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Title of Study:	A Retrospective Study to Establish a Historic Database on the Efficacy of Standard Antifungal Therapy in Patients With Invasive Fungal Infection (Protocol No. P02387)	
Studied Period:	23 OCT 2001 to 17 SEP 2002	Clinical Phase: 3
Objective(s):	The primary objective of this study was to document retrospectively the clinical efficacy of standard antifungal therapies in an external control group of refractory/intolerant invasive fungal infection (IFI) cases.	
Methodology:	Retrospective, multicenter, chart review study conducted largely at centers that enrolled subjects into the P00041 posaconazole study. Data were collected from medical charts for subjects treated for IFIs that were refractory or resistant to standard antifungal therapies, or who were intolerant of standard antifungal therapies.	
Number of Subjects:	279 subjects were selected from 2073 screened. In the Modified Intent-to-Treat (Eligible Subjects) subset (see Criteria for Evaluation below), there were 218 subjects, 68 females and 150 males, ages 14-93 years.	
Diagnosis and Criteria for Inclusion:	A case was selected for data collection if all the following criteria were met: <ul style="list-style-type: none">• Males or females of any race, greater or equal to 13 years of age• Treatment for an IFI between 30 APR 1996 and 30 APR 2001 at one of the centers participating in P00041 or at other non-P00041 centers• A diagnosis of proven or probable IFI based on Mycosis Study Group/European Organization for Research and Treatment of Cancer (MSG/EORTC) criteria• Refractory IFI or intolerance to standard therapy• The case must have enough post-baseline information to assess protocol-defined global response	
Duration of Treatment:	Not applicable.	
Test Product, Dose, Mode of Administration:	Not applicable.	
Reference Therapy, Dose, Mode of Administration:	Not applicable.	
Criteria for Evaluation:	Data were collected for the following parameters: demographics, documentation of proven/probable IFI, history of fungal infection, underlying conditions, medical history/physical findings, method of diagnosis, disease history and IFI diagnosis, selected previous/concomitant medications including prior antifungal therapy, vital signs, signs and symptoms, absolute neutrophil count (ANC), blood chemistry, protocol-defined global clinical response (investigator determined), and salvage antifungal therapy. Additionally, the following data were collected, if applicable: cerebrospinal fluid, fungal culture, serology, histopathology, diagnostic imaging, bronchoscopy, and death report. The primary efficacy variable was the global response at the end of treatment, as assessed by the Data Review Committee (DRC). The DRC reviewed all of the relevant clinical, radiographic, and mycological data to determine the global response. The five possible global responses were: complete, partial, stable, failure, and unable to determine. The global response was considered positive, or a success, if the response was either complete or partial. No safety data was collected.	
Statistical Methods:	The primary efficacy variable was protocol-defined global response as assessed by the DRC at the end of treatment with antifungal salvage therapy. The primary analysis subset consisted of subjects, in the Modified Intent-to-Treat (MITT) subset, having <i>Aspergillus</i> as a primary pathogen. A 95% confidence interval for the global response rate (proportion of subjects with complete or partial response) was provided for each of the 8 primary pathogen groups. Global response was also summarized for each level of the demographic and baseline/historical disease characteristics, prior and total antifungal treatment duration, and prior and concomitant pharmacotherapies with the potential to influence clinical outcomes. Kaplan-Meier survival curves for subjects having <i>Aspergillus</i> as a primary pathogen and for all pathogen groups combined were provided.	
	Four datasets of subjects were constructed: (1) Intent to Treat Subset (all treated subjects): All subjects who received at least one dose of treatment (salvage therapy) at the study center between 30 APR 1996 and 30 APR 2001 (Note: seven subjects had a start date after 30 APR 2001 and were included in this subset); (2) Modified Intent-to-Treat Subset (MITT ["eligible" subjects]): subset of all "treated" subjects with a proven or	

probable IFI as determined by the DRC based on 2001 MSG/EORTC criteria and evidence of a refractory IFI or intolerance to standard antifungal agents, as determined by the DRC based on established guidelines. The primary efficacy analysis is based on this subset; (3) Efficacy-Evaluable Subset ("evaluable" subjects): Subset of "modified intent to treat" subset consisting of subjects who have at least one assessment of global response (primary efficacy endpoint), which is not "Unable to Determine" as determined by the DRC based on the established guidelines; and (4) Per-Protocol Efficacy Subset: Subset of "efficacy evaluable" subjects who have received >80% of the scheduled days of dosing during the Treatment Phase. Efficacy analyses were primarily based on the Modified Intent-to-Treat Subset.

SUMMARY - CONCLUSIONS:

RESULTS:

Efficacy: The DRC-determined global response rates among the four analysis subsets for *Aspergillus* were very similar. The global response rate for subjects in the MITT subset having *Aspergillus* as a primary pathogen, and for each of the other 7 primary pathogen groups, were within the range of those expected based on previous studies of antifungal treatment for IFI in similar populations. Following are the numbers of subjects with a positive global response/number of subjects in the MITT subset and the percentage of subjects with positive global responses (complete or partial response) by pathogen group.

- *Aspergillus* – 22/86 (25.6%)
- *Candida* – 16/30 (53.3%)
- *Fusarium* – 2/4 (50.0%)
- *Cryptococcus* – 37/64 (57.8%)
- *Coccidioides* – 3/7 (42.9%)
- Zygomycetes – 4/8 (50.0%)
- Chromoblastomycosis/Mycetoma – 0/2 (0%)
- Other Fungi – 12/20 (60.0%)

The DRC-determined global responses for all subjects with proven or probable IFI (regardless of whether the infection was refractory to prior treatment or the subject was intolerant to prior treatment) were very similar to the global response results above for the MITT subset.

Safety: There was no safety evaluation as this was a retrospective chart review study of standard antifungal treatments for IFI, to provide an external control for the assessment of the efficacy of posaconazole in Study [P00041](#).

CONCLUSIONS:

The external control design for this study has provided subjects from the same centers who are representative of the population with refractory invasive fungal infections treated with usual salvage therapy during the time that the posaconazole salvage study was conducted. This is, therefore, the best possible control population for the uncontrolled, open label, P00041 study in subjects with refractory invasive fungal infections.

Date of the Report: 05 FEB 2004