EORTC
European Organisation for Research and Treatment of Cancer
AISBL International Non-Profit Association under Belgian law IVZW

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Short Study Report to Authorities

Name of Sponsor/Company: **EORTC**	Individual study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of the finished product	Caspofungin	
Name of Active Ingredient	Caspofungin acetate	
Title of the Study	A multicenter, Open, Phase II Study to Estimate the activity and safety of Caspofungin (CASP) in the First-line Treatment of probable and proven Invasive Aspergillosis (IA) in Patients with Hematological Malignances (HM) or recipients of autologous Haematopoeitic Stem Cell Transplantation and those with allogeneic Haematopoietic Stem Cell Transplantation (HSCT) – EORTC 65041	
Investigators & Study Centers	➢ *See appendix below*	
Publication (reference)	List here any existing reference for the presentation of the study results. If the final publication is not yet out, please list here any abstracts or formal presentations with the statement The overall study data have not been published yet, however, publications about part of the data were presented at several conferences: Group A (HM or autologous HSCT) TIMM 2007, Viscoli, C., Herbrecht, R., Akan, H., Baila, L., Doyen, C., Gallamini, A., Giagounidis, A., Marchetti, O., Martino, R., Meerts, L., Paesmans, M., Shivaprakash, M., Ullmann, A.J., Maertens, J.: Caspofungin (C) as first-line therapy of invasive aspergillosis (IA) in haematological patients (pts): a study of the EORTC Infectious Diseases Group ECCMID 2008, J. Maertens, R. Herbrecht, H. Akan, L. Baila, C. Doyen, A. Gallamini, A. Giagounidis, O. Marchetti, R. Martino, L. Meert, M. Paesmans, L. Ameye, M. Shivaprakash, A. Ullmann, C. Viscoli for the Infectious Diseases Group of the EORTC: Caspofungin as first-line therapy of invasive aspergillosis in haematological patients - impact of baseline characteristics on response rate at end of treatment and survival Group B (allogeneic HSCT) ICAAC 2008, R. Herbrecht, J. Maertens, L. Baila, M. Aoun, W.J. Heinz, R. Martino, S. Schwartz, A. Ullmann, L. Meert, M. Paesmans, L. Ameye, M. Shivaprakash, C. Viscoli: Caspofungin (C) as First-Line Therapy of Invasive Aspergillosis (IA) in Allogeneic Hematopoietic Stem Cell Transplant (HSCT) Recipients: a Study of the EORTC Infectious Diseases	

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	Group	
Objective(s)	➢ *The following parts are available from the Study Protocol Summary* The primary objective of this trial was to estimate the activity of caspofungin as first line therapy in the treatment of invasive aspergillosis in patients with haematological malignancies (HM)/autologous Hematopoietic Stem Cell Transplantation (HSCT) – group A – and patients with allogeneic HSCT transplantation – group B. The activity of caspofungin was assessed separately in these two groups of patients since response rates and survival differ substantially in these two patient populations.	
Methodology	*The trial was designed as a single arm multicentric phase II trial in a population of patients with proven or probable invasive aspergillosis according to EORTC-MSG criteria.*	
Number of patients Number planed (Statistical design) Number analyzed	This is a one stage Fleming design with two groups of patients. Group A (HM, autologous HSCT): Based on significance level of 0.10 and 95% power to detect an effective therapy if the true response rate was at least 55% (null hypothesis: true response rate ≤35%), this therapy would be recommended for further investigation if at least 23 out of 52 eligible patients had a response (estimated 87 registered patients). The analyzed number of patients was 61 in the MITT population and 54 in the PP population. Group B (allogeneic HSCT): Based on a significance level of 0.10 and 95% power to detect an effective therapy if the true response rate was at least 33% (null hypothesis: true response rate ≤13%), this therapy would be recommended for further investigation if at least 8 out of 37 eligible patients had a response (estimated 62 registered patients). The trial was stopped permaturely due to low accrual, with 42 patients registered and 24 patients analyzed in the MITT=PP population.	
Diagnosis and main criteria for inclusion	Patients were eligible if at least 18 years old, with HM or auto-HSCT (group A) or allo-HSCT (group B) and with a diagnosis of proven or probable IA, according to the EORTC-MSG criteria. Patients with possible IA were registered, but investigator had 7 days to upgrade them to proven or probable IA based on culture or serological tests performed prior to or	

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	within 48 hours after registration but with pending results. These included culture and/or histology results and Aspergillus galactomannan evaluations. Caspofungin treatment was stopped in the patients who were not upgraded, these patients were assessed for safety only.	

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Treatment Test product, dose and mode of administration (batch number if applicable)	All patients enrolled received a 70mg loading dose of caspofungin on day 1, followed thereafter by 50mg/day up for at least 15 days (or until failure) to a maximum duration of therapy of 84 days. Dose modifications were made for patients with body weight > 80kg (70mg/day), moderate hepatic failure (following 70mg loading dose, 35mg/day), and concomitant administration of liver inducers able to influence caspofungin concentrations.	
Duration of treatment	Minimal treatment duration was planned to be 15 days unless an adequate reason to stop early was present (toxicity, clear progression, death, …) and otherwise to be continued up to 84 days in patients with response or stable disease.	
Reference therapy, dose and mode of administration (batch number if applicable)	Not applicable	
Criteria for evaluation		
Efficacy	Response was assessed using Recist criteria in a modified intent to treat population (MITT).	
Safety	*Safety was graded according to the CTCAE version 3 in all patients who started therapy with caspofungin.*	
Statistical methods	In both strata, the primary endpoint was the proportion of MITT patients with complete or partial response to treatment at end of therapy (EOT). The secondary endpoints were response to treatment and survival at day 84 after enrollment, and safety, as defined by proportion of drug-related adverse events, serious drug-related adverse events, and drug-related adverse events leading to treatment discontinuation. Fisher's exact test	

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was used to test the statistical significance of differences in discrete data and Mann-Whitney's test to compare continuous variables such as Karnofsky score. A p value <0.05 was considered statistically significant. As most of the deaths attributable to IA occur by day 84, the binary survival status at day 84 was considered as an endpoint and logistic regression models were constructed to determine baseline characteristics independently related to survival at day 84 (stepwise forward selection of variables was used).

Summary of Results

- *The contents of this section should be prepared on the basis of the section "Summary of Results" from the Final Analysis Report. It may however be less extensive than that chapter from the FAR study summary.*

Efficacy Results

Group A: Median duration of caspofungin treatment was 15 days. In the MITT group (N=61) at EOT, 1 and 19 patients had complete and partial response, respectively [success rate 33% (20/61)], 9 (15%) achieved stabilization and 31 (51%) had disease progression. One patients was not evaluable. The 6 and 12-weeks survival rates were 66% (40/61) and 53% (32/60).

Group B: Median duration of caspofungin treatment was 24 days. In the MITT = PP group (N=24) at EOT, 10 patients had a complete or partial response [success rate 42% (10/24)], 1(4%) stable disease and 12 (50%) disease progression. The 6 and 12-weeks survival rates wee 79% (19/24) and 50% (12/24).

Safety Results

Group A: Caspofungin was well tolerated with no serious drug-related adverse events or discontinuation due to drug-related adverse events.

Group B: Caspofungin was well tolerated with no serious drug-related adverse events or discontinuation due to drug-related adverse events.

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Conclusions	Group A: The response rate of 33% (30/61) was compatible with the null hypothesis of a true response rate ≤35%. Group B: The response rate of 42% (10/24) was compatible with a true response rate of at least 33% and the drug should be recommended for further investigation.	
Date of Report & version	*Apr 30, 2010* *Version 1.0*	

Table Investigators and study centers

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						Total	172