protocol-specified diagnostic criteria. Both study drugs were effective in preventing candidiasis with an incidence of 0.9% in the FK463 arm and 0.4% in the fluconazole arm. Aspergillosis occurred in 1/425 (0.2%) FK463 patients and 7/457 (1.5%) fluconazole patients, suggesting a prophylactic benefit of FK463 therapy. The requirement for empirical antifungal therapy was lower in the FK463 arm (15.1%) as compared to the fluconazole arm (21.4%). A total of 64/425 (15.1%) FK463 patients and 77/457 (16.8%) fluconazole patients

experienced an adverse event that was considered by the investigator to be possibly or probably related to study drug.

5.4. Clinical studies in special populations

Information on pharmacokinetics in special populations was provided by 4 clinical studies. In terms of efficacy, special populations were largely incorporated into the pivotal or supportive studies, and will be described in the relevant sections.

5.5. Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analysis of efficacy was carried out for either of the three indications, invasive candidiasis, oesophageal candidiasis, or prophylaxis of invasive fungal infection.

5.6. Supportive studies

5.6.1. Invasive candidiasis

5.6.1.1. Study 98-0-047

This study was an open-label, non-comparative study of FK463 in the treatment of candidaemia or invasive candidiasis. The objective of this study was to evaluate the safety and efficacy of FK463 in the treatment of patients with confirmed candidaemia or invasive candidiasis caused by both *Candida albicans* and non-*C. albicans* organisms. A total of 353 patients (215 in the de novo group, 83 in the efficacy failure FK463 and other therapy group, and 55 in the efficacy failure FK463 alone group) were enrolled. Adult and paediatric patients with a confirmed diagnosis of candidaemia or invasive candidiasis were enrolled. Patients could be de novo patients (newly diagnosed with candidiasis who received no more than 48 hours of prior systemic antifungal therapy) or efficacy failure patients (patients with confirmed candidiasis who received more than 5 days of prior systemic antifungal therapy with no response). FK463 was administered intravenously as a daily 1-hour infusion for at least 5 days and up to a maximum of 6 weeks. De novo patients received FK463 alone. Efficacy failure patients received FK463 alone or in addition to their current systemic antifungal therapy. Dosage was variable, and depended on a number of factors. The overall treatment success rate for the investigator global assessment at the end of therapy was 82.6% (238/288) (95% CI: 78.3%, 87.0%) with complete response achieved in 185/288 (64.2%) patients. The success rates for each patient group were: 86.6% (162/187) in the de novo group, 72.4% (42/58) in the efficacy failure FK463 and other therapy group, and 79.1% (34/43) in the efficacy failure FK463 alone group. The overall treatment success rate for the full analysis set was 75.6% (267/353). Overall, 342/353 patients (96.9%) experienced one or more adverse events during the study (208/215, 96.7%, in the de novo group; 80/83, 96.4% in the efficacy failure FK463 and other therapy group; and 54/55, 98.2%, in the efficacy failure FK463 alone group). The more common adverse events across all patient groups were fever (85/353, 24.1%), vomiting (85/353, 24.1%), hypomagnesaemia (71/353, 20.1%), hypokalemia (68/353, 19.3%), sepsis (68/353, 19.3%), non-fungal infection (66/353, 18.7%), and nausea (64/353, 18.1%).

5.6.1.2. Study FJ-463-0003

This study was an open-label, non-comparative study of FK463 in the treatment of deep mycosis. The objective of this study was to study the efficacy, safety, and pharmacokinetics of FK463 in patients with deep mycosis in an open-label trial. This study was conducted in inpatients aged 20 to 79 years who had proven or probable deep mycosis caused by *Aspergillus* or *Candida* species, aged 20 to 74 years. A total of 70 patients were enrolled. A variety of different dosages were used under 5 different versions. The efficacy rates in overall clinical effect calculated according to with or without pre-treatment were 57.7 % (15/26) and 56.3 %

(9/16) for aspergillosis and 71.4 % (5/7) and 85.7 % (6/7) for candidiasis, respectively (the patients with pre-treatment represent patients who were switched to this study treatment due to ineffectiveness of pre-treatment or adverse events.); in both aspergillosis and candidiasis, the efficacy rate in patients with pre-treatment was comparable to that in patients without pre-treatment. For candidiasis, treatment success was observed in all patients (3 patients at 25mg/day, 1 patient at 50 mg/day, and 2 patients at 75 mg/day. For disseminated candidiasis, one patient receiving a dose of 75 mg/day experienced treatment failure. For oesophageal candidiasis, 2 patients in the 25 mg/day group experienced treatment failure, whereas all patients (3 patients at 50 mg/day and 2 patients at 75 mg/day) in both 50 mg/day and 75 mg/day groups experienced treatment success. Of the 70 patients with deep mycosis who received at least one dose of study drug, 67 patients were included in the safety analysis set (46 patents with aspergillosis, 18 with candidiasis, and 3 with unspecified species). Adverse events (accompanying symptoms and abnormal changes of clinical laboratory data values) were reported for 51 patients (76.1 %).

5.6.1.3. Study 98-0-046

This study was an open-label, non-comparative study of FK463 in the treatment of invasive aspergillosis. The objective of this study was to evaluate the safety and efficacy of FK463 in patients with proven or probable invasive infections due to *Aspergillus* species. This indication is not being sought in this application.

5.6.1.4. Study FJ-463-0006

This study was a phase III clinical study of FK463 in patients with severe or refractory deep mycosis. The objective of this study was to investigate the efficacy and safety of FK463 administered concurrently with other antifungal agents or administered as a monotherapy in patients with severe or refractory deep mycosis and patients with deep mycosis for whom currently available antifungal agents could not be used. For severe or refractory candidiasis, treatment could be started at an initial dose of up to 150 mg (potency) a day. If the efficacy was insufficient, the dose could be appropriately increased to a maximum of 150 mg (potency) and, for the sake of safety, could be reduced or discontinued temporarily. Subjects were inpatients (aged >l6 years) with severe or refractory deep mycosis caused by a fungus belonging to the genus *Aspergillus* or *Candida* for whom currently available antifungal agents could not be used.

A total of 35 patients were enrolled. The treatment duration was within 56 days. Of the 35 patients receiving FK463, 29 (17 with aspergillosis, 8 with candidiasis, and 4 with other forms of mycosis) were included in efficacy analysis. The rating "effective" for overall clinical effects on all forms of candidiasis was obtained in 5/8 patients (62.5%). When analyzed by maximum dose level, the rating "effective" was obtained in 1/1 patient at 75 mg/day, 1/1 patient at 100 mg/day, and 3/6 patients (50.0%) at 150 mg/day. When analyzed by diagnosis, the rating "effective" was obtained in 3/3 patients with candidaemia, 1/1 patient with candidal peritonitis, and 1/1 patient with oesophageal candidiasis. FK463 was ineffective in 3 patients with disseminated candidiasis. When overall clinical effects were analyzed by usage of concomitant medication, the rating "effective" for candidiasis was obtained in 4/6 patients (66.7%) using concomitant medication. The most frequently used concomitant medication were AMPH-B (i.v.) for aspergillosis, azole antifungal drugs for candidiasis, and AMPH-B (i.v.) for other forms of mycosis with the rating "effective" in 2/6 patients (33.3%), 3/3 patients, and 1/2 patients, respectively. A total of 14/35 patients (40.0%) died within 2 weeks after completion or discontinuation of treatment. Serious adverse events were observed in 16/35 patients (45.7%).

5.6.1.5. Study FJ-463-FP01

This study was a phase III non-blinded uncontrolled clinical study of FK463 in paediatric patients with deep mycosis. The objective of this study was to estimate the appropriate dosage and administration of FK463, as well as investigate the drug's safety, pharmacokinetics and efficacy in the treatment of deep mycosis in paediatric patients. FK463 was administered by

intravenous drip infusion at a starting dose of 1.0 mg/kg/day over a period of 1 hour or longer once daily. For severely affected patients, however, the starting dose may exceed 1.0 mg/kg/day; treatment may begin at 2.0 or 3.0 mg/kg/day. The starting dose may be escalated by an increment of 1.0 mg/kg/day up until a maximum of 6.0 mg/kg/day (but shall not exceed 300 mg/day). The dose shall not be increased unless the same level has been maintained for at least 7 days. However, for severely affected patients with concern about possible aggravation of fungal infections due to an insufficient dose of FK463 started at 1.0, 2.0 or 3.0 mg/kg/day, the dose may be increased to a maximum of 6.0 mg/kg/day (but shall not exceed 300 mg/day). Subjects were paediatric patients considered to be suffering from deep mycosis caused by *Aspergillus* or *Candida.* A total of 20 patients were enrolled. The efficacy rate in terms of overall clinical effects (primary endpoint) was 63.6% (7/11 patients) for the candidiasis patients, who received a maximum dose of 1-3 mg/kg. For aspergillosis, the investigational product was effective in all 3 patients, all of whom received a maximum dose of 3 mg/kg. The efficacy rate for the patients with candidiasis for whom previous medication was ineffective was 71.4% (5/7 patients), with the treatment having been effective for all 2 of such patients with aspergillosis. Adverse events (all events) occurred in 20 of the 20 patients (100%), including adverse drug reactions in 6 patients (30.0%), with treatment discontinued in 1 patient (5.0%).

5.6.1.6. Study 01-0-125

This study was an open-label, non-comparative study of FK463 in the treatment of invasive aspergillosis. The objective of this study was to evaluate the safety and efficacy of FK463, in combination with Ambisome, in patients with proven or probable invasive infections due to *Aspergillus* species. This indication is not being sought in this application.

5.6.1.7. Study 9463-CL-1302

This study was a phase II, multicentre, randomised, open-label, active controlled study to evaluate the efficacy and safety of micafungin salvage monotherapy versus active control intravenous salvage monotherapy in patients with invasive aspergillosis. The objective of this study was to evaluate the efficacy and safety of micafungin in subjects with proven (probable only in case of pulmonary aspergillosis) invasive aspergillosis and who were also refractory or intolerant to previous systemic antifungal therapy. This indication is not being sought in this application.

5.6.1.8. Study MCFGCAN-03

This study was a single centre, open, parallel, comparative, randomized study of Micafungin (FK463) versus Fluconazole (Diflucan) in the treatment of invasive candidiasis and candidaemia. The objective of this study was to determine the efficacy and safety of micafungin (FK463) versus fluconazole (Diflucan) in treating patients with invasive candidiasis or candidaemia. Subjects were of both gender, aged 16 years and above with confirmed diagnosis of invasive candidiasis or candidaemia caused by *Candida albicans* or *non-albicans Candida* species. The Full Analysis Set included 23 patients, 12 in the micafungin group and 11 in the fluconazole group, respectively. Micafungin was intravenously administered at an initial dose of 100mg/day and the dose should be remained constant for the first five days. If, in the opinion of the investigator, a dose increase was considered necessary, the dose of micafungin was increased in 50mg increments up to 300mg/day. Fluconazole was intravenously administered at an initial dose of 400mg daily followed by 200mg daily. The maximum dose of fluconazole was 400mg daily. Each patient would be treated for at least 14 days and up to a maximum of 8 weeks depending on his/her clinical status. The primary efficacy endpoint was the response rate based the investigator's assessment of overall treatment success. Overall treatment success was defined as clinical (complete or partial) and mycological (eradication or presumed eradication) response at the End of Therapy. A total of 11/12 (91.7%) of the micafungin group and 8/9 (88.8%) of the fluconazole group were considered a treatment success (complete or partial response) at the end of the therapy, respectively. Of these patients, 9/12 (75.0%) in the

micafungin group and 4/9 (44.4%) in the fluconazole group achieved a complete response based on the investigator's global assessment. No statistically significant difference in the overall treatment success between treatment groups was observed (p=0.830). All 23 patients in both treatment groups experienced more than one adverse event during the study. However, a significant difference was observed for the incidence of treatment-related adverse event between the two treatment groups (3 AEs in micafungin and 9 AEs in fluconazole; p=0.014). A total of eight patients died during the study: 5/12 (41.6%) in the micafungin group and 3/11 (27.3%) in the fluconazole group.

5.6.2. Oesophageal candidiasis

5.6.2.1. Study 97-7-003

This study was a phase II, multicentre, study to determine the minimal effective dose of FK463 in the treatment of oesophageal candidiasis in HIV positive patients. The objective of this study was to determine the minimal effective dose (MED) of FK463 required for a positive clinical response (cure or improvement in clinical signs/symptoms) in HIV positive patients with oesophageal candidiasis. Secondary objectives were to ascertain the improvement of oesophageal lesions assessed by endoscopic examination and the mycological response to FK463. A total of 120 patients were enrolled. Subjects were HIV positive male or female patients 18 years of age or older with signs and symptoms of oesophageal candidiasis. FK463 was administered intravenously as a 1-hour infusion once daily for up to 21 days. The primary efficacy endpoint was the investigator's evaluation of clinical response at the end of therapy (successful response was defined as cleared or improved clinical signs and symptoms [dysphagia, odynophagia, and retrosternal pain]). The minimal effective dose was defined as the lowest dose of intravenous FK463 required to produce clinical cure or improvement in at least 65% of patients after at least 10 days of therapy. All doses of FK463 evaluated (12.5 to 100.0 mg/day) were safe and effective. A MED was not determined, but the response trend in the data suggests that the protocol-defined MED can be considered to be 12.5 mg/day. The 75.0 and 100.0 mg/day doses were substantially more effective than the other evaluated doses at resolving oesophageal mucosal lesions and eradicating the fungal infection. No safety concerns were identified.

5.6.2.2. Study FG-463-21-09

This study was a phase II, multicentre, double-blind, four parallel group, randomised study to investigate the dose response of Micafungin (FK463) compared with Fluconazole administered to HIV positive patients with confirmed oesophageal candidiasis. The objective of this study was to investigate the dose response of micafungin relating to three different dose levels (50 mg/day, 100 mg/day and 150 mg/day) compared with 200 mg/day fluconazole in HIV positive patients with confirmed oesophageal candidiasis. Eligible patients were randomised 1:1:1:1 to 50, 100 or 150 mg/day micafungin or 200 mg/day fluconazole. The planned treatment period was 14 days, but was allowed to extend to 21 days for patients who did not achieve endoscopic clearance by Day 14. Subjects were HIV positive male or female patients 18 years of age or older with confirmed oesophageal candidiasis. A total of 251 patients were enrolled. Response rate was defined as the proportion of patients with an endoscopy grade of 0 at EOT. The rate of endoscopic cure for patients treated with fluconazole was similar to that of patients treated with 100 or 150 mg/day micafungin. For both the FAS and PPS, the 95% confidence intervals for the difference between treatment groups included 0 in all instances except for the comparison between fluconazole and 50 mg/day micafungin. Clinical response at EOT in the FAS showed a clearance rate of 75.8% (47/62), 92.9% (52/56), 92.7% (51/55) for the 50 mg/day, 100 mg/day and 150 mg/day micafungin groups, respectively, and 93.0% (53/57) for the fluconazole group. Mycological findings at EOT in the FAS showed mycological eradication for 35.1% (20/57), 78.3% (36/46) and 57.1% (28/49) of patients in the 50 mg/day, 100 mg/day and 150 mg/day micafungin groups, respectively, and 67.3% (35/52) of patients in the

fluconazole group. Overall dose response findings from this study indicated greater efficacy with 100 mg/day and 150 mg/day micafungin compared with 50 mg/day micafungin.

5.6.3. Prophylaxis of invasive fungal infection

5.6.3.1. Study 01-0-124

This study was a phase III, randomized, double-blind, comparative study of Micafungin (FK 463) versus placebo as pre-emptive prophylactic antifungal therapy in patients in the Intensive Care Unit. The objective of this study was to determine the efficacy and safety of intravenous micafungin (FK463) versus placebo as prophylactic therapy for invasive fungal infections in patients in the ICU who were considered to be at high risk for invasive fungal infection. Eligible patients were stratified by study centre and length of stay in the ICU (< 7 days and ≥ 7 days) and randomized (1:1) to receive micafungin (100 mg/day) or placebo (0.9% sodium chloride). A total of 104 patients enrolled in the study, of a planned 600, as the study was discontinued. Subjects were male and female patients > 16 years of age were to have a predicted ICU stay of at least 72 hours, and were defined as high risk. Micafungin was administered at 100 mg/day in 100 mL of 0.9% sodium chloride infused intravenously (IV) over 30 minutes once daily for the duration of the patient's ICU stay. No micafungin patients and 2/51 (3.9%) placebo patients were diagnosed with proven fungal infections during the study. Early termination of the study, due to the low incidence of fungal endpoints observed, precluded definitive efficacy conclusions based on the study data.

5.6.3.2. Study 97-0-041

This study was a phase I/II study to determine the maximum tolerated dose and pharmacokinetics of FK463 in combination with Fluconazole for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. The objective of this study was to determine the maximum tolerated dose (MTD) of FK463 with concomitant fluconazole administration that can be safely administered to adult cancer patients receiving a bone marrow or peripheral stem cell transplant. FK463 was intravenously administered beginning between 48 hours prior to initiation of transplant and 24 hours after initiation of transplant. Treated patients received either FK463 and fluconazole (FK463 treatment group) or a normal saline infusion and fluconazole (control group). FK463 was administered at dosages of 12.5 mg/day, 25 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 150 mg/day, or 200 mg/day. Fluconazole (400 mg/day) was administered either orally (whenever clinically feasible) or intravenously. The control group received fluconazole and a 1 hour normal saline infusion (100 mL). A total of 79 patients were randomized and 74 patients received at least one dose of assigned therapy (full analysis set). Patients were treated until neutrophil recovery (absolute neutrophil count [ANC] of at least 500 cells/mm3), to a maximum of 4 weeks. Efficacy was assessed based on the incidence of fungal infections (suspected, probable, or proven) through the 4-week posttreatment period, the incidence of mortality during treatment and posttreatment, and the use of additional antifungal therapy during the posttreatment period. In the full analysis set, 41.7% (5/12) of control patients compared with 22.6% (14/62) of FK463 treated patients had a suspected fungal infection by the end of treatment. Four (6.5%) patients in the FK463 treatment group developed different grade 3 or greater toxicities, possibly or probably related to study drug (atrial fibrillation, hypokalemia, pancreatitis, maculopapular rash). Thus the criteria for MTD was not fulfilled.

5.6.3.3. Study 98-0-043

This study was a phase I study to determine the safety and pharmacokinetics of FK463 in febrile neutropenic paediatric patients. The objective of this study was to determine the safety and pharmacokinetics of FK463 in neutropenic paediatric patients at doses of 0.5 mg/kg per day and higher. Patients were enrolled into one of two age groups; 2 to 12 years or 13 to 17 years. The first eight patients in each age group received 0.5 mg/kg per day. Escalation to higher dose levels of 1.0, 1.5, 2.0, 3.0, and 4.0 mg/kg per day continued until two patients in the same age

group experience the same dose-limiting toxicity at that dose level. A total of 78 patients were enrolled in this study. Subjects were Patients 2 to 17 years of age with neutropenia (absolute neutrophil count [ANC] <500 cells/mm^3) and one of the following conditions: leukaemia or lymphoma, except patients on maintenance therapy; bone marrow or peripheral stem cell transplant; chemotherapy inducing >10 days of neutropenia; aplastic anaemia; or myelodysplastic syndrome. FK463 was initiated within 24 hours of the initiation of antibacterial therapy for febrile neutropenia. FK463 was administered for a minimum of 3 days or until neutrophil recovery (ANC ≥ 250 cells/mm^3). Overall, 70.1% (54/77) of patients did not develop a breakthrough systemic fungal infection or require alternative empirical antifungal therapy during FK463 therapy. A total of 27.3% (21/77) of patients had a suspected systemic infection by the end of therapy, which was defined as a patient who met their institutional criteria for initiating empirical therapy with amphotericin B. There was no evidence of a dose-limiting toxicity; no patients had a grade 3 or 4 adverse event considered by the investigator to be possibly related to FK463.

5.6.3.4. Study FG463-21-03

This study was a phase I/II study to determine the safety profile, the maximum tolerated dose and pharmacokinetics of FK463 for prophylaxis of fungal infections in adult patients undergoing bone marrow or peripheral stem cell transplant. The primary objective of this study was to determine the safety profile and maximum tolerated dose of FK463 administered to patients undergoing bone marrow or peripheral stem cell transplantation. Patients undergoing bone marrow or peripheral stem cell transplantation were allocated one of four doses of FK463 (3.0, 4.0, 6.0 or 8.0 mg/kg/day) for prophylaxis of fungal infections for up to 28 days. A total of 36 patients were enrolled and received at least one dose of FK463. Subjects were male and female patients, 18-60 years of age, who were scheduled to undergo bone marrow or peripheral stem cell transplantation. In total, 11/36 patients (30.6%) had a “suspected” fungal infection. Systemic fungal infection could not be confirmed for any patient, i.e., there were no “probable” or “proven” infections during the study. The criterion for maximum tolerated dose (the same adverse event, with a Grade 3 or 4 and assessed as causally related, in at least three different patients) was not met. No patient had a Grade 3 or 4 adverse event that was assessed by the investigator as causally related.

5.6.3.5. Study MCFGCN02-0

This study was a multi-centre, randomized, open label, parallel study to evaluate and compare the efficacy and safety of Mycamine vs Itraconazole Oral Solution for prophylaxis of fungal infections in patients undergoing a haematopoietic stem cell transplant. The objective of this study is to compare the efficacy and safety between Mycamine and Itaconazole oral liquid in preventing IFI in autologous (malignant blood diseases) or allogenic HSCT patients. The total number of subjects who took at least one study drug was 284, including 137 in the Mycamine group and 147 in the Itraconazole group. Subjects were between 18 and 70 years old, and undergoing an autologous hematopoietic stem cell transplant or an allogeneic hematopoietic stem cell transplant. Mycamine was administered at 50 mg/day (and 1.0 mg/kg/d if the weight is less than 50 kg) with duration no longer than 42 days. Itraconazole was administered 5 mg/kg/d twice a day, with duration no longer than 42 days. The CMH weighted 95% CI of difference of treatment successful rate was calculated between treatment groups. If the lower limit of the 95% confidence interval is more than -10%, it is considered that Mycamine is non-inferior to Itraconazole. If the lower limit of the 95% confidence interval is greater than 0%, it is considered that Mycamine is superior to Itraconazole. for the primary efficacy endpoint, the treatment successful rates were 92.6% (126/136) in Mycamine group and 94.6% (139/147) in Itraconazole group in FAS, and the CMH weighted 95% CI on the difference between two groups was (- 7.562%, 3.482%). The treatment successful rates were 92.0% (115/125) in Mycamine group and 93.2% (96/103) in Itraconazole group in PPS, and the CMH weighted 95% CI on the difference between two groups was (-7.489%, 5.767%). The lower limits of confidence intervals

were more than -10%. It was therefore considered that Mycamine was non-inferior to Itraconazole. There were a total of 143(50.4%) subjects who had 346 adverse events, of which there were 60 (43.8%) subjects with 149 AEs in the Mycamine group, and 83 (56.5%) subjects with 197 AEs in the Itraconazole group.

5.7. Evaluator's overall conclusions on clinical efficacy

Information on clinical efficacy was provided by a total of 19 studies. Claims of clinical efficacy were separated into the three specific indications, oesophageal candidiasis and prophylaxis of candidiasis. For invasive candidiasis, there were 2 pivotal studies and 8 supporting studies, for oesophageal candidiasis there were 2 pivotal studies and 2 supporting studies, and for prophylaxis there was one pivotal study and 5 supporting studies. The 2 pivotal studies for efficacy and safety of micafungin in **invasive candidiasis** were Phase III reference therapy controlled non-inferiority trials FG-463-21-08 and 03-0-192. These studies had the following characteristics:

- Micafungin 100 mg once daily was included as one of the treatment arms.
- Entry criteria were similar. Patients could be neutropenic or non-neutropenic; Study 03-0-192 allowed 2 days of prior therapy while Study FG-463-21-08 allowed 3 days of prior therapy; Study 03-0-192 excluded patients with known endocarditis, osteomyelitis or meningitis due to *Candida*.
- Patients had to have proven invasive candidiasis/candidaemia documented by culture and clinical signs and symptoms within 4 days prior to study entry.
- Patients were stratified by APACHE II score and region in Study 03-0-192 and by neutropenic status in Study FG-463-21-08.
- Length of treatment was at least 14 days for both Study 03-0-192 and Study FG-463-21-08; in Study 03-0-192, patients could be switched to an oral antifungal after 10 doses of intravenous study drug if predefined criteria were met, including two negative blood cultures drawn at least 24 hours apart.
- Non-inferiority margin was set at 15% for both studies.
- The definition of the primary endpoint was similar; patients with missing efficacy data at the end of therapy were counted as failures in both studies. The primary endpoint was the response rate from the investigator's assessment of overall treatment success, which was defined as a clinical response (complete or partial) and a mycological response (eradication or presumed eradication) at EOT.
- The primary analysis set was the full analysis set in Study 03-0-192 and the per protocol set in Study FG-463-21-08. The full analysis set in Study 03-0-192 excluded patients with endocarditis, osteomyelitis or meningitis due to *Candida*; these patients were included in the per protocol set in Study FG-463-21-08.
- An independent review panel was utilized to confirm diagnosis and outcome for each patient who received at least one dose of study medication.
- Patients were followed for 6 weeks after the last dose of study drug for relapse and safety in both studies; Study FG-463-21-08 also included a 12-week follow-up visit.

Guidance on study design for clinical evaluation of antifungal agents is provided by EMEA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease.* This requires that for monotherapy, data from at least one randomised and double blind study that compares test and reference antifungal regimens would normally be considered necessary to demonstrate a satisfactory risk-benefit relationship for use of an agent in a specific type of IFD. These studies should be of adequate

power to demonstrate at least non-inferiority for the test versus reference regimen using an appropriate value of delta. For this indication, 2 studies were provided that met this requirement.

FG-463-21-08 was a multicentre, double blind, comparative, randomised study to evaluate the efficacy and safety of Micafungin (FK463) versus liposomal Amphotericin B (Ambisome) in the treatment of invasive candidiasis and candidaemia. Treatment success was experienced by 89.6% (181/202) and 89.5% (170/190) of patients in the micafungin and Ambisome groups, respectively (PPS). The difference in proportions of micafungin *minus* Ambisome adjusted for neutropenic status was 0.7%. Noninferiority of micafungin compared with Ambisome was demonstrated; the lower bound of the 1-sided 97.5% CI adjusted for neutropenic status at baseline of [-5.3%, 100%] was above the pre-defined non-inferiority margin of -15%.

03-0-192 was a multicentre, double-blind, comparative, randomised study to evaluate the efficacy and safety of Micafungin (FK463) versus Caspofungin in the treatment of invasive candidiasis and candidaemia. A total of 147/199 (73.9%), 142/202 (70.3%), and 137/192 (71.4%) patients in the micafungin 100 mg, micafungin 150 mg, and caspofungin treatment groups, respectively, were assessed by the investigator as treatment successes at the end of blinded therapy. The 95% CI for the comparison of micafungin 100 mg to caspofungin was [-5.9%, 11.0%]. The 95% CI for the comparison of micafungin 150 mg to caspofungin was [-9.3%, 7.8%]. The 95.0% CIs constructed around the treatment differences (experimental regimen – caspofungin) for the investigator's assessment of treatment success at the end of blinded therapy had lower bounds > -15%, indicating both micafungin regimens were non-inferior to caspofungin for the primary endpoint.

There were 8 supporting studies. Three of the studies were not applicable to the indication, as they considered aspergillosis only (98-0-046, 01-0-125, and 9463-CL-1302). Of the remaining studies, 4 were open-label (98-0-047, FJ-463-0003, FJ-463-0006 and FJ-463-FP01) and 1 study (MCFGCAN-03) was an RCT conducted in China comparing micafungin with fluconazole.

The two pivotal studies for **oesophageal candidiasis** were phase III studies 03-7-005 and 03-7-008. The primary endpoint for both studies was treatment success (endoscopic cure), which was defined as an oesophageal mucosal grade of 0 at EOT. Both studies were formally designed as non-inferiority studies, and met the requirement of EMEA CHMP/EWP/1343/01 Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease.

03-7-005 was a phase III, randomized, double-blind, comparative trial of Micafungin (FK463) versus Fluconazole for the treatment of oesophageal candidiasis. The endoscopic cure rate was 87.7% for micafungin patients as compared to 88.0% for fluconazole patients. The -0.3% treatment difference had a 95% CI of [-5.9%, 5.3%]. Since the -5.9% lower bound was greater than -10%, micafungin was considered non-inferior to fluconazole.

03-7-008 was a phase III, randomized, double-blind, comparative trial of two dosing regimens of Micafungin (FK463) versus Caspofungin for the treatment of oesophageal candidiasis. The treatment difference for success (mucosal grade = 0) at end of therapy between the micafungin 150 mg qd and caspofungin 50 mg qd treatment groups was 0.6%, with a 95% CI of (-5.6%, 6.8%). These data indicate micafungin 150 mg qd was non-inferior to caspofungin 50 mg qd based on the pre-defined non-inferiority limit of 15%. The treatment differences and 95% CIs in treatment success for the modified full analysis set and per protocol set supported the conclusion that micafungin 150 mg qd was non-inferior to caspofungin 50 mg qd. The 95% CI for the difference in treatment success (mucosal grade = 0) at the end of therapy was (-2.5%, 8.9%) for micafungin 300 mg qod versus caspofungin 50 mg qd and (-3.1%, 8.2%) for micafungin 300 mg qod versus micafungin 150 mg qd. These results indicate that micafungin 300 mg qod was non-inferior to caspofungin 50 mg qd and comparable to micafungin 150 mg qd.

There were 2 supporting studies. Study 97-7-03 was an open-label study in adult HIV-positive patients with oesophageal candidiasis. Study FG-463-21-09 was a RCT/ dose response study comparing micafungin and fluconazole in adult HIV-positive patients with oesophageal candidiasis. Clinical response at EOT in the FAS showed a clearance rate of 75.8% (47/62), 92.9% (52/56), 92.7% (51/55) for the 50 mg/day, 100 mg/day and 150 mg/day micafungin groups, respectively, and 93.0% (53/57) for the fluconazole group. Mycological findings at EOT in the FAS showed mycological eradication for 35.1% (20/57), 78.3% (36/46) and 57.1% (28/49) of patients in the 50 mg/day, 100 mg/day and 150 mg/day micafungin groups, respectively, and 67.3% (35/52) of patients in the fluconazole group. Overall dose response findings from this study indicated greater efficacy with 100 mg/day and 150 mg/day micafungin compared with 50 mg/day micafungin.

It should be noted for this indication that over 90% of the subjects for all clinical studies were HIV-positive. Several patient groups are at risk for developing oesophageal candidiasis, including HIV infected patients, cancer patients, transplant patients and hospitalised patients on antibiotics and steroids. As such, only limited data was available for non HIV-positive patients with oesophageal candidiasis. EMEA CHMP/EWP/1343/01 Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease requires that if it is anticipated that the study population will include a substantial proportion of subjects infected with HIV it would be appropriate that the analyses should include an assessment of outcomes according to response to anti-retroviral therapy (i.e. maintenance of viral suppression and CD4 count). Study 3-7-005 indicated that exploratory logistic regression analysis of the effect of potential prognostic factors on endoscopic cure rate indicated that the odds of curing HIV patients was approximately 3.6 times higher than the odds of curing non-HIV patients. In addition, every 1-point increase in the total baseline clinical symptom score was associated with a 16% reduction in the odds of achieving endoscopic cure. In HIV patients with a baseline CD4 count ≥100, the odds of endoscopic cure was approximately 2.6 times higher than the odds in HIV patients with a baseline CD4 count <100. Every 1-point increase in total baseline clinical symptom score was associated with an 18% reduction in the odds of achieving endoscopic cure.

The pivotal study for **prophylaxis of candidiasis** was study 98-0-050. The primary efficacy endpoint was treatment success, defined as the absence of a proven, probable, or suspected systemic fungal infection through the EOT and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period. Both criteria had to be met in order for the patient to be considered a treatment success. The difference in the success rates between patients treated with micafungin and those treated with fluconazole defined the magnitude of the treatment effect. A large sample normal approximation of the binomial distribution was used to construct a 2-sided 95% CI for the difference in the success rates. If the lower limit of the CI was ≥ -10%, then micafungin was considered to be non-inferior to fluconazole. If the lower limit of the CI exceeded 0%, then micafungin was considered to be statistically superior to fluconazole.

98-0-050 was a phase III, randomized, double-blind, comparative trial of Micafungin (FK463) versus Fluconazole for prophylaxis of fungal infections in patients undergoing a haematopoietic stem cell transplant. In the full analysis set, the overall success rate for FK463 was significantly higher than the rate for fluconazole patients (80.0% versus 73.5%). The treatment difference was +6.5% (95% CI: 0.9%, 12.0%). The Kaplan-Meier estimate of treatment success was significantly different between the two treatment arms (p=0.025). This treatment difference was consistent in patients who underwent an allogeneic (+3.0%) or autologous (+9.1%) transplant. The treatment benefit of FK463 was consistent across all subgroups analyzed, including the per protocol set which required an ANC <200 cells/mm3. A Cox regression analysis showed that FK463 and the use of haematopoietic growth factors were associated with treatment success. The overall incidence of proven or probable systemic fungal infections was 1.6% in the FK463 treatment arm and 2.4% in the fluconazole treatment arm based on a blinded review of the cases using the protocol-specified diagnostic criteria. Both study drugs

were effective in preventing candidiasis with an incidence of 0.9% in the FK463 arm and 0.4% in the fluconazole arm.

There were 5 supporting studies. Study 01-0-124 was an RCT in intensive care patients, and was terminated early due to low incidence of fungal endpoints. Study 97-0-041 was an RCT to assess the MTD of micafungin in combination with fluconazole, which is not the proposed indication. Study 98-0-043 was an open-label study to assess MTD in paediatric patients. Study FG463-21-03 was an open-label study to assess MTD in adults undergoing bone marrow or peripheral stem cell transplant. Study MCFGN02 was an RCT to assess efficacy of micafungin versus itraconazole in patients undergoing autologous or allogenic HSCT.

EMEA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease* requires that it is expected that studies that assess the use of an antifungal agent for prophylaxis of IFD would be conducted only after an agent has demonstrated satisfactory clinical efficacy in the treatment of several types of IFD. The general principles outlined in respect of the design of studies for the treatment of IFD are relevant to studies of prophylaxis. At least one randomised, comparative study with sufficient statistical power to demonstrate superiority or exclude inferiority of the investigational regimen versus an appropriate active comparative regimen would be necessary in order to support the use of an anti-fungal agent for prophylaxis against IFD. These principles appear to have been met by the clinical study information provided.

Specific information on dose selection was also provided in the application for each of the three proposed indications. EMEA CHMP/EWP/1343/01 Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease notes that the need for and extent of formal dose-ranging studies in patients with IFD and the possibility of conducting confirmatory studies that employ an adaptive design may be considered on a case by case basis. This requirement appears to have been met in the clinical information and justification provided. For invasive candidiasis, dosage information was largely based on study 98-0-047/FG-463-21-02, in which a mean ± SD daily dose of 74.9 ± 34.1 mg for adults and 1.5 ± 0.9 mg/kg for children were associated with high success rates in candidaemia and IC patients who received micafungin monotherapy. The treatment success rate for these patients was 79.5% (105/132) of patients, with 79/98 (80.6%) newly diagnosed patients and 26/34 (76.5%) efficacy failure patients having experienced treatment success (PPS). For oesophageal candidiasis, dosage information was obtained from 2 dose response studies, studies 97-7-003 and FG-463-21-09. No rationale for a paediatric dosage was given, and the vast majority of subjects were HIV positive adults. Use of Micafungin in the paediatric population for this indication is not being sought in this application. For prophylaxis of invasive fungal disease, paediatric dosage information was based on the consideration of a 30% lower body weight in children than adults. An adult body weight of 54 kg was used (the mean body weight in study FG-463-21-09) for this calculation, as micafungin is likely to be used in patients who weigh less than the normal population (generally 70 kg). For adult patients, dosage information was supported by study 98-0-050. At a daily dose of 50.0 mg (1.0 mg/kg for patients < 50 kg), micafungin was significantly more effective in preventing IFI and reducing the use of empirical antifungal therapy than fluconazole (400 mg/day, 8 mg/kg/day for patients weighing < 50 kg) in high risk patients (HSCT patients with neutropenia).

No pivotal study was provided that assessed efficacy in only paediatric patients, although some studies did include paediatric patients. EMEA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease* notes that the in general, factors that predispose to IFD in children are similar to those in adults and the range of fungal pathogens encountered is the same. Therefore, a demonstration of efficacy in specific circumstances in adults may be extrapolated to use in the same circumstances in children. Information provided in the clinical development program supported this extrapolation.

6. Clinical safety

6.1. Introduction

Information on safety was available from the clinical development program, as well as extensive post-marketing experience. In addition, a total of 8 post-marketing surveillance studies were conducted.

6.2. Patient exposure

The cumulative safety population comprises 5102 subjects who were enrolled and received at least one dose of study drug in 41 clinical studies. Of these, 3584 subjects ("all micafungin subjects"), including 3083 patients ("all micafungin-treated patients") and 501 volunteers, received at least one dose of micafungin. A total of 82.8% of the 3083 patients who received at least on dose of micafungin had ≥10 days of treatment with a mean duration of treatment of 20 days.

Table 22. Summary of patient exposure.

	Micafungin	Fluconazole	Caspofungin	AmBisome	Placebo	Total
Volunteers	501	0	0	0	14	515
Patients	3083	787	345	321	51	4587
TOTAL	**3584**	**787**	**345**	**321**	**65**	**5102**

Subject base: all randomized/enrolled subjects who received at least one dose of study drug.

Indication	Cumulative Safety Population		
	Patients	Volunteers	Total
Prophylaxis	1226	142	1368
	1405	176	1581
Esophageal candidiasis	1667	416	2083
	1980	422	2402
Esophageal candidiasis Alternative dosing regimen	2310	443	2753
	2650	501	3151
Invasive candidiasis/ candidemia	3083	501	3584

6.3. Adverse events

The most frequent adverse events with an incidence ≥ 2%, regardless of causality, that occurred in volunteers who received at least one dose of micafungin were headache NOS (10.4%), cannula site reaction (7.2%), injection site pain (6.4%), nausea (6.2%), increased blood triglycerides (3.4%), dizziness (3.4%), erythema (3.2%), phlebitis NOS (3.2%), pharyngitis (3.0%), increased alanine aminotransferase (3.0%), feeling hot (2.6%), injection site erythema (2.6%), abnormal liver function tests (2.4%), injection site swelling (2.2%), increased aspartate aminotransferase (2.2%), paraesthesia (2.2%), back pain (2.2%), and rash NOS (2.0%).

Table 23. Summary of overall adverse events for all micafungin-treated patients

Type of Adverse Events	All micafungin-treated patients (n = 3083)
Any TEAE	2810 (91.1%)
Related TEAE	993 (32.2%)
Serious TEAE	873 (28.3%)
Related serious TEAE	111 (3.6%)
Drug withdrawals due to TEAE	409 (13.3%)
Drug withdrawals due to related TEAE	106 (3.4%)
Deaths	671 (21.8%)

TEAE: treatment-emergent adverse event.

Patient base: all randomized patients who received at least one dose of study drug.

The most frequent adverse events with an incidence ≥ 10%, regardless of causality, that occurred in patients who received at least one dose of micafungin were diarrhoea NOS (23.3%), vomiting NOS (22.0%), nausea (21.7%), pyrexia (20.0%), hypokalaemia (18.0%), headache (15.9%), thrombocytopenia (15.4%), mucosal inflammation NOS (14.2%), neutropenia (14.1%), hypomagnesaemia (13.3%), and constipation (11.1%).

Table 24. Incidence of common related treatment-emergent adverse events in patients who received Micafungin in clinical studies

Adverse Events (MedDRA System Organ Class and Preferred Term, v 5.0)	All micafungin-treated patients (n=3083)
ALL SYSTEMS	993 (32.2%)
Leukopenia NOS	57 (1.8%)
Neutropenia	38 (1.2%)
Anemia NOS	30 (1.0%)
Thrombocytopenia	26 (0.8%)
Lymphopenia	12 (0.4%)
Nausea	84 (2.7%)
Vomiting NOS	75 (2.4%)
Diarrhea NOS	62 (2.0%)
Abdominal pain NOS	26 (0.8%)
Abdominal pain upper	13 (0.4%)
Pyrexia	63 (2.0%)
Rigors	33 (1.1%)
Infusion site phlebitis NOS	13 (0.4%)
Hyperbilirubinemia	29 (0.9%)
Increased blood alkaline phosphatase	86 (2.8%)
Increased aspartate aminotransferase	77 (2.5%)
Increased alanine aminotransferase	66 (2.1%)
Abnormal liver function tests NOS	44 (1.4%)
Blood creatinine increased	23 (0.7%)
Blood lactate dehydrogenase increased	22 (0.7%)
Blood bilirubin increased	20 (0.6%)
Blood urea increased	19 (0.6%)
Transaminases increased	13 (0.4%)
Hypokalemia	63 (2.0%)
Hypocalcemia	36 (1.2%)
Hypomagnesemia	36 (1.2%)
Hyponatremia	14 (0.5%)
Headache NOS	54 (1.8%)
Somnolence	12 (0.4%)
Rash NOS	60 (1.9%)
Pruritus NOS	25 (0.8%)
Phlebitis NOS	75 (2.4%)
Hypertension NOS	19 (0.6%)

NOS: not otherwise specified.

Patient base: all randomized/enrolled patients who received at least one dose of micafungin.

Common: incidence of adverse event ≥ 0.5%.

Related: Considered by the investigator to have a possible, probable, or definite relationship to study drug.

Within a MedDRA system organ class, patients may have experienced more than one adverse event. The sum of the terms may exceed 100%.

The overall percentage of related adverse events in all micafungin-treated patients was 32.2% (993/3083).

6.4. Serious adverse events and deaths

Overall, 28.3% (873/3083) of micafungin-treated patients had a serious treatment-emergent adverse event during study participation. Serious treatment-emergent adverse events considered to be related to study drug by the investigators were reported in 3.6% (111/3083) of micafungin-treated patients.

The most frequent serious treatment-emergent adverse events in micafungin-treated patients, regardless of relationship to study drug, were respiratory failure (3.1%), sepsis NOS (2.8%), septic shock (1.7%), hypotension NOS (1.4%), pneumonia NOS (1.2%), and multi-organ failure

(1.2%), and respiratory distress (1.0%). Related treatment emergent serious adverse events that occurred in four or more micafungin-treated patients were thrombocytopenia (5 patients), abnormal liver function tests NOS (5 patients), pancytopenia (4 patients), increased blood alkaline phosphatase (4 patients), hyperbilirubinemia (4 patients), and acute renal failure (4 patients). The most frequent of these events had a 0.2% incidence.

In the overall safety population, death occurred in 671 of 3083 (21.8%) of micafungin-treated patients: 134 (4.3%) deaths occurred in patients during study drug treatment, and 537 (17.4%) deaths occurred during the post treatment period.

Table 25. Mortality, clinical efficacy and safety studies – No. patients (%)

	Overall	Adults, non-elderly (16-64 years)	Adults, elderly (≥ 65 years)	Pediatric (< 16 years)
	N=3028	N=2345	N=387	N=296
Overall	654 (21.6)	454 (19.4)	138 (35.7)	62 (20.9)
During treatment †	357 (11.8)	242 (10.3)	77 (19.9)	38 (12.8)
After the end of treatment ‡	297 (9.8)	212 (9.0)	61 (15.8)	24 (8.1)

Patient base: all patients who received at least a single dose of micafungin.
† Death occurred in the time window between the first dose of study medication and three days after the last dose.
‡ Six patients died after the end of the study.

The most common primary causes of death that were reported for micafungin-treated patients were: septic shock (1.6% [50/3083]), sepsis NOS (1.6% [48/3083]), respiratory failure (1.6% [50/3083]), and multi-organ failure (1.3% [40/3083]).

Table 26. Summary of primary causes of death during study (treatment and follow-up), clinical efficacy and safety studies – No. patients (%)

MedDRA *System Organ Class* Preferred Term †	Overall N=3028	Adults, non-elderly (16-64 years) N=2345	Adults, elderly (≥ 65 years) N=387	Pediatric (< 16 years) N=296
Infections and Infestations	265 (8.8)	191 (8.1)	53 (13.7)	21 (7.1)
Septic shock	50 (1.7)	30 (1.3)	17 (4.4)	3 (1.0)
Sepsis NOS	47 (1.6)	34 (1.4)	13 (3.4)	0
Aspergillosis	19 (0.6)	12 (0.5)	1 (0.3)	6 (2.0)
Neoplasms Benign, Malignant and Unspecified (incl cysts & polyps)	67 (2.2)	45 (1.9)	16 (4.1)	6 (2.0)
Acute myeloid leukemia NOS	12 (0.4)	9 (0.4)	1 (0.3)	2 (0.7)
Nervous System Disorders	34 (1.1)	20 (0.9)	7 (1.8)	7 (2.4)
Intracranial hemorrhage NOS	8 (0.3)	4 (0.2)	0	4 (1.4)
Cardiac Disorders	70 (2.3)	44 (1.9)	19 (4.9)	7 (2.4)
Cardiac arrest	21 (0.7)	17 (0.7)	3 (0.8)	1 (0.3)
Cardio-respiratory arrest	21 (0.7)	10 (0.4)	9 (2.3)	2 (0.7)
Cardiac failure NOS	11 (0.4)	8 (0.3)	2 (0.5)	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	108 (3.6)	75 (3.2)	19 (4.9)	14 (4.7)
Respiratory failure	45 (1.5)	31 (1.3)	8 (2.1)	6 (2.0)
General Disorders and Administration Site Conditions	41 (1.4)	26 (1.1)	13 (3.4)	2 (0.7)
Multiorgan failure	38 (1.3)	23 (1.0)	13 (3.4)	2 (0.7)

Patient base: all patients who received at least a single dose of micafungin.

† MedDRA System Organ Class (SOC) terms with an incidence of ≥ 1% and preferred terms with an incidence of ≥ 0.5% for any age group with a SOC of ≥ 1%.

There were no apparent patterns in the primary causes of death by micafungin mean daily dose. Five patient deaths were considered by the investigators to be either probably or possibly related to micafungin. An additional patient death in Study 03-0-192 was considered related to study drug; a patient in the micafungin 100 mg treatment group, whose data was not included in the database due to legal issues between the hospital and the patient's family, died during the study due to peritonitis and probable sepsis that were considered by the investigator to have a possible relationship to blinded study drug.

6.5. Laboratory findings

Information on laboratory findings was provided for all clinical studies. Specific issues are noted in the relevant safety sections.

6.6. Safety in special populations

Information on any differences in safety profile between non-elderly adults (16 to 64 years), elderly adults (≥65 years) and children (<16 years) was given during the pooled analysis of safety. There were no clinically meaningful differences in safety profile among the three age groups. However, the incidence of some adverse events (AEs) in the clinical study database (thrombocytopenia, tachycardia, hypertension, hypotension, hyperbilirubinemia, hepatomegaly, renal failure acute, blood urea increased) was higher in paediatric patients than adult patients. Additionally, paediatric patients < 1 year of age experienced about two times more often an increase in ALT, AST and AP than older paediatric patients. The most likely reason for these differences were the large differences in the underlying conditions of children compared with

adults or older paediatric patients observed in clinical studies. At the time of entering the study, the proportion of paediatric patients with neutropenia was several-fold higher than in adults patients (40.2% and 7.3% of children and adults, respectively), as well as allogeneic hematopoietic stem cell transplant (HSCT) (29.4% and 13.4%, respectively) and haematological malignancy (29.1% and 8.7%, respectively).

No clinically meaningful differences in the safety profile could be discerned by paediatric age strata of <4 weeks, 4 weeks to <1 year, 1 to 4 years, 5 to 8 years, 9 to 12 years and 13 to <16 years. The incidence of almost all AEs, were far lower for infants <1 year than older children. These differences are likely to be attributable to the differences in underlying condition. Approximately 60% of children <1 year old had premature birth status as the primary underlying condition with many of these infants also suffering bacterial sepsis/pneumonia and IC. The majority of older (≥1 year old) children were undergoing HSCT or other treatment for a haematological malignancy.

For AEs assessed by the investigator as least possibly related to micafungin, children 1 to 4 years of age tended to experience more haematological AEs and electrolyte disturbances than children ≥5 years old. Otherwise, there were no further remarkable differences in the AE profile by age group.

In paediatric patients, the mortality rate was 20.9% (62/296), compared with 21.70% (592/2732) for adults. AEs that led to treatment discontinuation were reported in 10.1% (30/296) of children versus 13.4% (365/2732) of adults. The daily dose for the paediatric patients in well controlled studies was generally 2.0 mg/kg for C/IC and 1.0 mg/kg for prophylaxis (few paediatric EC patients were enrolled). In the pooled analysis of safety for the paediatric population, the micafungin dose was < 2.0 mg/kg for 218 patients, ≥ 2.0 to < 3.0 mg/kg for 70 patients, ≥ 3.0 to ≤ 4.0 mg/kg for 41 patients and > 4.0 mg/kg for 19 patients; the mean duration of treatment ranged from 19 to 69 days with an overall mean of 30 days. For paediatric patients, no dose effects with regard to the incidence of AEs were apparent from the analyses for AEs irrespective of causality, AEs suspected of being treatment related or special interest clusters.

Table 27. Summary of overall adverse event profile for Micafungin-treated paediatric patients

Type of Adverse Event **MedDRA v. 5.0**	**Micafungin** **n=335**
Any adverse event	313 (93.4%)
Drug-related adverse event	88 (26.3%)
Serious adverse event	113 (33.7%)
Drug-related serious adverse event	15 (4.5%)
Adverse event resulting in discontinuation	36 (10.7%)
Drug-related AE resulting in discontinuation	9 (2.7%)
Death	68 (20.3%)

Patient base: All pediatric patients who received at least one dose of micafungin. Table includes patients ≤ 16 years of age.

Drug-related adverse events are any event considered to be at least possibly related to study drug by the Investigator.

Table 28. Primary causes of death for paediatric patients: All studies

System Organ Class, MedDRA v. 5.0 Preferred Term	Total (n=335)
All Systems	**68 (20.3%)**
Infections and Infestations	
Aspergillosis	6 (1.8%)
Septic shock	4 (1.2%)
Adenovirus infection NOS	1 (0.3%)
Alternaria infection NOS	1 (0.3%)
Bronchopulmonary aspergillosis	1 (0.3%)
Endocarditis fungal NOS	1 (0.3%)
Meningitis	1 (0.3%)
Meningitis bacterial NOS	1 (0.3%)
Mycotic sepsis	1 (0.3%)
Neonatal infection NOS	1 (0.3%)
Pneumonia Aspergillus	1 (0.3%)
Pneumonia cytomegaloviral	1 (0.3%)
Pneumonia NOS	1 (0.3%)
Sepsis neonatal	1 (0.3%)
Sepsis NOS	1 (0.3%)
Respiratory, Thoracic and Mediastinal Disorders	
Respiratory failure	7 (2.1%)
Acute respiratory distress syndrome	4 (1.2%)
Pulmonary hemorrhage	3 (0.9%)
Pneumonitis NOS	1 (0.3%)
Pulmonary fibrosis	1 (0.3%)
Respiratory distress	1 (0.3%)
Cardiac Disorders	
Cardio-respiratory arrest	2 (0.6%)
Arrhythmia NOS	1 (0.3%)
Cardiac arrest	1 (0.3%)
Cardiac failure NOS	1 (0.3%)
Cardiopulmonary failure	1 (0.3%)
Pulmonary oedema NOS	1 (0.3%)
Nervous System Disorders	
Intracranial hemorrhage NOS	4 (1.2%)
Brain edema	1 (0.3%)
Cerebral artery embolism	1 (0.3%)
Cerebral artery occlusion	1 (0.3%)

Table 28 continued. Primary causes of death for paediatric patients: All studies

System Organ Class, MedDRA v. 5.0 Preferred Term	Total (n=335)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	
Acute myeloid leukemia NOS	2 (0.6%)
Leukemia NOS	2 (0.6%)
Acute lymphocytic leukemia	1 (0.3%)
Germ cell cancer NOS	1 (0.3%)
General Disorders and Administration Site Conditions	
Multi-organ failure	3 (0.9%)
Blood and Lymphatic System Disorders	
Autoimmune hemolytic anemia NOS	1 (0.3%)
Disseminated intravascular coagulation	1 (0.3%)
Injury, Poisoning and Procedural Complications	
Post procedural hemorrhage	1 (0.3%)
Renal and Urinary Disorders	
Renal failure NOS	1 (0.3%)
Vascular Disorders	
Vascular rupture	1 (0.3%)

Patient base: all pediatric patients who received at least one dose of micafungin. Table includes patients ≤ 16 years of age.

NOS: not otherwise specified; MedDRA: Medical Dictionary for Regulatory Activities.

Table 29. Incidence of Serious Adverse Events related to study drug, paediatric patients

System Organ Class, MedDRA v. 5.0 Preferred Term	Micafungin (n=335)
Any Related Serious Adverse Event	**15 (4.5%)**
Respiratory, Thoracic and Mediastinal Disorders	
Acute respiratory distress syndrome	2 (0.6%)
Hypoxia	2 (0.6%)
Renal and Urinary Disorders	
Renal failure acute	2 (0.6%)
Renal failure aggravated	1 (0.3%)
Vascular Disorders	
Hypertension NOS	2 (0.6%)
Flushing	1 (0.3%)
Hypotension NOS	1 (0.3%)
Hepatobiliary Disorders	
Hyperbilirubinaemia	1 (0.3%)
Hyperbilirubinaemia aggravated	1 (0.3%)
Blood and Lymphatic System Disorders	
Thrombocytopenia	1 (0.3%)
Cardiac Disorders	
Cyanosis NOS	1 (0.3%)
Gastrointestinal Disorders	
Nausea	1 (0.3%)
Infections and Infestations	
Meningitis	1 (0.3%)
Injury, Poisoning and Procedural Complications	
Anaphylactoid reaction	1 (0.3%)
Investigations	
Blood potassium decreased	1 (0.3%)
Metabolism and Nutrition Disorders	
Hypokalaemia	1 (0.3%)
Psychiatric Disorders	
Anxiety	1 (0.3%)

Patient base: all pediatric patients who received at least one dose of micafungin. Table includes patients ≤ 16 years of age.

NOS: not otherwise specified; MedDRA: Medical Dictionary for Regulatory Activities.

6.7. Immunological events

No information on immunological events was provided.

6.8. Safety related to drug-drug interactions and other interactions

No significant events were identified with regard to drug-drug or other interactions.

6.9. Discontinuation due to adverse events

A total of 13.3% (409/3083) of all micafungin-treated patients were withdrawn from study drug due to adverse events, regardless of causality. In all micafungin-treated patients, the most frequent adverse events leading to drug withdrawal, regardless of relationship to study drug, were septic shock (0.9%), sepsis NOS (0.8%), respiratory failure (0.8%), and multiorgan failure (0.8%).

Related adverse events leading to drug withdrawal were reported in 3.4% (106/3083) of all micafungin-treated patients. In all micafungin-treated patients, the most frequent related

adverse events leading to drug withdrawal were abnormal liver function tests NOS (0.3%), AST/SGOT increased (0.2%), increased blood alkaline phosphatase (0.2%), rash NOS (0.2%), and hyperbilirubinemia (0.2%).

6.10. Post marketing experience

Micafungin was first approved for marketing in Japan on 08 October 2002 and was first launched in Japan on 06 December 2002. The medicinal product is currently approved in 55 countries and marketed in 38. The range of approved indications are treatment of *Candida* infection, *Aspergillus* infection, Oesophageal *Candida* infection, and prophylaxis of *Candida* and *Aspergillus* infection. A copy of the most recent PSUR was provided as part of this application. In the period covered by this report, the total exposure was 38,498 patient-months. The cumulative exposure to date is estimated to be 436,885 patient-months. There were no actions taken regarding micafungin for safety reasons by either the regulatory authorities or by the Marketing Authorization Holder (MAH). Overall, a total of 106 medically confirmed case reports fulfilled the criteria for inclusion as significant adverse events. The cumulative number of cases that fulfilled these criteria was 1,498. There were 22 case reports with a fatal outcome. In most of the fatal cases, patients were immunocompromised after solid organ or bone marrow transplantation. In other cases, available information is insufficient for a reliable assessment. Most fatal cases occurred in extremely ill patients, in critical clinical settings. In addition to PSUR, 8 post-marketing surveillance studies were also provided in support of this application. These are described below.

6.10.1. Study 463-JC-001

This study was an open-label post-marketing surveillance study in patients with fungal infections receiving Micafungin. The objective of the study was to determine safety and efficacy of Micafungin under actual post-marketing conditions. Subjects were patients between 16 and 100 years of age with fungal infections. A total of 1142 subjects were enrolled. In 1074 patients included in the safety analysis, 562 adverse reactions were reported from 306 patients. The incidence of adverse reactions was 28.5%. The incidence of adverse reactions in 81 patients who received a maximum daily dose >150 mg/day at the initial onset of adverse reactions was 30.9% (25/81 patients), while that in 991 patients who received a dose ≤150 mg/day was 28.2% (279/991). There was no significant difference. The incidence of adverse reactions in 230 patients aged ≥80 years was 24.8% (57/230 patients. It was almost the same as that in patients aged <80 years at 29.5% (249/844). The adverse reactions noted after 57 days in 34 patients administered for ≥57 days were 3 events in 3 patients (8.8%), and an increase in the incidence of adverse reactions by long-term administration was not found. The adverse reactions noted after 57 days of administration were renal disorder (occurring after 69 days of administration), spinal compression fracture (occurring after 71 days of administration), and liver function test abnormal (occurring after 104 days of administration) (1 each). The incidence of adverse reactions in the group with concomitant drugs (29.3% (302/1030 patients)) was significantly higher than that in the group without concomitant drugs, 9.1% (4/44) (Fisher's exact test, p=0.003). The overall clinical effect (effective patients / (effective patients + ineffective patients) × 100) in 765 patients, excluding 259 unevaluable patients from the 1024 patients for the efficacy analysis was 83.0% (635/765).

6.10.2. Study 463-JC-006

This study was an open-label post-marketing surveillance study in patients with pulmonary aspergillosis receiving Micafungin. The objective of the study was to determine safety and efficacy of Micafungin under actual post-marketing conditions. Subjects were patients between 24 and 90 years of age with pulmonary aspergillosis. A total of 117 subjects were enrolled. This indication is not being sought in this application.

6.10.3. Study 463-JC-004

This study was an open-label post-marketing surveillance study in neutropenic patients with deep mycosis and haematological diseases receiving Micafungin. The objective of the study was to determine safety and efficacy of Micafungin under actual post-marketing conditions. Subjects were neutropenic patients between 17 and 94 years of age with deep mycosis and haematological diseases. A total of 552 subjects were enrolled. Among the 531 patients included in the safety analysis set, 160 adverse reactions were reported by 98 patients. The incidence of adverse reactions was 18.5%. Excluding 4 unassessable cases, the efficacy rate among 419 of the 423 patients in the efficacy set was 60.9% (255/419 patients). The efficacy rate by diagnosis was 33.3% (2/6 patients) for cases with a definitive diagnosis, 33.5% (11/31 patients) for suspected cases of mycosis (A), 58.8% (60/102 patients) for suspected cases of mycosis (B), 63.0% (29/46 patients) for suspected cases of mycosis (C), and 65.4% (153/234 patients) for cases with fever refractory to antibacterial agents.

6.10.4. Study 463-JC-003

This study was an open-label post-marketing surveillance study in patients with deep mycosis after haematopoietic stem cell transplantation receiving Micafungin. The objective of the study was to determine safety and efficacy of Micafungin under actual post-marketing conditions. Subjects were patients between 14 and 70 years of age with deep mycosis after haematopoietic stem cell transplantation. A total of 91 subjects were enrolled. Among the 91 patients included in the safety analysis set, 57 adverse reactions were reported by 32 patients. The incidence of adverse reactions was 35.2%.The incidence of adverse reactions in patients who received a maximum daily dose >150 mg/day was 40.6% (13/32 patients), while that in patients who received a dose ≤150 mg/day was 32.2% (19/59 patients). Concomitant drugs were used in all 91 patients in the safety analysis set, and the incidence of adverse reactions was 35.2% (32/91 patients). In 63 patients, excluding the 1 unassessable case from the 64 patients in the efficacy analysis set, the efficacy rate was 71.4% (45/63 patients). It appears that the combined use of an antibacterial agent and an antifungal agent was more effective than monotherapy with an antibacterial agent.

6.10.5. Study 463-JC-007

This study was an open-label post-marketing surveillance study in patients with deep mycosis in Surgery, Emergency, and Intensive Care receiving Micafungin. The objective of the study was to determine safety and efficacy of Micafungin under actual post-marketing conditions. Subjects were patients between 3 and 92 years of age with deep mycosis in Surgery, Emergency, and Intensive Care. A total of 180 subjects were enrolled. Among the 178 patients included in the safety analysis set, 69 adverse reactions were reported by 37 patients. The incidence of adverse reactions was 20.8%. The efficacy rate among 100 of the 112 patients in the efficacy analysis set, excluding 12 unassessable cases, was 72.0% (72/100 patients).

6.10.6. Study 463-JC-002

This study was an open-label post-marketing surveillance study in patients with deep mycosis and haematological diseases receiving Micafungin. The objective of the study was to determine safety and efficacy of Micafungin under actual post-marketing conditions. Subjects were patients between 16 and 91 years of age with deep mycosis and haematological diseases. A total of 186 subjects were enrolled. Among the 186 patients included in the safety analysis set, 90 adverse reactions were reported by 52 patients. The incidence of adverse reactions was 28.0%.Excluding 3 unassessable cases, the efficacy rate among 134 of 137 patients in the efficacy analysis set was 66.4% (89/134 patients).

6.10.7. Study 463-JC-005

This study was an open-label post-marketing surveillance study in patients aged under 16 years at the start of Micafungin. The objective of the study was to determine safety and efficacy of

Micafungin under actual post-marketing conditions. Subjects were patients between 0 and 16 years of age. A total of 201 subjects were enrolled. Among the 191 patients included in the safety analysis set, 54 adverse reactions were reported in 42 patients (22.0%). Of 141 patients included in the efficacy analysis set, 50 patients in whom the overall clinical effect was considered unassessable due to the difficulty of diagnosis on fungal infection were excluded from analysis. Among the remaining 91 patients, the efficacy rate was 86.8% (79/91 patients).

6.10.8. Study 463-JC-008

This study was an open-label post-marketing surveillance study in patients receiving prophylactic treatment with Micafungin immediately after haematopoietic stem cell transplantation. The objective of the study was to determine safety and efficacy of Micafungin under actual post-marketing conditions. Subjects were patients between 0 and 72 years of age receiving prophylactic treatment with Micafungin immediately after haematopoietic stem cell transplantation. A total of 256 subjects were enrolled. Among the 241 patients included in the safety analysis set, 143 adverse reactions were reported by 86 patients. The incidence of adverse reactions was 35.7% (86/241 patients). Among 228 patients, excluding 9 unassessable cases due to insufficient administration period of Micafungin (including death) or other reasons from the 237 patients included in the efficacy analysis set, the success rate of prophylactic treatment (hereinafter referred to as "success rate") at the end of Micafungin administration was 77.2% (176/228 patients). The incidence of mycosis was 3.5% (8/228 patients). Among 225 patients, excluding 3 unassessable cases due to death or other reasons by the end of the observation period (4 weeks after the end of administration) from 228 patients, the success rate was 76.4% (172/225 patients). The incidence of mycosis at the end of the observation period was 4.0% (9/225 patients). The 9 cases of mycosis consisted of 3 patients with candidaemia, 2 patients with invasive pulmonary aspergillosis, 1 patient with trichosporonosis, and 3 patients with suspected fungal infection (no specific diagnosis).

6.11. Evaluator's overall conclusions on clinical safety

Information on safety was available from the clinical development program, as well as extensive post-marketing experience. In addition, a total of 8 post-marketing surveillance studies were conducted. The safety database comprised 5102 subjects who were enrolled and received at least one dose of study drug in 41 clinical studies. Of these, 3584 subjects, including 3083 patients and 501 volunteers, received at least one dose of micafungin. A total of 82.8% of the 3083 patients who received at least on dose of micafungin had ≥10 days of treatment with a mean duration of treatment of 20 days.

Guidance on study design for clinical evaluation of antifungal agents is provided by EMEA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease*. This notes that the evaluation of the safety of anti-fungal agents is not straightforward due to factors such as serious underlying diseases in the majority of patients with IFD, large numbers of concomitant medications, and, in many cases, the considerable potential for clinically significant drug-drug interactions to occur.

The most frequently reported AEs irrespective of causality were diarrhoea NOS, nausea, vomiting, pyrexia. A treatment-related AE was experienced by 32.2% of patients. The most frequently reported AEs assessed by the investigator as having at least a possible relationship to micafungin (≥ 1%, MedDRA preferred term) in the clinical database or in a pivotal study were the hepatic AEs (AST increased, ALT increased, AP increased, LFT abnormal and hyperbilirubinemia); the hematological AEs (leukopenia, neutropenia and anemia); the electrolyte disturbances (hypokalemia, hypocalcemia and hypomagnesaemia); the allergic like/histamine-related AEs (rash and rigors); the injection-site reaction phlebitis; as well as headache, nausea, vomiting, diarrhoea, pyrexia, thrombocytopenia, abdominal pain, pruritus, blood creatinine increased, blood bilirubin increased, blood urea increased, blood LDH

increased, hypertension, hypophosphataemia, renal impairment, cholestasis and infusion site inflammation. Treatment-related hemolytic AEs were rare.

A total of 28.3% (873/3083) of micafungin-treated patients had a serious treatment-emergent adverse event during study participation. Serious treatment-emergent adverse events considered to be related to study drug by the investigators were reported in 3.6% (111/3083) of micafungin-treated patients. The most frequent serious treatment-emergent adverse events in micafungin-treated patients, regardless of relationship to study drug, were respiratory failure (3.1%), sepsis NOS (2.8%), septic shock (1.7%), hypotension NOS (1.4%), pneumonia NOS (1.2%), and multi-organ failure (1.2%), and respiratory distress (1.0%).

Death occurred in 671 of 3083 (21.8%) of micafungin-treated patients: 134 (4.3%) deaths occurred in patients during study drug treatment, and 537 (17.4%) deaths occurred during the post treatment period. The most common primary causes of death that were reported for micafungin-treated patients were septic shock (1.6% [50/3083]), sepsis NOS (1.6% [48/3083]), respiratory failure (1.6% [50/3083]), and multi-organ failure (1.3% [40/3083]).

In the paediatric population, the incidence of some adverse events (AEs) in the clinical study database (thrombocytopenia, tachycardia, hypertension, hypotension, hyperbilirubinemia, hepatomegaly, renal failure acute, blood urea increased) was higher in paediatric patients than adult patients. Additionally, paediatric patients < 1 year of age experienced about two times more often an increase in ALT, AST and AP than older paediatric patients. No clinically meaningful differences in the safety profile could otherwise be discerned.

A total of 13.3% (409/3083) of all micafungin-treated patients were withdrawn from study drug due to adverse events, regardless of causality. In all micafungin-treated patients, the most frequent adverse events leading to drug withdrawal, regardless of relationship to study drug, were septic shock (0.9%), sepsis NOS (0.8%), respiratory failure (0.8%), and multiorgan failure (0.8%).

Considerable post-marketing information was also provided. The total exposure was 38,498 patient-months. The cumulative exposure to date is estimated to be 436,885 patient-months. There were no actions taken regarding micafungin for safety reasons by either the regulatory authorities or by the Marketing Authorization Holder (MAH). Overall, a total of 106 medically confirmed case reports fulfilled the criteria for inclusion as significant adverse events. The cumulative number of cases that fulfilled these criteria was 1,498. There were 22 case reports with a fatal outcome. In addition, results from 8 post-marketing surveillance studies were provided. No new safety issues were identified as a result of these studies.

7. Overall summary and discussion

7.1. Pharmacokinetics

The PK of micafungin is consistent across studies and has been extensively characterised. Studies with both healthy subjects and patients have shown: a bi-exponential decline in micafungin concentrations; mean half-life values of approximately 15 hours which remained constant with increases in dose; no evidence of systemic accumulation with repeated administration; increases in systemic exposure (AUC and C_{max}) proportional to increases in dose; and steady-state reached by Day 7 after repeated daily administration. The blood to plasma ratio was approximately 0.85 and was independent of concentration over the range of 0.1 to 10 µg/mL micafungin. Faecal excretion was the major route of elimination accounting for a mean recovery of 43.8% of administered ^{14}C dose. The metabolism of micafungin involves multiple CYP isozymes including CYP1A2, 2B6, 2C and 3A4. Five metabolites have been detected after administration of micafungin to humans: M-5 (main metabolite in plasma), M-1 and M-2 (minimal to undetectable in plasma), and M-3 and M-11 (faeces/urine). In vitro, M-2 has a

potency and spectrum of activity similar to that of the parent compound; M-1 is 4- to 16-fold less potent than the parent compound; and M-5 has no activity (< 1% of parent compound).

With regard to pharmacokinetics in special populations, subjects with severe renal impairment, moderate hepatic dysfunction or severe hepatic dysfunction showed no marked differences in micafungin PK compared with age-, weight-, and sex-matched normal subjects, and elderly male subjects showed no significant differences in micafungin PK parameters compared with young male subjects. With regard to pharmacokinetic interactions, no interaction that altered the PK of micafungin was observed. There was no effect of single-dose or steady-state micafungin on the PK of MMF, cyclosporin, tacrolimus, prednisolone, fluconazole, voriconazole, ritonavir or rifampicin. Increases in exposure (AUC) for sirolimus (by 21%), nifedipine (by 18%) amphotericin B (by 30%) and itraconazole (by 22%) in the presence of steady-state micafungin were noted.

7.2. Pharmacodynamics

Micafungin is a member of the echinocandin lipopeptide family and inhibits non-competitively the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls which is not present in mammalian cells. Micafungin displayed potent activity against clinically relevant *Candida* species. The Minimum Inhibitory Concentration (MIC) rank order was: *C. albicans* (including azole resistant strains) < *C. tropicalis*, *C. glabrata* < *C. krusei* << *C. parapsilosis*, *C. guilliermondii.* With the exception of *C. parapsilosis* and *C. guilliermondii*, micafungin was generally more potent against the tested *Candida* species than amphotericin B, fluconazole and itraconazole. MIC values for micafungin were lower compared to caspofungin. Micafungin has virtually no activity against *Cryptococcus neoformans*, *Trichosporon cutaneum*, *Trichosporon asahii*, *Fusarium solani*, *Pseudallescheria boydii*, *Absidia corymbifera*, *Cunninghamella elegans, Rhizopus oryzae or Rhizopus microspores.*

7.3. Clinical efficacy

7.3.1. Dose-response studies and main clinical studies

There were 5 pivotal studies provided in support of the application. The application separately addressed the three different proposed indications, invasive candidiasis, oesophageal candidiasis and prophylaxis of invasive fungal infection. The efficacy and safety of micafungin in IC was assessed in the pivotal Phase III reference therapy controlled non-inferiority trials FG-463-21-08 and 03-0-192. Clinical studies that assessed the efficacy and safety of micafungin in the treatment of EC include the pivotal phase III studies 03-7-005 and 03-7-008. A pivotal phase III, reference therapy controlled trial was also conducted for prophylaxis of IFI, study 98-0-050. All studies were non-inferiority studies, with adequate size to provide statistically meaningful results. Appropriate comparators were used. Rationale for dose for each of the proposed indications was provided and was meaningful. Guidance on study design for clinical evaluation of antifungal agents is provided by EMEA CHMP/EWP/1343/01 Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease was followed and met. For invasive candidiasis, non-inferiority of micafungin was demonstrated against Ambisome and caspofungin. For oesophageal candidiasis, non-inferiority of micafungin was demonstrated against fluconazole. For prophylaxis of invasive fungal infection, non-inferiority of micafungin was demonstrated against fluconazole.

The oesophageal candidiasis indication remains a potential issue. The clinical trials supporting this indication were predominantly conducted in HIV-positive patients, who made up over 90% of the subject population. While there appears to be little doubt that micafungin will be efficacious in non HIV-positive subjects with this indication, this should be clearly stated in the product information, and be a particular issue for post-marketing surveillance. In addition, the clinical study information also indicated that in HIV patients with a baseline CD4 count ≥100,

the odds of endoscopic cure was approximately 2.6 times higher than the odds in HIV patients with a baseline CD4 count <100. This needs to be made clear in the product information.

7.3.2. Clinical studies in special populations

No pivotal study was provided that assessed efficacy in only paediatric patients, although some studies did include paediatric patients. EMEA CHMP/EWP/1343/01 Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease notes that the In general, factors that predispose to IFD in children are similar to those in adults and the range of fungal pathogens encountered is the same. Therefore, a demonstration of efficacy in specific circumstances in adults may be extrapolated to use in the same circumstances in children. Information provided in the clinical development program supported this extrapolation.

7.3.3. Analysis performed across trials (pooled analyses and meta-analysis)

No analysis was performed across studies for efficacy.

7.3.4. Supportive studies

There were a total of 15 supportive studies provided, consisting of 8 studies for invasive candidiasis, 2 studies for oesophageal candidiasis and 5 studies for prophylaxis of invasive fungal infections. While there were limitations in the applicability and design of some of these studies, results were generally consistent with the pivotal studies.

7.4. Clinical safety

7.4.1. Patient exposure

The safety database comprised 5102 subjects who were enrolled and received at least one dose of study drug in 41 clinical studies. Of these, 3584 subjects, including 3083 patients and 501 volunteers, received at least one dose of micafungin. A total of 82.8% of the 3083 patients who received at least on dose of micafungin had ≥10 days of treatment with a mean duration of treatment of 20 days.

7.4.2. Adverse events

The most frequently reported AEs irrespective of causality were diarrhoea NOS, nausea, vomiting, pyrexia. A treatment-related AE was experienced by 32.2% of patients. The most frequently reported AEs assessed by the investigator as having at least a possible relationship to micafungin (≥ 1%, MedDRA preferred term) in the clinical database or in a pivotal study were the hepatic AEs (AST increased, ALT increased, AP increased, LFT abnormal and hyperbilirubinemia); the hematological AEs (leukopenia, neutropenia and anemia); the electrolyte disturbances (hypokalemia, hypocalcemia and hypomagnesemia); the allergic like/ histamine-related AEs (rash and rigors); the injection-site reaction phlebitis; as well as headache, nausea, vomiting, diarrhoea, pyrexia, thrombocytopenia, abdominal pain, pruritus, blood creatinine increased, blood bilirubin increased, blood urea increased, blood LDH increased, hypertension, hypophosphataemia, renal impairment, cholestasis and infusion site inflammation. Treatment-related hemolytic AEs were rare.

7.4.3. Serious adverse events and deaths

A total of 28.3% (873/3083) of micafungin-treated patients had a serious treatment-emergent adverse event during study participation. Serious treatment-emergent adverse events considered to be related to study drug by the investigators were reported in 3.6% (111/3083) of micafungin-treated patients. The most frequent serious treatment-emergent adverse events in micafungin-treated patients, regardless of relationship to study drug, were respiratory failure (3.1%), sepsis NOS (2.8%), septic shock (1.7%), hypotension NOS (1.4%), pneumonia NOS (1.2%), and multi-organ failure (1.2%), and respiratory distress (1.0%). Death occurred in 671

of 3083 (21.8%) of micafungin-treated patients: 134 (4.3%) deaths occurred in patients during study drug treatment, and 537 (17.4%) deaths occurred during the post treatment period. The most common primary causes of death that were reported for micafungin-treated patients were septic shock (1.6% [50/3083]), sepsis NOS (1.6% [48/3083]), respiratory failure (1.6% [50/3083]), and multi-organ failure (1.3% [40/3083]).

7.4.4. Laboratory findings

Please refer above.

7.4.5. Safety in special populations

In the paediatric population, the incidence of some adverse events (AEs) in the clinical study database (thrombocytopenia, tachycardia, hypertension, hypotension, hyperbilirubinemia, hepatomegaly, renal failure acute, blood urea increased) was higher in paediatric patients than adult patients. Additionally, paediatric patients < 1 year of age experienced about two times more often an increase in ALT, AST and AP than older paediatric patients. No clinically meaningful differences in the safety profile could otherwise be discerned.

7.4.6. Immunological events

No significant immunological events were identified.

7.4.7. Safety related to drug-drug interactions and other interactions

No significant issues were identified.

7.4.8. Discontinuation due to adverse events

A total of 13.3% (409/3083) of all micafungin-treated patients were withdrawn from study drug due to adverse events, regardless of causality. In all micafungin-treated patients, the most frequent adverse events leading to drug withdrawal, regardless of relationship to study drug, were septic shock (0.9%), sepsis NOS (0.8%), respiratory failure (0.8%), and multiorgan failure (0.8%).

8. Benefit-risk assessment

8.1. Assessment of benefits

From the clinical information provided, application has been sought for micafungin for treatment of invasive candidiasis, oesophageal candidiasis and prophylaxis for invasive fungal infections. As part of the clinical development program, a total of 5 pivotal phase III studies were provided, with 2 studies addressing each of the first 2 indications, and 1 study addressing the latter indication. These studies demonstrated non-inferiority of micafungin compared to active comparators which are registered for use in Australia. Given the morbidity and mortality associated with the three proposed indications, it would appear that there are significant benefits to the introduction of this therapeutic product.

8.2. Assessment of risks

The safety profile has been well characterised from both the clinical development program and an extensive post-marketing surveillance program. While the target population has significant morbidity and mortality due to their underlying conditions, the safety profile of micafungin appears to be at least comparable to other antifungal agents. This has been further reinforced by the post-marketing surveillance and experience with other antifungal agents in the same pharmacological class.

8.2.1.1. Safety specification

A safety specification was provided within Module 1 of the application. The safety specification outlines specific actions to be undertaken for each specific risk. Safety concerns were identified from clinical studies or PSUR reports. This appears reasonable in view of the safety information and post-marketing surveillance presented.

8.3. Assessment of benefit-risk balance

On balance, micafungin appears to have an acceptable benefit-risk profile.

The application provided includes an assessment of possible benefits and risks of micafungin. This assessment is supported, and appears to be reasonable. The safety specification provided appears to address all significant risks.

9. Recommendation regarding authorisation

This report supports the indications as proposed by the sponsor.

10. Clinical questions

There are no clinical questions

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