The study listed may include approved and nonapproved uses, formulations, or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this registry, healthcare professionals should consult prescribing information for the product approved in their country.

Title of Study: OPEN-LABEL, TREATMENT PROTOCOL FOR THE SAFETY AND EFFICACY OF POSACONAZOLE (SCH 56592) IN THE TREATMENT OF INVASIVE FUNGAL INFECTIONS (Protocol P00041)

Studied Period: 11 FEB 1999 to 26 MAR 2002 | **Clinical Phase:** 3

Objective(s): The current study was designed to evaluate the safety, tolerance, and efficacy of posaconazole (POS) under an open-label treatment protocol in subjects with:

- invasive fungal infections (IFI) that were resistant or refractory to standard antifungal therapies or for which there was no effective therapy available; or
- a prior history of serious, severe, or life-threatening toxicity while receiving antifungal therapy, or high risk of developing toxicity as a result of pre-existing organ dysfunction (such as renal dysfunction) and required standard antifungal therapy.

Methodology: Subjects were to receive POS 200 mg four times daily (QID) while hospitalized, then 400 mg twice daily (BID) following discharge from hospital. Nonhospitalized subjects were to receive POS 400 mg BID from the outset. Clinical and mycological responses were to be evaluated by the investigator periodically during and after the end of treatment with POS. Survival was evaluated throughout the study and for 30 days after the end of therapy. An independent Data Review Committee (DRC) confirmed the diagnosis, re-evaluated subject eligibility for the study, and reviewed the results of this study and those of an external control data set (**P02387**) simultaneously in blinded fashion to make assessment of a global response to treatment. Infections were grouped into eight clinically meaningful categories for evaluation ("primary pathogen"): *Aspergillus*, *Candida*, *Fusarium*, *Cryptococcus*, *Coccidioides*, Zygomycetes, Chromoblastomycosis / Mycetoma, and Other Fungi.

Safety and tolerance were evaluated based on occurrence of adverse events (AEs), laboratory and other test results, and study discontinuations and deaths.

Number of Subjects: 336 subjects were enrolled. 330 subjects received at least one dose of POS (Intent-to-Treat [ITT] subset): 217 male subjects and 113 female subjects aged 8 to 84 years (16 were <18 y; 281 were 18-64 y; 33 were ≥65 y). Distribution by race was 199 Caucasian, 26 Black, 27 Asian, 77 Hispanic, 1 Other.

238 subjects were included in the Modified Intent-to-Treat (MITT) subset (treated subjects with proven/probable IFI and refractory infection or subject intolerant of standard therapy according to the DRC): 161 male subjects and 77 female subjects aged 8 to 83 years (11 were <18 y; 202 were 18-64 y; 25 were ≥65 y). Distribution by race was 143 Caucasian, 21 Black, 17 Asian, 56 Hispanic, 1 Other. Subjects in each primary pathogen group were typical of subjects usually treated for these infections: >70% of subjects with infection from *Aspergillus*, *Fusarium*, or Zygomycetes had a history of hematologic malignancy, as did ~50% of those with *Candida* or Other Fungi, and many subjects with hematologic malignancy also had allogeneic bone marrow transplant; only one subject with coccidioidomycosis and no subject with cryptococcosis, chromoblastomycosis, or mycetoma had a hematologic malignancy; cryptococcosis was mainly HIV-associated meningitis.

Diagnosis and Criteria for Inclusion: Subjects with IFI (definition based on criteria of the Mycosis Study Group and the European Organization for Research and Treatment of Cancer) AND infection refractory or resistant to standard anti-fungal therapies (as described by the National Committee for Clinical Laboratory Standards) or for which there was no effective therapy available, OR subject with a history of serious, severe, or life-threatening toxicity while receiving previous antifungal therapy or with pre-existing organ dysfunction that precluded the administration of standard anti-fungal therapy.

Duration of Treatment: The protocol specified a maximum of 12 months.

Test Product, Dose, Mode of Administration: POS 200 mg QID while hospitalized, 400 mg BID when not in hospital; orally with food or nutritional supplement whenever possible.

Reference Therapy, Dose, Mode of Administration, Batch No(s): None

Criteria for Evaluation: The primary measure for evaluation was the global response at end of treatment as determined by the blinded DRC (data blinded between this study and the data from the external control data set, **P02387**) for subjects in the MITT subset; the primary pathogen of greatest interest was *Aspergillus*. A positive response was a complete response (resolution of all attributable symptoms, signs, and radiographic or bronchoscopic abnormalities, if present at enrollment) or partial response (clinically meaningful improvement in attributable symptoms, signs and radiographic or bronchoscopic abnormalities, if present at enrollment).

Nonresponses included stable disease, failure of therapy, relapse, or indeterminate response for whatever reason. Global response was also determined at various intervals during treatment. An unblinded assessment of clinical response was made by the investigator using similar criteria. The investigator also attempted to determine mycologic response based on pretreatment and posttreatment culture/histology results.

Statistical Methods: No inferential statistical analysis was performed. The DRC global response at end of treatment was calculated for each primary pathogen group, along with a 95% confidence interval.

SUMMARY – CONCLUSIONS:

RESULTS:

Efficacy: The MITT subset included 238 subjects with a heterogeneous variety of fungal infections; 9 subjects had infections from 2 primary pathogen groups. Overall, 50% of the subjects (119/238) had a positive response to treatment. Response to treatment by primary pathogen group was as follows:

Positive Global Responses[a] at the End of Treatment:
Modified Intent-to-Treat Subset

Primary Pathogen Group	Positive Responses / Infections Treated[b]	95% Confidence Interval for Positive Responses in Infections Treated
Aspergillus	45/107 (42%)	33% - 51%
Candida	11/23 (48%)	27% - 69%
Fusarium	7/18 (39%)	17% - 64%
Cryptococcus	15/31 (48%)	31% - 66%
Coccidioides	11/16 (69%)	41% - 89%
Zygomycetes	6/11 (55%)	23% - 83%
Chromoblastomycosis/ Mycetoma	9/11 (82%)	48% - 98%
Other Fungi	19/30 (63%)	46% - 81%

a: Global response of "complete response" or "partial response" at the end of treatment, as determined by the Data Review Committee.

b: Subjects with infection from 2 primary pathogen groups appear in each primary pathogen group as appropriate.

Most of the responses for *Aspergillus* (38/45), the primary efficacy variable, represented a clinically meaningful improvement (partial response) in the subject's condition, and a small proportion (7/45) represented complete resolution of all evidence of disease. Most nonresponses (39/62) were true failures, and had evidence of further deterioration of condition. The most common identified pathogen was *A fumigatus*, followed by *A flavus* and *A terreus*; positive global responses were recorded for 41.4%, 52.6%, and 28.6% of these infections, respectively.

Safety: Treatment-emergent adverse events (TEAEs) were reported for 98% of subjects, and treatment-related TEAEs (considered by the investigator to be at least possibly related to treatment) were reported for 42% of subjects. Subjects with a history of bone marrow transplant tended to have a greater occurrence of any individual TEAE than subjects without such history, but this might be expected in a generally sicker, more medically fragile population. The display below shows occurrences of some of the more common treatment-related TEAEs and corresponding occurrences for all TEAEs. Although fever was the most commonly reported TEAE overall (39%), it was considered treatment related in only 1% of subjects.

Occurrences of the More Common Treatment-Related TEAEs and Corresponding Occurrences for All TEAEs

Adverse Events	Treatment-Related TEAEs (n = 330)	All TEAEs (n = 330)
Nausea	31 (9)	105 (32)
Vomiting	19 (6)	91 (28)
Abdominal pain	16 (5)	67 (20)
Headache	15 (5)	95 (29)
Diarrhea	11 (3)	99 (30)
SGPT increased	11 (3)	25 (8)
Rash	9 (3)	50 (15)
SGOT increased	9 (3)	18 (5)
Anorexia	8 (2)	59 (18)

Gastrointestinal disturbances and mild increases in SGOT and SGPT as reported by investigators were considered the most likely adverse events caused by posaconazole. Severe or life-threatening TEAEs were infrequent, especially so when considering treatment-related TEAEs. Rare events that were likely associated with posaconazole therapy were increases in concentration of coadministered drugs that are metabolized through the CYP3A4 enzyme system (eg, cyclosporine, tacrolimus).

Serious adverse events occurred in 74% of the subjects, and were characterized by events typical of severely ill subjects with infection and significant underlying conditions, eg, fever (21%), respiratory insufficiency (12%), dyspnea (11%), hypotension (8%), diarrhea (7%). The profile of adverse events associated with discontinuation or death was similar to that of serious adverse events, but with decreased occurrences.

Occurrences of adverse events were evaluated over time and by baseline subject characteristics of sex, age, and race. There was no evidence that adverse events increased in frequency or severity over time, or of the late appearance of previously unreported adverse events with long-term treatment. There was no indication that the adverse event profiles were different among pediatric and adult, including geriatric, subjects, between male and female subjects, or between Caucasian and nonCaucasian subjects. Pharmacokinetic profiles were roughly similar among the groups, suggesting similar exposure to posaconazole.

Detailed evaluation of adverse events and objective data in areas of special interest yielded no evidence of an identifiable adverse effect in the following areas: cardiac (including QTc prolongation or negative inotropy), neurologic, hepatobiliary, hematologic/lymphatic, hypersensitivity, steroidogenesis, visual disturbances, or calcium homeostasis.

Evaluation of measurements of vital signs and body weight and results of laboratory tests, electrocardiograms (ECGs), and neurologic examinations yielded no suggestion of an untoward effect of treatment.

CONCLUSIONS: In this open-label, noncomparative trial, posaconazole was studied as oral salvage therapy in patients with invasive fungal infections that were refractory to standard therapy, or for which no standard therapy existed, or in subjects who were intolerant or likely to be intolerant of standard therapy based on medical history.

Efficacy

Confirming the broad antifungal activity reported in nonclinical in vitro and in vivo studies, the results of this study demonstrated that posaconazole is clinically effective as salvage therapy against a broad range of

invasive fungal infections, from yeasts to moulds. More specifically, the study showed in a relatively large population that favorable clinical efficacy was achieved in patients with infections caused by *Aspergillus*, *Candida*, *Fusarium*, zygomycetes, *Coccidioides*, *Cryptococcus*, and the agents of chromoblastomycosis and mycetoma. In addition, several other organisms, diseases, or groups of organisms, although in a much smaller population, responded positively to therapy, including histoplasmosis, pseudallescheriasis, phaeohyphomycosis, and several less common infections. Thus, posaconazole appears to be effective as salvage therapy in a wide variety of invasive fungal infections.

Safety

Posaconazole was generally well tolerated in this severely ill population. The most common adverse events were related to tolerability and were mostly gastrointestinal in origin (nausea, vomiting, abdominal pain) and headache. There was no specific identifiable difference in effect with regard to age, sex, or race. Long-term administration did not result in a different safety profile from short-term administration. Posaconazole did not appear to be associated with QTc prolongation or negative inotropic effects. Mild transient increases in aminotransferase (transaminase) activities were noted, which rarely required discontinuation of posaconazole. Posaconazole did not cause visual disturbances. No specific adverse effect was identified from detailed evaluation of other types of adverse events of interest, including neurologic events, hematologic/lymphatic events, calcium homeostasis, steroidogenesis, and hypersensitivity. Posaconazole may affect the pharmacokinetics of other drugs that are metabolized through the CYP3A4 enzyme system; thus, the serum levels of the other drugs should be monitored as appropriate.

Date of the Report: 01 MAR 2004