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Title of Report: Data Review Committee Procedures and Analysis for the Comparison of Data From P00041 and P02387 (Report P02952)
P00041: Open-Label, Treatment Protocol for the Safety and Efficacy of Posaconazole (SCH 56592) in the Treatment of Invasive Fungal Infections
P02387: A Retrospective Study to Establish a Historic Database on the Efficacy of Standard Antifungal Therapy in Patients With Invasive Fungal Infection

Studied Period: 11 FEB 1999 to 12 JUN 2002 for data collection
20 APR 2002 to 16 JUN 2003 for adjudication by the Data Review Committee

Clinical Phase: 3

Objective(s): The objective of this report is to compare the efficacy of the posaconazole-treated group of subjects (from study P00041) with the control group of subjects (from study P02387) treated with any standard salvage regimen. The comparison will be based on the global response at the End of Treatment as determined by the Data Review Committee (DRC) and survival. The efficacy of posaconazole will be primarily demonstrated in subjects who either had refractory infections or are intolerant of other antifungal therapies and who had proven or probable infection due to *Aspergillus*. The primary efficacy comparison (posaconazole vs other antifungal therapies) in subjects with aspergillosis will be based on a logistic regression which controls for key prognostic factors and other baseline/disease characteristics that have the potential to influence treatment outcome. The efficacy of posaconazole in other less common pathogens (including *Fusarium*, Zygomycetes, agents of chromoblastomycosis, mycetoma, or phaeohyphomycosis, *Coccidioides*, *Candida*, *Cryptococcus*, *Pseudallescheria*, and *Histoplasma*) will be based on a detailed clinical description with comparisons to the control group where the numbers and kinds of subjects are similar, and with literature reference where they are not similar or sufficient.

Methodology: Clinical, mycological, and radiological data recorded by investigators from subjects who were treated with posaconazole in the open-label study P00041 were compared with similar data collected in an external control study P02387 from patients treated with other salvage antifungal therapies from mostly the same study centers and similar time periods as for P00041. The radiologic study films were blinded (for treatment and protocol) and reviewed by one or, as a consistency measure in 30% of the subjects, two of the DRC radiologists, who prepared a CAMR™ report and selected representative snapshots to be presented to DRC clinical members for review. The blinded study data for each subject was reviewed by a DRC working group consisting of three or two DRC clinical reviewers; two-member groups were used only after every effort to convene three-member groups had been exhausted. The DRC assessed the eligibility of each subject for inclusion into the Modified Intent-to-Treat (MITT) subset by reviewing baseline study data, without access to postbaseline data. Additionally, the DRC selected a primary diagnosis by specifying the infecting pathogen(s). After assessment of the eligibility of the subject, the DRC assessed clinical outcome at Months 1, 3, and 6 and at End of Treatment based on full (baseline and postbaseline) data up to 7 days after the first of any of the following events: 365 days after the start of salvage therapy, the last dose, or the last dose before the first interruption in dosing of at least 14 days. When applicable, the DRC assessed the death status. Adjudication among reviewers within a working group was required for major discrepancies in predetermined key data points necessary for the eligibility assessment at Baseline or the global response assessments at Month 1 for *Candida* and at Month 3, Month 6, and End of Therapy for all pathogens. The assessments of the reviewers for each variable were combined into one assessment by applying majority-rules algorithms.

Number of Subjects: In the Intent-to-Treat (ITT) subset (subjects who received at least one dose of salvage therapy) there were 330 posaconazole-treated subjects and 279 control subjects. In the MITT subset (proven or probable and refractory or intolerant as outlined in the next section) there were 238 posaconazole-treated subjects and 218 control subjects. For the primary efficacy analysis, there were 107 posaconazole-treated subjects and 86 control subjects in the MITT subset who were infected with *Aspergillus*.

Diagnosis and Criteria for Inclusion: Subjects eligible for the MITT subset were those classified by the DRC as having proven or probable invasive fungal infection (IFI) according to the MSG/EORTC criteria in which the infection was refractory to and/or the subject was considered intolerant of, or at high risk of developing intolerance to standard antifungal therapy. The primary analysis was performed on subjects in the MITT subset who were infected with *Aspergillus* as predetermined in the Statistical Data Analysis Plan. Given the smaller sample sizes for pathogen groups other than *Aspergillus*, the comparison was based on the clinical features of the cases since the smaller number precluded a meaningful statistical analysis. Where relevant, subjects with proven or probable infections that did not meet the criteria for refractory or intolerance (thus excluded from the MITT subset) were included in the discussion of the less common organisms to provide as complete an experience with posaconazole therapy as possible for the treatment of these organisms.

Duration of Treatment: The maximum limit of observation for data analysis extended to Day 372; if the treatment duration went beyond Day 372, only the data up to Day 372 was considered.

Test Product, Dose, Mode of Administration: Posaconazole 800 mg daily in divided oral doses in the open-label posaconazole study P00041.

Reference Therapy: Other antifungal drugs in the external control study P02387.

Criteria for Evaluation: The subject's eligibility (proven/probable IFI status and refractory/intolerant status) at Baseline and outcome (global response and, when applicable, death status) at Months 1, 3, and 6 and at the End of Treatment were assessed by the DRC based on the following components of study data: (1) clinical signs and symptoms attributable to IFI noted on physical examinations performed by the principal investigators; (2) radiographic assessments (reviewed by expert radiologists when available or based on official site reports); and (3) mycologic test results (cultures, serologic testing, or histopathology/cytopathology). The study data were blinded as to contributing study (P00041 or P02387) and study treatment (posaconazole or the control regimens, respectively). The eligibility and outcome assessments were done in two sequential steps: (1) baseline study data were presented to the DRC members for evaluation of eligibility; (2) after indicating that an assessment of eligibility had been made, the DRC members were provided with postbaseline data for the assessment of outcome.

Statistical Methods: The subject's global response status at the End of Treatment as assessed by the DRC is the primary efficacy endpoint. The global response was categorized into Complete Response, Partial Response, Stable Disease, Failure, or Unable to Determine. Each subject was determined to be either a responder (with Complete Response or Partial Response) or a nonresponder (with Stable Disease, Failure, or Unable to Determine) at Months 1, 3, and 6, and at the End of Treatment. Subjects were grouped by their infecting pathogen, determined by the DRC, into the following eight (8) Primary Pathogen groups: *Aspergillus*, *Fusarium*, Zygomycetes, Chromoblastomycosis/ Mycetoma, *Coccidioides*, *Candida*, *Cryptococcus*, and Other Fungi. Subjects infected with two Primary Pathogens were included in both groups. The primary efficacy endpoint is the global response (as assessed by the DRC) at End of Treatment. The primary analysis dataset is the subset of subjects from MITT with *Aspergillus* as a Primary Pathogen. The primary efficacy comparison between posaconazole and control is based on the odds ratio resulting from a logistic regression model adjusting for key and other prognostic factors. The key prognostic indicators used as covariates were site of infection, enrollment status (ie, refractory status and intolerant status), baseline neutropenia ($ANC < 500/mm^3$), duration of prior effective antifungal therapy, age, and geographic region. Additionally, any of the following other prognostic factors that showed a significant ($p < 0.10$) imbalance in their baseline distribution were included in the model: sex, race, body weight, time of enrollment, BMT, solid organ transplant, hematologic malignancy, nonhematologic malignancy, nonmalignant hematologic disorder, immunocompromised - acquired, immunocompromised - congenital, renal disease, hepatic disease, prior corticosteroid use, and concomitant corticosteroid use. A significance level of 0.05 (two-sided) was used to compare the odds ratio of treatments based on this model.

SUMMARY - CONCLUSIONS:**RESULTS:**

Potential sources of bias when comparing treatments outside the confines of a randomized, controlled study were evaluated by the sponsor and certain measures were implemented during the design of the control study. To reduce potential differences in standards of care between sites and time periods, an external control design was chosen rather than an historical control. In an external control, data is gathered retrospectively from the same sites as the original study over the same time period, thus providing a contemporaneous control group that is less likely to have as many significant differences from the treatment group as an historical control would. To reduce selection bias, P02387 employed a broad screening process with inclusion criteria common to P00041. To permit statistical adjustments for potential effects due to differences in the treatment groups, the same important prognostic variables and fungal disease and treatment characteristics as in P00041 were recorded. Finally, to ensure that the eligibility and outcome were based on similar information for cases in both treatment groups, the sponsor took the additional step to convene an external DRC to review the data from both studies in a simultaneous, blinded fashion and to assess the eligibility and outcome of each subject.

Baseline Characteristics: For each of the primary pathogen groups, the control group (from P02387) was generally well matched to the posaconazole-treated group (from P00041). Additionally, both groups were comprised of subjects who had typical baseline characteristics and disease manifestation of the particular infection as described in the literature.

Aspergillus: The subjects in the MITT subset with *Aspergillus* as a primary pathogen were well matched between the posaconazole-treated and control groups. Specifically most subjects had hematologic malignancies (79/107, or 74%, for posaconazole and 70/86, or 81%, for the control), with about half of those requiring BMT as therapy prior to Baseline (48/79 and 34/70, respectively). Most subjects in both studies had refractory pulmonary disease (61% and 58%, respectively), and most subjects had received amphotericin B formulations as the mainstay of therapy prior to enrollment into either treatment group (92% and 93%, respectively). Additionally, the distributions with regard to age, sex, and race were similar. The majority of subjects in both studies were enrolled from sites in the USA (88% and 79%, respectively). The groups were imbalanced with regard to a history of renal and hepatic dysfunction, with relatively more subjects in the posaconazole-treated group appearing to have underlying renal dysfunction (64% and 24%, respectively) or hepatic dysfunction (40% and 7%, respectively). Medications with potential to influence immune function (immunosuppressives or growth factors) were administered to a similar proportion of subjects in each study. A relatively smaller proportion of posaconazole-treated subjects had neutropenia at Baseline (20% and 30%, respectively) and a slightly greater percentage had a history of BMT (51% and 44%, respectively) compared with the control group.

Fusarium: There are 18 subjects in the posaconazole-treated MITT group and four (4) in the control. Most (13/18) of the posaconazole-treated group had hematologic malignancies. About one third had neutropenia (ANC < 500/mm³) at Baseline and one third had a history of BMT, half of whom had evidence of GVHD. Half (9/18) of the posaconazole-treated subjects had disseminated disease. The majority (14/18) had refractory disease (with or without intolerance) which had been initially treated with amphotericin B (including liposomal formulations) for a median duration of 9 days. There were only four (4) control subjects so their baseline characteristics are not described since a meaningful comparison cannot be made.

Zygomycetes: There are 11 subjects in the posaconazole-treated MITT group and eight (8) in the control. In the posaconazole-treated group, 8/11 subjects had malignancies while only 3/8 in the control group had malignancies. In contrast, the control group had 5/8 subjects with diabetes while only 2/11 in the posaconazole-treated group had diabetes. There was a greater proportion of disseminated infections in the posaconazole-treated group (3/11 vs 0/8) while more of the control group had refractory infections (7/8 vs 6/11). A greater proportion of the posaconazole-treated group had received corticosteroids, immunosuppressive therapy, or growth factors than the control group. Overall, the posaconazole-treated group appeared to have a worse prognosis than the control group.

Chromoblastomycosis/mycetoma: There are 11 subjects in the posaconazole-treated MITT group and two (2) in the control. The posaconazole-treated group was a cohort of mostly middle-aged Hispanic men without significant underlying medical conditions who were treated in Latin America for these refractory IFIs of the skin and subcutaneous tissue. Previous antifungal treatments included azoles for all subjects, with treatment periods of several months to several years, and additional antifungal agents for six (6) of the subjects. There were only two (2) control subjects so their baseline characteristics are not described since no meaningful comparison could be made.

Coccidioides: There are 16 subjects in the posaconazole-treated MITT group and seven (7) in the control. At least one half of the (8/16 for posaconazole and 4/7 for control) subjects had no underlying medical conditions that would predispose to the development of invasive coccidioidomycosis. Half (8/16) of the posaconazole-treated subjects had pulmonary infections and one fourth (4/16) had disseminated infections. In the control group, most (6/7) of the infections were localized pulmonary infections. The infection was judged to be refractory to standard therapy in 15/16 (94%) posaconazole-treated subjects who had been initially treated with antifungal therapy for a median of 306 days. In the control group, three (3) subjects were enrolled as a result of refractory infections.

Candida: There are 23 subjects in the posaconazole-treated MITT group and 30 in the control. Approximately half of the subjects in each treatment group had a history of hematologic malignancy with more subjects in the control group requiring BMT prior to Baseline. The posaconazole-treated group had relatively more HIV-infected subjects than the control group whereas the control group had relatively more subjects with diabetes. Extrapulmonary infections, with or without dissemination, were the most common sites of infection in the posaconazole-treated group. More subjects with candidemia were enrolled in the control group than the posaconazole-treated group. Most, 19/23 (83%), of the posaconazole-treated subjects and 23/30 (77%) of the control subjects had refractory disease with prior antifungal therapy (amphotericin B or an azole) administered for a median of 30 and 10 days, respectively.

Cryptococcus: There are 31 subjects in the posaconazole-treated MITT subgroup and 64 in the control. The subjects were mainly relatively young Asian or Hispanic men, from outside the USA, with HIV infection who were being treated for cryptococcal meningitis. Most, 28/31 (90%), of the posaconazole-treated group and 47/64 (73%) of the control group had refractory disease (with or without intolerance) of which 27 in the posaconazole-treated group had been initially treated with antifungal therapy (mostly amphotericin B and fluconazole) for a median of 27 days versus 15 days for the control group.

Other Fungi: There are 30 subjects in the posaconazole-treated MITT group and 20 in the control. The distribution of characteristics reflects the wide range of pathogens and types of infections included in this category. Half (15/30) of the posaconazole-treated subjects and one fifth (4/20) of the control subjects had hematologic malignancies. Most of the infections were refractory (27/30 for posaconazole and 16/20 for control).

Efficacy:

Aspergillus: As shown in the table below, in the MITT subset, based on a statistical model, described in the statistical methods section, designed to account for imbalances between the treatment groups, posaconazole treatment was significantly better than the control regimens, which consisted mostly of amphotericin B (lipid formulations) with or without other drugs including itraconazole or echinocandins ($p = 0.006$).

Primary Efficacy and Unadjusted Efficacy Analysis of the Global Response at End of Treatment for Subjects Infected With *Aspergillus*: Modified Intent-to-Treat Subset

ASPERGILLUS	Posaconazole (P00041)			Control (P02387)		
	Total N	Responders n	(%)	Total N	Responders n	(%)
Analysis						
ALL SUBJECTS HAVING ASPERGILLUS AS A PRIMARY PATHOGEN	107	45	(42.1)	86	22	(25.6)
Treatment Versus Control	Estimated Odds Ratio		95% CI for the Odds Ratio	P Value		
Primary Efficacy Analysis ^a	4.06		(1.5, 11.04)	0.006		
Unadjusted Efficacy Analysis ^b	2.11		(1.14, 3.92)	0.018		

a: Treatment versus control comparison was performed using logistic regression with the following key factors of site of infection, enrollment reason (split into refractory status and intolerant status), baseline neutropenia, duration of prior effective antifungal therapy, age, and study center location (USA or non USA), and other covariates of race, time interval of enrollment, nonmalignant hematologic disorder, renal disease, and hepatic disease.

b: Treatment versus control comparison was performed using logistic regression without adjustment for covariates.

This table presents Modified Intent-to-Treat subjects infected with *Aspergillus* alone or, in seven posaconazole-treated subjects and three control subjects, concurrently with another primary pathogen.

CI = Confidence interval.

N = Number of subjects from the Modified Intent-to-Treat subset.

Responders = Subjects with a Data Review Committee-adjudicated global response of Complete Response or Partial Response.

Kaplan-Meier survival curves show a survival benefit for posaconazole relative to the external control which was apparent after 30 days of treatment and which lasted throughout the 372-day study period. The two Kaplan-Meier survival curves were significantly different ($p = 0.0003$) based on a log rank statistic. In the MITT subset, 13 (12.1%) of the posaconazole-treated subjects and 5 (5.8%) of the control subject had global responses of Unable to Determine which means that most of the nonresponders were not due to an inability to assess, making the analysis more compelling. The treatment advantage for posaconazole was maintained for most subgroups examined including baseline neutropenia, allogeneic BMT, refractory disease (as reason for enrollment), hematologic malignancy, and immunosuppressive therapy. Of particular note, when the subjects are divided into predetermined poor outcome risk categories (low, medium, high) based on these baseline characteristics, the treatment effect is preserved, suggesting that treatment with posaconazole is effective regardless of underlying disease. When the species of *Aspergillus* are considered, posaconazole therapy resulted in positive outcomes for organisms that are becoming more common and are relatively refractory to amphotericin B, for example, *A terreus* (28.6%) and *A flavus* (52.6%). Outcome differences were not influenced by age, sex, race, baseline weight, region of enrollment, and time period of enrollment. By the end of 12 months, the survivors were essentially the responders: 79.0% (49/62) of the posaconazole-treated subjects and 82.8% (53/64) control subjects who were nonresponders died whereas only 15.6% (7/45) of the posaconazole-treated subjects and 18.2% (4/22) of the control subjects who were responders died.

Pathogen Groups Other Than *Aspergillus*: For pathogen groups other than *Aspergillus*, the global responses at the End of Treatment in subjects with proven or probable IFI are summarized below. For each primary pathogen, the inclusion of subjects with proven or probable IFI who did not meet the refractory/intolerant criteria to be eligible for the MITT subset resulted in a treatment difference that was similar to that seen for the MITT subset. The additional subjects were included to provide as much clinical experience as practicable for the less common pathogens, some of which are rare. Overall, the subject populations were generally typical of those described in the literature for the infections treated.

Positive Global Response ^a at the End of Treatment for Pathogen Groups Other Than <i>Aspergillus</i> : Subjects With Proven or Probable IFI According to the DRC				
Primary Pathogen Group	MITT Subset		ITT Subset	
	Posaconazole	Control	Posaconazole	Control
<i>Fusarium</i>	38.9% (7/18)	50.0% (2/4)	45.8% (11/24)	50.0% (3/6)
Zygomycetes	54.5% (6/11)	50.0% (4/8)	53.8% (7/13)	50.0% (5/10)
Chromoblasto-mycosis/Mycetoma	81.8% (9/11)	0.0% (0/2)	81.8% (9/11)	0.0% (0/2)
<i>Coccidioides</i>	68.8% (11/16)	42.9% (3/7)	63.2% (12/19)	42.9% (3/7)
<i>Candida</i>	47.8% (11/23)	53.3% (16/30)	45.8% (12/28)	46.9% (23/49)
<i>Cryptococcus</i>	48.4% (15/31)	57.8% (37/64)	48.9% (22/45)	56.3% (45/80)
Other Fungi	63.3% (19/30)	60.0% (12/20)	69.4% (25/36)	65.4% (17/26)

a: Positive global response comprises Complete Response and Partial Response according to the DRC.
DRC = Data Review Committee; IFI = invasive fungal infection.

***Fusarium*:** For an infection with an extremely high expected mortality rate (70% or higher), especially devastating in the immunocompromised host, posaconazole produced a clinically meaningful response when compared with that of other agents in the setting of salvage therapy. As expected, subjects with neutropenia or a history of BMT at baseline did less well than other subjects. Response to posaconazole seemed not to be affected by administration of cancer chemotherapy, systemic corticosteroids, or growth factors. Of particular importance is that this result was achieved with an oral drug in severely ill subjects, after they had failed to respond to an IV regimen.

Zygomycetes: Zygomycosis also has a high expected mortality rate (>70%) in some settings, with the only apparently effective therapy being high-dose, intravenously administered, amphotericin B, and radical surgery. The response rate of 54.5% (50% in subjects with hematologic malignancy) with posaconazole is very promising, given that the drug is administered orally, largely to subjects that had failed previous IV therapy. Subjects with a history of allogeneic BMT tended to fare less well than others, but both subjects with diabetes responded; no other factor seemed to affect response. Thus, posaconazole is the first azole to have demonstrated in vitro and in vivo nonclinical activity against Zygomycetes that has translated into apparent clinical utility. Posaconazole should provide an oral alternative for treatment of this infection.

Chromoblastomycosis/Mycetoma: Complete or partial response to posaconazole was noted for 5/6 cases of chromoblastomycosis and 4/5 cases of mycetoma. Disease was stable in one (1) case each of chromoblastomycosis and mycetoma, which may have clinical significance for these generally deep-seated, progressive infections, all of which had failed to respond previously to other azoles and treatments such as flucytosine and terbinafine.

***Coccidioides*:** This "re-emerging" infection is of increased concern because of the ease of travel to and from areas where infection is endemic, and because subjects immunosuppressed as a result of underlying disease or treatment are often at increased risk of severe, disseminated infection. The high proportion of subjects with a successful response to posaconazole reflects the positive in vivo and in vitro nonclinical results, and is consistent with published literature of other experiences in the treatment of disease that had not already failed previous therapy. The response for the control subjects was 42.9% in mostly (6/7) pulmonary infections. By comparison, posaconazole was successful in 100.0% (4/4) of the subjects with disseminated disease and in 62.5% (5/8) of the subjects with pulmonary disease. The one (1) posaconazole-treated subject with a CNS infection had a positive outcome. Response was not affected by subject characteristics, including, apparently, race, even though Blacks are known to have a poorer prognosis. Based on these data, posaconazole should be considered as a treatment option for refractory coccidioidomycosis.

***Candida*:** *Candida* infections are some of the most commonly encountered fungal infections in clinical practice, with many available treatment options. However, the availability of these drugs has resulted in the development of resistant organisms, which limits the treatment options for many patients. Of note, 4/5 subjects with *C. krusei* infection, often resistant to other azoles, responded to posaconazole. In addition, 5/7 of the HIV-infected subjects (mostly with esophageal candidiasis) responded to posaconazole. For those subjects with

candidemia, the outcome was similar for posaconazole and the control—57.1% versus 54.5%.

Cryptococcus: The positive outcome with posaconazole (48.4%) in this infection is encouraging in that almost all of the subjects had cryptococcal meningitis and had failed previous therapy. Overall, the results suggest that posaconazole has clinical utility for patients with this infection, who have limited therapeutic options when first-line therapy fails.

Other Fungi: Global responses at the End of Treatment for subgroups of pathogens in the Other Fungi group are summarized below for the ITT subset of subjects with proven or probable IFI to provide as much clinical experience as possible for these pathogens, some of which are rare. In this group, 3/7 subjects with *Pseudallescheria boydii* infection, generally refractory to amphotericin B, had successful outcomes. Among the successful histoplasmosis cases was a *Histoplasma* meningitis, and among the successful phaeohyphomycosis cases was a cerebral infection with *Ramichloridium mackenziei*. Additional organisms that were treated successfully were *Trichosporon beigelii* and *T. asahii*, *Acremonium* spp, and *Paecilomyces lilacinus*. These results demonstrate the broad spectrum of activity of posaconazole.

Culture-identified Organism	N	Posaconazole	
		n	(%)
<i>Pseudallescheria boydii</i>	7	3	(42.9)
<i>Histoplasma capsulatum</i>	7	7	(100.0)
Phaeohyphomycetes	5	4	(80.0)
Other Organisms	17	11	(64.7)

CONCLUSIONS: The data, generated from the comparison of the posaconazole-treated group with the external control group and literature where relevant, is sufficiently robust and convincing to show that posaconazole is effective for the treatment of invasive fungal infections under the following circumstances: Infections that are either refractory to standard therapy or where no standard therapy exists, or where the patient has developed intolerance to those therapies or is at high risk of intolerance based on medical history and are caused by *Aspergillus*, *Fusarium*, Zygomycetes, the agents of chromoblastomycosis and mycetoma, *Coccidioides*, *Candida*, and *Cryptococcus*. In addition, for the other organisms studied in somewhat smaller numbers, which included *Pseudallescheria*, *Histoplasma*, Phaeohyphomycetes, and several others, the clinical response to posaconazole therapy was favorable in the majority of cases.

Date of the Report: 19 MAR 2004