This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2.0 SYNOPSIS

SCHERING-PLOUGH RESEARCH INSTITUTE, A DIVISION OF SCHERING CORPORATION, A SUBSIDIARY OF MERCK & CO., INC.
MK-5592 (SCH 56592)
Posaconazole, IV Solution
Fungal infection

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: An Evaluation of the Safety and Pharmacokinetics of Posaconazole (POS, SCH 56592) IV Solution via Peripheral Administration in Healthy Volunteers #P06356

INVESTIGATOR/STUDY CENTER: [redacted] The Netherlands

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: 07-Sep-2010 through 16-May-2011. The frozen file date was 17-Oct-2011.

CLINICAL PHASE: 4

DURATION OF TREATMENT: In Part 1 (rising single-dose [RSD] study), subjects from 6 cohorts received a peripheral intravenous (IV) infusion on Day 1 (1-day treatment). In Part 2 (rising multiple-dose [RMD] study), subjects from 4 cohorts were to receive 2 peripheral infusions 12 hours apart on Day 1 followed by 1 daily infusion in the morning on Days 2 through 10 (10-day treatment). Due to unacceptably high rates of thrombophlebitis, the multiple-dose (MD) component of this study was discontinued. The duration of the study was approximately 9 months.

OBJECTIVES:

Primary Objective: To evaluate safety and tolerability of posaconazole IV solution as single and multiple doses via peripheral infusion.

Secondary Objective: To obtain pharmacokinetic and metabolite profiles of posaconazole IV solution.

[redacted]

STUDY STATUS: Due to cases of thrombophlebitis in Part 2, the MD component of this study was discontinued and the single-dose (SD) component of the study was amended to test the 250 mg and 300 mg dose levels, instead of the 300 mg and 400 mg dose levels. In addition, to minimize the risk of thrombophlebitis, it was determined that after completion of the 30-minute SD infusion, the infusion site should be immediately flushed with 20 mL of 5% dextrose for injection (D5W) by IV push.

STUDY DESIGN: This was a randomized, 2-part, third-party blind, placebo-controlled, rising single and MD study, performed at a single site to evaluate the safety, tolerability, and pharmacokinetics of posaconazole IV solution in healthy volunteers 18 to 65 years of age. To qualify for randomization, subjects were evaluated during the 21-day screening period to ensure they met all of the inclusion and none of the exclusion criteria.

Part 1 (RSD): Subjects were admitted to the study center at approximately 20:00 on Day -2 for baseline assessments to confirm their eligibility. Subjects were required to fast overnight on Days -2 and -1 starting at approximately 22:00. Subjects were randomized in the morning of Day 1 after confirming their inclusion/exclusion criteria, and then received their IV infusion. A total of 72 subjects were randomized in 1 of the 6 cohorts of 12 subjects each (9 active and 3 placebo) and received a peripheral IV solution with vehicle IV solution (without posaconazole, Cohort 1 only) or posaconazole IV solution (Cohorts 2 - 6) or placebo (D5W). The dosing range of posaconazole was 0 (vehicle IV solution only), 50, 100, 200, 250, and 300 mg. Each cohort was divided into 3 subgroups of 4 subjects, and subjects received their single dose a minimum of 1 day apart. In each subgroup, 3 subjects received the vehicle IV solution (Cohort 1 only) or posaconazole IV solution (Cohorts 2 - 6) and 1 subject received the placebo (D5W).

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Part 2 (RMD): Subjects were to be admitted to the study center at approximately 20:00 on Day -3 for baseline assessments to confirm their eligibility. Subjects were to fast overnight on Days -2 and -1 starting at approximately 22:00. Subjects were to be randomized in the morning of Day 1 after confirming their inclusion/exclusion criteria, and then were to receive their first peripheral IV infusion. A total of 48 subjects were to be randomized in 1 of the 4 cohorts of 12 subjects each (9 active and 3 placebo) and were to receive 2 peripheral infusions 12 hours apart on Day 1 followed by 1 daily infusion in the morning of Days 2 through 10. Subjects were to receive peripheral IV infusion with vehicle IV solution (without posaconazole, Cohort 7 only), or posaconazole IV solution (Cohorts 8 - 10) or placebo (D5W). The dosing range of posaconazole was to be 0 (vehicle IV solution only), 100, 200, and 300 mg. Each cohort was to be divided into 3 subgroups of 4 subjects and was to receive their first dose a minimum of 2 days apart. In each subgroup, 3 subjects were to receive the vehicle IV solution (Cohort 7 only) or posaconazole IV solution (Cohorts 8 - 10) and 1 subject was to receive the placebo (D5W). Due to adverse events (AEs) at the infusion site following multiple dosing, Part 2 was prematurely terminated following the initial 100 mg infusions. The actual number of subjects enrolled in Part 2 was 18.

SUBJECT/PATIENT DISPOSITION: In Part 1, 72 subjects were enrolled (Cohorts 1 – 6), randomized to treatment, and completed the study. In Part 2, 18 subjects were enrolled (Cohorts 7 - 8) and randomized to treatment, while 10 subjects (Cohort 7) completed the study. For Cohort 8 in Part 2, 4 subjects were discontinued from the study due to infusion site AEs and 4 subjects discontinued when Part 2 was terminated with Protocol Amendment 2 [16.1.1.5].

DOSAGE/FORMULATION NOS.: In Part 1 (RSD), 6 cohorts of 12 subjects received a peripheral IV infusion with vehicle IV solution (without posaconazole, Cohort 1 only) or posaconazole IV solution (50, 100, 200, 250, and 300 mg, Cohorts 2 - 6) or placebo (D5W, all cohorts). In Part 2 (RMD), 4 cohorts of 12 subjects were to receive multiple peripheral IV infusions with vehicle IV solution (without posaconazole, Cohort 7 only) or posaconazole IV solution (100, 200 and 300 mg, Cohorts 8 - 10) or placebo (D5W, all cohorts).

Drug	Potency	Formulation No.	Dosage Form	Control No.
Posaconazole	18 mg/mL	[redacted]	IV solution	NA
Captisol® solution (vehicle IV solution)†	N/A		IV solution	
Placebo (D5W)	N/A		IV solution	NA

†Captisol® solution (a product of Ligand) was purchased by the Investigator.

DIAGNOSIS/INCLUSION CRITERIA: Healthy adult male and female subjects, 18 to 65 years of age, were enrolled in this study.

EVALUATION CRITERIA:

Safety: Clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms (ECGs), ejection fracture measurements from echocardiography, and physical examinations were performed for safety monitoring in Parts 1 and 2. Adverse events were collected and infusion site reactions were monitored using a semi-quantitative scoring scale to grade short peripheral catheter thrombophlebitis (SPCT) severity during each part of the study. [redacted]

Pharmacokinetics:

Part 1 (RSD): Blood samples for pharmacokinetic evaluation of posaconazole in plasma were collected for each cohort at specified time points over 168 hours post Day 1 infusion. Individual posaconazole plasma concentration data per dose group, and actual sampling times, were used to determine the Cmax, tmax, AUC0-last, AUC0-∞, λz, t½, CL, and Vz after SD administration.

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Part 2 (RMD): Blood samples for pharmacokinetic evaluation of posaconazole in plasma were to be collected over 12 hours post Day 1 infusion, and over 168 hours post Day 10 infusion. An additional sample was to be collected at predose on Days 8 and 9 for use in the steady-state analysis (PK samples were not collected from Cohort 7). Individual posaconazole plasma concentration data per dose group, and actual sampling times, were to be used to determine the AUCτ, Cmax, and tmax.
Dose proportionality was to be graphically assessed by visual inspection of dose normalized AUC versus the dose plot. Steady-state was to be graphically assessed by visual inspection of trough values versus Days plot.

STATISTICAL PLANNING AND ANALYSIS: Safety data were summarized by dose group. The pharmacokinetic parameters were summarized by dose group using descriptive statistics.
Part 1 (RSD): To assess dose proportionality, the log-transformed, dose-normalized AUC and Cmax were analyzed using an analysis of variance (ANOVA) model extracting the effect due to dose. Geometric mean ratio (GMR) estimates along with the 90% confidence intervals (CIs) were provided for each dose versus the corresponding lower doses.
In addition, the power-law model was also applied to assess preliminary dose proportionality. The power law model used log-transformed Cmax, AUC0-∞, or AUC0-last as response variables and contained log-transformed dose as covariate. The slope estimates for the model as well as the 90% CIs were calculated. The fold increase along with the 90% CIs for Cmax, AUC0-∞, and AUC0-last were calculated from the lowest dose to the highest dose in the model.
Part 2 (RMD): The primary pharmacokinetic parameter was to be the AUCτ following multiple-dose administration in Part 2. The hypothesis that at least one well-tolerated dose of posaconazole IV solution produces a plasma exposure (AUCτ) of at least 21000 ng·hr/mL was to be tested using the following stepwise procedure. At the highest safe and well-tolerated dose, a two-sided 90% CI for the geometric mean of AUCτ was to be constructed. The hypothesis was to be supported (i.e., the true geometric mean AUCτ exceeds 21000 ng·hr/mL at this dose level) if the lower limit of this 90% CI was greater than 21000 ng·hr/mL. If the hypothesis was supported in the previous step, then the same procedure was to be applied to the next lowest safe and well tolerated dose. The procedure was to continue in this stepwise fashion until the lower limit of the 90% CI at a particular dose failed to exceed 21000 ng·hr/mL (i.e. the true geometric mean AUCτ failed to exceed 21000 ng·hr/mL at this dose level, and all lower doses). For estimation purposes, 90% CIs were also to be constructed for all doses at which the true geometric mean AUCτ failed to exceed 21000 ng·hr/mL.
To assess preliminary dose proportionality in Part 2, the log transformed, dose normalized AUC and Cmax was to be analyzed separately from Part 1 using an ANOVA model extracting the effect due to dose. GMR estimates along with the 90% CIs were to be provided for each dose vs. the corresponding lower doses. For part 2 only, geometric mean and 90% CIs were to be provided for accumulation ratio by dose. In additional, steady-state was to be graphically assessed using Days 8, 9, 10 and 11 trough concentrations for each dose separately.

RESULTS:
Safety: [redacted] decreasing the time of infusion to 30 minutes in this study markedly lowered the rate of thrombophlebitis (as measured with the SPCT scoring scale and reported as infusion site AEs) following SD infusions administered up to the 300 mg dose level. Infusion site reactions were experienced by 2 (22%) of 9 subjects following SD infusion containing only the vehicle solution and by 7 (16%) of 45 subjects following any SD infusion containing active posaconazole in Part 1. These AEs at the infusion site were experienced by 1 subject following the 50 mg dose, 1 subject following the 200 mg dose, 2 subjects following the 250 mg dose, and 3 subjects following the 300 mg dose.

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Additionally, 1 subject experienced infusion site paraesthesia (200 mg).
After MD administration in Part 2, decreasing the time of infusion led to an unacceptably high rate of thrombophlebitis (as measured with the SPCT scoring scale and reported as infusion site AEs). Adverse events at the infusion site (reaction, pain, and thrombophlebitis) were experienced by 1 (25%) of 4 subjects following placebo, 3 (33%) of 9 subjects following only the vehicle solution, and 4 (80%) of 5 subjects following the 100 mg dose. The Investigator discontinued treatment for 4 subjects (1 following placebo, 1 following only the vehicle solution, and 2 following 100 mg) due to the AE of thrombophlebitis. Due to the high incidence of thrombophlebitis after 30-minute MD peripheral infusions of this 100 mg posaconazole formulation, the Sponsor discontinued the MD part of the study (Part 2), and Cohorts 9 and 10 (200 and 300 mg RMD, respectively) were not performed. However, the RSD part (Part 1) was continued to evaluate the safety of this posaconazole IV drug formulation administered peripherally at dose levels beyond 200 mg (i.e., 250 mg and 300 mg).
Excluding the infusion site reactions, there were no significant AEs reported in this study. There were no decreases in ejection fraction (EF) or liver function test abnormalities of clinical concern in this study. Overall, there were no treatment- or dose-related trends in the EF, clinical laboratory, vital sign, or 12-lead electrocardiogram (ECG) findings.

[redacted]

Pharmacokinetics: A summary of mean (coefficient of variation as a percent [CV%]) pharmacokinetic (PK) parameters following single IV doses of 50 - 300 mg on Day 1 in healthy subjects are presented in the table below.

Posaconazole Arithmetic Mean (%CV) Pharmacokinetic Parameters Following IV Single-Dose Administration of 50 - 300 mg Posaconazole to Healthy Volunteers

Dose (mg)	Cohort	n	λz (hr)	t½ (hr)	tmax[a] (hr)	Cmax (ng/mL)	AUC0-last (ng·hr/mL)	AUC0-∞ (ng·hr/mL)	AUC%	Vz (L)	CL (L/hr)
50	2	9	0.0410 (34)	18.7 (34)	0.6 (0.5-0.7)	313 (30)	4620 (31)	4890 (30)	5.95 (62)	294 (39)	10.9 (25)
100	3	9	0.0360 (14)	19.6 (16)	0.5 (0.5-0.5)	1330 (7)	10800 (27)	11200 (26)	4.47 (47)	262 (22)	9.40 (23)
200	4	9	0.0307 (23)	23.6 (23)	0.5 (0.5-24)[b]	2250 (29)	34600 (52)	35400 (50)	2.75 (97)	226 (38)	6.54 (32)
250	5	9	0.0279 (21)	26.0 (23)	0.5 (0.5-0.5)	2260 (26)	40600 (39)	41500 (41)	1.84 (85)	245 (33)	6.68 (29)
300	6	9	0.0292 (20)	24.6 (20)	0.5 (0.5-1.0)	2840 (30)	45500 (26)	46400 (26)	1.74 (46)	236 (17)	6.90 (27)

(a) Median (range); Infusion time = 30 min
(b) One subject had a high concentration at the 24 hr sample; therefore, the tmax is 24 hr for that subject

The mean exposure (AUC0-∞) achieved for posaconazole ranged from 4890 to 46400 ng·hr/mL for single doses of 50 - 300 mg posaconazole IV solution in healthy subjects. Posaconazole was slowly eliminated from the body following administration of single IV doses of 50 - 300 mg posaconazole IV solution. The posaconazole mean apparent terminal half-life (t½) appeared to be longer (range: 23.6 - 26.0 hr) at the higher doses (≥200 mg) compared to the lower doses (range: 18.7 - 19.6 hr). The mean systemic clearance (CL) appeared to be lower at doses equal to and above 200 mg (range: 6.54 - 6.90 L/h) as compared to the lower doses (range: 9.40 - 10.9 L/h).

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The mean apparent volume of distribution (Vz) was lower at doses equal to and above 200 mg (range: 226 - 245 L) as compared to the lower doses (range: 262 - 294 L). The lower doses (50 and 100 mg) only had detectable plasma concentration up to 120 hours after dosing whereas the higher doses had detectable plasma concentrations up to 168 hours. The mean maximal posaconazole concentration (Cmax) following single IV doses of 50, 100, 200, 250, and 300 mg given as a 30-minute infusion ranged from 313 to 2840 ng/mL with moderate variability (CV% range: 26 - 30%).
The slope estimate as well as the 90% CI obtained from power law model to assess the preliminary dose proportionality is presented in the table below. The slope estimates (90% CIs) obtained from the power law model for Cmax, AUC0-last, and AUC0-∞ were 1.159 (1.018, 1.300), 1.328 (1.215, 1.441), and 1.302 (1.191, 1.414), respectively. The results of the dose proportionality assessment showed that a more than dose proportional increase in Cmax, AUC0-last, and AUC0-∞ occurs. Visual inspection shows that this more than dose proportional increase mainly occurs at doses below 200 mg and less at the more clinically relevant doses from 200 - 300 mg.

Dose Proportionality Assessment of Posaconazole Following Intravenous Administration of a Single Dose of Posaconazole Ranging from 50 - 300 mg

		90% CI			Estimate	90% CI	
Parameter	**Slope**	**Lower**	**Upper**	**Dose Range**	**fold increase**	**Lower**	**Upper**
Cmax	1.159	1.018	1.300	50 - 300 mg (6 fold)	7.979	6.197	10.27
AUC0-last	1.328	1.215	1.441		10.80	8.824	13.21
AUC0-∞	1.302	1.191	1.414		10.32	8.452	12.59

RMD: After multiple-dose infusion of the IV solution only 5 subjects were treated with a dose of 100 mg infused over 30 minutes. The mean Cmax (%CV) was 1000 ng/mL (41%) and AUC0-last (%CV) was 34500 ng·hr/mL (33%). Median tmax (range) was 0.50 hours (0.50 - 0.60 hr). The mean t½ was approximately 27 hours. As data are limited, no conclusions can be made on the comparison between single- and multiple-dose administration.

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CONCLUSIONS:

- Peripheral IV administration of the posaconazole solution in single doses up to 300 mg infused over 30 minutes appeared to be generally safe and well tolerated by the healthy males and females in this study. Specifically, thrombophlebitis (as measured by a SPCT scoring scale and reported as infusion site AEs) was experienced by 2 of 9 subjects following only the vehicle solution, and by 7 of 45 subjects following posaconazole. Additionally, 1 subject experienced infusion site paraesthesia.
- Peripheral IV administration of the posaconazole solution in multiple doses of 100 mg infused over 30 minutes was not well tolerated by the healthy males and females in this study as evidenced by the incidence of thrombophlebitis (as measured by an SPCT scoring scale and reported as infusion site AEs): 1 of 4 subjects following placebo, 3 of 9 subjects following only the vehicle solution, and 4 of 5 subjects following the 100 mg dose experienced infusion site reactions and/or thrombophlebitis.
- Following IV administration of a single dose of posaconazole ranging from 50 - 300 mg, a more than dose proportional increase in Cmax, AUC0-last, and AUC0-∞ occurs. Visual inspection shows that this more than dose proportional increase mainly occurs at doses below 200 mg and less at the more clinically relevant doses from 200 - 300 mg.

REPORT DATE: 21-AUG-2012

AMENDED REPORT DATE: 01-MAY-2014