The study listed may include approved and non-approved 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 LIMITED ACCESS PROTOCOL OF POSACONAZOLE (SCH 56592) IN INVASIVE FUNGAL INFECTIONS (P02095)**
Study Centers:	310 centers including 221 centers in the United States that enrolled subjects in the study. In addition, the following countries participated in the study: Argentina, Australia, Austria, Belgium, Brazil, Canada, Colombia, Costa Rica, Denmark, Finland, France, Germany, Greece, Italy, Israel, Jordan, Lebanon, Mexico, Netherlands, Norway, Peru, Poland, Puerto Rico, Romania, Saudi-Arabia, Slovenia, South Africa, Spain, Sweden, Switzerland, and United Kingdom.
Studied Period:	23 APR 2001 to 08 MAR 2007 **Clinical Phase:** 3 B

Objectives: This study is designed to evaluate the safety of posaconazole (POS) under an open-label treatment use study for subjects with invasive fungal infections (IFIs):

a) which are refractory or resistant to standard antifungal therapies, AND
b) for which there are currently no effective therapies, OR
c) with a prior history of serious, severe, or life-threatening toxicities while receiving standard antifungal therapies, OR
d) with pre-existing organ dysfunction which precludes the administration of standard antifungal therapies, OR
e) who require long-term suppressive/maintenance therapy with POS to prevent recurrence of a serious fungal infection, who have been successfully treated with POS in a prior clinical trial (P00041, P00298, or P01893).

A site-specific amendment (S1) had the objective to evaluate the efficacy of POS in the salvage treatment of zygomycosis. -

Methodology: This was an open-label, noncomparative, multi-center treatment use program providing access to qualified physicians to use POS in the treatment of IFIs.

Number of Subjects:

A total of 985 subjects received at least one dose of POS and were included in the clinical trial database. This database was used in this document to report on demographics, adverse events, (AEs), dosing, electrocardiograms (ECGs), etc.

A total of 989 subjects who signed informed consent were considered the denominator for the Global Pharmacovigilance (GPV) database. This database was used in this document to report SAEs, deaths, and pregnancies.

Diagnosis and Criteria for Inclusion: Adults (≥18 years of age) and children (age ≥2 years) of either gender and of any race with proven or probable IFIs were eligible to participate in this trial.

Each subject was to have had:

1. a proven or probable IFI which had failed a reasonable trial of other licensed antifungal agents, either due to progression or lack of improvement of the infection or
2. a proven or probable IFI with a prior history of serious, severe or life-threatening toxicities related to antifungal therapy, or
3. a proven or probable IFI with documented organ dysfunction (such as renal dysfunction defined as serum creatinine >2.5 mg/dL or estimated creatinine clearance <25 mL/minute) which precluded the continued administration of standard antifungal therapy, or
4. a proven or probable, IFI for which there were currently no effective therapies
5. a history of a proven or probable IFI in patients requiring ongoing antifungal therapy as chronic maintenance after initial control of disease with other antifungal agents, but who had become intolerant to licensed azoles. In these cases where long-term parenteral antifungal therapy (eg, amphotericin B or echinocandins) was not considered practical or clinically reasonable by the physician, POS could be considered to be a potential treatment option.
6. patients with debilitating but not immediately life threatening fungal diseases, where significant morbidity could result in disability and where prior antifungal therapy had been unsuccessful (eg, chronic mucocutaneous candidiasis, recurrent oropharyngeal or esophageal candidiasis with dehydration and malnutrition, or cutaneous phaeohyphomycosis and mycetoma).

Amendment S1 had the same inclusion criteria as noted above and in addition, subjects must have had invasive zygomycosis infection meeting one or more of the following criteria:

- Proven or probable zygomycosis which was refractory or resistant to amphotericine B deoxycholate (AMB-D) or lipid formulations of amphotericine B (LFAB) (at least 7 days and up to 14 days of AMB-D or LFAB), either due to disease progression or lack of improvement; OR,
- Proven or probable zygomycosis infection with a prior history of serious, severe, or life threatening toxicities while receiving AMB-D or LFAB; OR,
- Proven or probable zygomycosis infection with documented organ dysfunction (such as renal dysfunction defined as serum creatinine >2.5 mg/dL or estimated creatinine clearance <25 mL/minute) which precluded the continued administration of standard antifungal therapy; OR,
- Pre-existing organ dysfunction which precluded the administration of AMB-D or LFAB.

Test Product, Dose, Mode of Administration: Posaconazole oral suspension (40 mg/mL, administered as follows: for seriously ill subjects, POS was to be initially administered at a dose of 200 mg four times daily (QID) orally/enterally with meals or nutritional supplements, then once stable the regimen was to be changed to 400 mg orally/enterally twice daily (BID). Stable, ambulatory subjects could have been started on 400 mg orally (PO) BID. The sponsor's medical monitor was to provide written instructions for modified dosing regimens for patients weighing less than 34 kg.

Subjects were to be instructed to take the medication with food, preferably with meals if subjects had oral intake. For subjects who were receiving enteral feeding, medication was to be administered QID or BID.

Duration of Treatment: The investigator was to use discretion in determining the appropriate duration of therapy for an individual subject. Duration was to be based on the following:

- Clinical diagnosis of the IFI;
- Causative fungal pathogen;
- Severity of the IFI;
- Severity of the subject's underlying disease;
- Recovery from immune suppression;
- Rapidity of clinical response.

In general, all subjects were to be treated with POS for a minimum of 28 days, or until at least partial clinical response had been achieved. Partial response was defined as significant improvement in the baseline signs and symptoms of infection. For patients with complete clinical response, POS was to be discontinued 7 days after resolution of all signs and symptoms of infection. Patients who required life-long therapy or who were expected to require ≥ 2 years of therapy were to be evaluated at least annually for safety and tolerability, and a narrative update was to be required to provide ongoing treatment use access.

Subjects with Candida infections of the bloodstream, or disseminated/metastatic (deep-organ) or hepatosplenic candidiasis, or endocarditis were to be treated with POS for a minimum of 14 days or for at least 7 days after resolution of symptoms.

For neutropenic subjects, POS was to be administered for at least 14 days after resolution of neutropenia (absolute neutrophil count $\geq$ 500 cells/mm^3) if complete clinical response was obtained.

Maintenance therapy was to be continued for up to 2 years under this protocol; the need for continued therapy for more than 2 years was to be evaluated and the sponsor's project physician was to be contacted to authorize extension of therapy.

Reference Therapy, Dose, Mode of Administration: Not applicable.

Criteria for Evaluation: This trial was to provide access to qualified physicians to use POS in the treatment of IFIs and ongoing safety surveillance in the treatment experience with POS in adult, adolescent, and pediatric patients (2 years of age or older) with IFIs.

Amendment S1 (03 FEB 2006) added a substudy (within P02095) with the objective to evaluate the efficacy of POS in the salvage treatment of zygomycosis.

Statistical Methods: Not applicable.

SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy: Amendment S1 to the protocol (03 FEB 2006) added a substudy within Protocol 2095 to allow evaluation of the efficacy of POS in the salvage treatment of zygomycosis.

Six subjects were enrolled in the Amendment S1 substudy on treatment of zygomycosis. No efficacy conclusions could therefore be derived from the data collected.

Safety:

Subjects were to be started on POS under emergency use guidelines for treatment of life-threatening diseases. Therefore the use of POS consistent with the provisions of this protocol was to be considered treatment use. Data collection was limited but was to fulfill US and local regulatory requirements for safety reporting of an investigational new drug (IND).

After Amendment #3, Case Report Forms (CRFs) were to contain only data for all serious adverse events, as well as entries for nonserious, related and unexpected adverse events. Due to this, safety information regarding serious adverse events, pregnancies, and deaths is provided by the GPV database, as it is more complete for these events.

This study enrolled subjects with complicated underlying medical conditions (ie, subjects with IFIs which were refractory or resistant to standard antifungal therapies, and for which there were currently no effective available therapies). There were a large number of SAEs and deaths reported reflecting the morbidity and mortality expected in this subject population. The most frequently reported SAEs (disease progression, pyrexia, respiratory failure, pneumonia, dyspnoea, multi-organ failure, sepsis, and febrile neutropenia) were expected in this study population, since they are commonly associated with the underlying conditions and treatments.

In the GPV database there were 384 subjects (39%) with SAEs with outcome of death. The majority of deaths that occurred in this study were considered unlikely related to study drug treatment, and were associated with a number of events and disorders including progression of the underlying disease, infectious complications in general, and other AEs that are often observed in this severely ill subject population. Only 22 deaths (2%) resulted from SAEs considered possibly or probably related to POS by the investigator. The sponsor considers many of these events to be more likely related to the underlying (pre-existing) medical conditions, intercurrent infection, or failure to control advanced refractory fungal infection. There were related SAEs with an outcome of death associated with liver failure (n=2) and QT abnormalities (n=1). These SAEs have been previously observed in subjects treated with POS and are described in the POS Company Core Data Sheet and Risk Management Plan. The overall mortality reported in this study is within the expected mortality for the enrolled population.

Of the 989 subjects included in the GPV database, 684 subjects (69%) reported at least one SAE. Of these, 118 subjects (12%) had SAEs that were considered at least possibly related to POS.

In addition, there appears to be no difference in the type or frequency of AEs reported in subjects $\geq$ 65 years of age or $<$18 years of age as compared to other subjects.

Overall, the types and frequencies of AEs reported in this study are consistent with the known safety profile of POS and with the underlying disease states and their treatment.

There was a baseline ECG and at least one post-dose ECG available for 219 subjects. Of these, 217 had data on QT interval. No consistent pattern suggestive of a treatment effect with POS on QT/QTc interval prolongation was identified in the matched ECGs.

CONCLUSIONS:

P02095 was an open-label, multicenter, limited access study in subjects with IFIs. The objective of the study was to provide POS to subjects with IFIs who were refractory or resistant to standard antifungal therapies, had toxicity while receiving standard antifungal therapy, or required long-term suppressive/maintenance therapy with POS to prevent recurrence of serious fungal infection having been previously treated successfully with POS in clinical trial (P00041, P00298, or P01893).

Current treatments are only 50%-70% effective. Subjects were not solicited for this trial. Investigators contacted the sponsor to request POS for their patients. There was significant demand for enrollment during the years of the study (2001-2007) indicating a significant medical need for new antifungal treatments. The demand in this trial was a global one with approximately 300 participating sites worldwide.

Although this protocol was designed initially to evaluate clinical response, efficacy evaluation was eliminated in Amendment #1 and it became a limited-access trial with only safety information to be collected and evaluated. The focus had to be on responding to this need for POS rather than efficacy data generation. The study-related procedures and the required data collection parameters were further modified in Amendments #2 and #3.

As a result of the medical need for new antifungal therapy, subjects enrolled in this study had severe and complicated diseases for which other treatment options had been exhausted.

Using data from the 989 subjects in the GPV database, 384 deaths were reported for an overall mortality rate of 39%. This mortality rate is similar to that reported for other studies of refractory IFIs. Marr, et al reported a 3-month mortality of approximately 60% in patients treated with voriconazole for refractory invasive aspergillosis.[1] Fukuda, et al reported a 1-year survival of 32% after diagnosis of mold infections.[2] A mortality rate of 50% in patients with aspergillosis refractory or intolerant to amphotericin treated with caspofungin in a compassionate use study was noted by Kartsonis, et al.[3] Thus, the mortality rate for POS of 39%, in this limited-access protocol is similar to that reported for other drugs treating a similar patient population. In addition, in a study of refractory or intolerant patients with IFIs performed by the sponsor (P00041), 35% died during POS treatment or within 30 days after the last dose of POS,[4] further confirming the consistency of these results.

The following conclusions can be derived form this study:

- Conclusion 1: posaconazole is generally safe and well tolerated in subjects with invasive fungal infections.
- Conclusion 2: overall, the types and frequencies of SAEs/AEs reported in this study are consistent with the known safety profile of posaconazole and with the underlying disease states and their treatment.
- Conclusion 3: there appears to be no difference in the incidence and type of SAEs/AEs reported in the different age groups.

Date of the Report: 04 FEB 2008

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