CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205596Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 205-596
Supporting document/s:	1
Applicant's letter date:	September 12, 2013
CDER stamp date:	September 13, 2013
Product:	NOXAFIL® (posaconazole) injection
Clinical formulation	Posaconazole (18 mg/mL), sulfobutylether β-cyclodextrin (SBECD), edetate disodium, hydrochloric acid, sodium hydroxide, and water for injection. Prior to administration drug is to be diluted 10-fold in 5% dextrose in water or sodium chloride 0.9 %
Indication:	Prophylaxis of invasive *Aspergillus* or *Candida* infections in adults, 18 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.
Dosage and administration	Loading dose: 300 mg, twice a day on the first day Maintenance dose: 300 mg, once a day
Applicant:	Merck Sharp and Dohme One Merck Drive P.O. Box 100 Whitehouse Station, New Jersey 08889-0100
Review Division:	Division of Anti-infective Products
Reviewer:	Owen McMaster, Ph.D.
Supervisor/Team Leader:	Wendelyn Schmidt, Ph.D.
Division Director:	Sumathi Nambiar, M.D.
Project Manager:	Alison Rodgers

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

There are no nonclinical pharmacology or toxicology data that preclude the approval of NOXAFIL (posaconazole) injection.

1.1.2 Additional Non Clinical Recommendations

No additional nonclinical pharmacology or toxicology studies of NOXAFIL (posaconazole) injection are being recommended at this time.

1.1.3 Labeling

No labeling changes are being recommended at this time.

1.2 Brief Discussion of Nonclinical Findings

The Pharmacology and Toxicology studies submitted to support Noxafil® (posaconazole) Injection represent an abbreviated toxicology program. Many nonclinical Pharmacology and Toxicology studies of posaconazole were conducted under the NDAs that supported the approval of Noxafil® (posaconazole) delayed-release tablets, and Noxafil® (posaconazole) oral suspension. Some of the data from these studies are described in the physician's prescribing information. On the first day of dosing, two 300 mg doses of Noxafil® (posaconazole) Injection are administered (loading dose) followed by daily maintenance dose of 300 mg (5 mg/kg for a 60 kg patient). In clinical trials, patients were dosed with Noxafil® (posaconazole) Injection for a median of 9 days.

The nonclinical data submitted with the current NDA included a 1-month monkey study, a 3-month dog study and a 6-week study in juvenile dogs. In the 1-month monkey study, higher doses were associated with findings similar to those seen in previous posaconazole studies. Findings in the adrenals included increased adrenal weights, single cell necrosis, lymphohistiocytic infiltrates, congestion, hemorrhage, edema, decreased vacuolation and hyperplasia /hypertrophy of the zona fasciculata and atrophy of the zona reticularis and zona glomerulosa, while thyroids showed increased weight and increased colloid. Phospholipidosis was also observed (as vacuolated macrophages in the aorta, ileum, spleen, mandibular lymph node, mesenteric lymph node, liver, lungs). The NOAEL was 4 mg/kg/day. Although the exposure at the clinical dose (36,100 ng*h/mL) was higher than exposure at the NOAEL (23,400 ng*h/mL), the patients would only be exposed to about (1/3) of the exposures associated with adverse effects in monkeys (123,000 ng*h/mL at 8 mg/kg/day).

In "*An age-targeted 6-week intravenous injection toxicity study of posaconazole (MK-5592) with a five-month postdose period in juvenile beagle dogs"*, animals were dosed for six weeks (10 mg/kg/day posaconazole) beginning on day 14 postpartum and were followed for a 5-month reversibility period. At the end of dosing, posaconazole-treated animals showed ventricular dilatation in the brain of 5/8 animals compared to 0/8 placebo and 0/8 vehicle control animals. At the end of the recovery period 1/8 posaconazole treated dog and 1/8 placebo dog showed ventricular dilatation. A targeted follow-up study "*Three-Month Intravenous Infusion Toxicity Study in Dogs"* was subsequently conducted in older (31 week-old) dogs, dosed for three months at 9 mg/kg/day, using MRI, to better assess the effect of posaconazole on the lateral ventricle in the dog. In contrast to the study in younger animals, 31-week old dogs treated with intravenous posaconazole showed no statistically significant difference in ventricular volume compared to control animals. It appears that the increase in volume in the lateral ventricles is seen only when very young dogs, two weeks old, are exposed to intravenous posaconazole injection. The applicant has included the following statement in the physician's prescribing information:

8.4 Pediatric Use
The safety and effectiveness of Noxafil Injection in pediatric patients below the age of 18 years of age has not been established. Noxafil Injection should not be used in pediatric patients because of nonclinical safety concerns [see Nonclinical Toxicology (13.2)].

13.2 Animal Toxicology and/or Pharmacology:
In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2 to 8 weeks of age) an increase in the incidence of brain ventricle enlargement was observed in treated as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5 month treatment-free period. There were no neurologic, behavioral or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to

juvenile dogs (4 days to 9 months of age) The clinical significance of this finding is unknown; therefore, the use of posaconazole Injection to patients under 18 years of age is not recommended.

This reviewer agrees with this approach.

The identical drug substance approved for POS Oral Suspension, is used in POS IV solution. There are no outstanding concerns regarding impurities or degradants associated with this drug. All impurities have been qualified or are controlled to within acceptable limits.

Conclusion

NOXAFIL® (Posaconazole) Injection represents the third posaconazole formulation to be marketed. It is unique among the posaconazole formulations in that it is formulated with sulfobutylether-β-cyclodextrin. The toxicity profile of NOXAFIL® (Posaconazole) Injection is similar to the other formulations except that the sulfobutylether-β-cyclodextrin (SBECD) in the NOXAFIL® (Posaconazole) Injection results in kidney effects that are not found in formulations that do not contain SBECD. In addition, NOXAFIL® (Posaconazole) Injection was associated with increased ventricular volumes in very young dogs. The drug is therefore being restricted to patients above 18 years of age. There are no nonclinical data that would preclude the approval of NOXAFIL® (Posaconazole) Injection for use as prophylaxis of invasive *Aspergillus* or *Candida* infections in patients, 18 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised.

Study title:	28-day intravenous infusion toxicity and toxicokinetics study with SCH56592 in cynomolgus monkeys
Key study findings:	A single death at 12 mg/kg/day. Adrenal and thyroid changes and phospholipidosis consistent with previous studies of posaconazole at 8 and 12 mg/kg/day. Clinical exposure (36,100 ng*h/mL) was higher than exposure at the NOAEL of 4 mg/kg (23,400 ng*h/mL) but much less than the exposures associated with adverse effects 8 mg/kg (123,000 ng*h/mL)
Schering study no.:	08110
(b) (4) study number	6377-633
Document location	EDR NDA 205596 SDN 1
Conducting laboratory:	(b) (4)
Date of study initiation:	June 2, 2008
GLP compliance:	Yes
QA report :	Yes
Drug, lot #,	K-H09158
Doses:	0, 4, 8 and 12 mg/kg
Species/strain:	*Macaca fascicularis*/ cynomolgus monkey
Number/sex/group):	4
Age	33 to 50 months old
Weight	Males: 2.9 to 3.7 kg Females: 2.4 to 3.4 kg
Route	Intravenous infusion over 60 minutes via the femoral vein
Placebo/Formulation	Sulfobutylether-β-cyclodextrin (SBEβCD), edetate disodium (EDTA), 5 % Dextrose for injection, water, [Hydrochloric Acid and Sodium Hydroxide used to adjust pH to 2.6])
Volume	5 mL/kg
Infusion rate	Approximately 0.3 mL/min

Male and females cynomolgus monkeys were dosed intravenously daily for 28 days with posaconazole as shown on Table 1, below.

Table 1. Study design

Group	Test/Control Article	No. of Monkeys/Sex		Total Daily Dose (mg/kg)		Dose Concentration (mg/mL)	
		Male	Female	Male	Female	Male	Female
1	Control (Placebo)	4	4	0	0	0	0
2	Low-Dose (SCH 56592)	4	4	4	4	0.8	0.8
3	Mid-Dose (SCH 56592)	4	4	8	8	1.6	1.6
4	High-Dose (SCH 56592)	4	4	12	12	2.4	2.4

Results

Mortality:

One high dose female was sacrificed moribund on Day 23 of dosing. This animal showed dehydration, hunched appearance, abnormal, black, few, liquid, non-formed feces and low body temperature. This animal had not responded to treatment for an inguinal site infection. No definitive cause of death was determined.

Clinical signs:

Skin at the right inguinal area (infusion site) was red and/or swollen in slightly more drug-treated animals, but there was no dose response relationship. Clinical signs were evaluated twice daily.

Body weights:

There were no drug-related effects on bodyweight during this study period. Bodyweights were recorded during the predose phase, before dosing on Day 1, weekly thereafter and on the day of scheduled sacrifice.

Food consumption:

There were no drug-related effects on food consumption during this study period. Food consumption was measured qualitatively once daily starting 2 weeks prior to the initiation of dosing and during the dosing phase.

Ophthalmoscopy:

No drug-related ophthalmic abnormalities were observed during this study. Ophthalmoscopic examinations were conducted once during the predose phase and during week 4.

EKG:

There were no drug-related effects on ECG parameters. Electrocardiogram (ECG) examinations were performed on animals twice during the predose phase and during Week 4.

Hematology, Coagulation and Clinical Chemistry

At the end of dosing, serum albumin was about 18 % reduced in high dose animals compared to control animals, and this was associated with a 20% reduction in albumin/globulin ratio. There were no other biologically significant drug-related effects on hematology, coagulation or clinical chemistry parameters. Parameters were measured twice during the predose phase and during Week 4.

Urinalysis:

There were no drug-related effects on urinalysis parameters. Urine for urinalysis was collected during the predose phase (once) and during Week 4.

Necropsy/Gross pathology:

There were no drug-related findings detected during gross pathology evaluations. After 29 days of dosing, animals were fasted overnight, sacrificed by exsanguination under sodium pentobarbital-induced anesthesia and necropsied.

Organ weights:

Absolute and relative adrenal weights were increased by 21 to 33 % at 8 mg/kg/day and by 36 to 55 % at 12 mg/kg/day. Absolute and relative thyroid weights also increased by up to 31 % in females and 75 % in males. The following organs were weighed: adrenals(2), brain, epididymis (2) heart, kidney (2), liver with gallbladder (drained), lung, ovary (2), pituitary gland, prostate, spleen, testis (2), thymus, thyroid (2 lobes) with parathyroid, uterus (with cervix).

Histopathology:

Consistent with the increased thyroid weights, findings included increased colloid in the thyroid gland of 1/4 low, mid and high dose females, and 2/4, 4/4 and 3 /4 males in the low, mid and high dose groups.

All cortical subdivisions of the adrenal cortex were adversely affected in males and females at 8 and 12 mg/kg and findings included single cell necrosis, lymphohistiocytic infiltrates, congestion, hemorrhage, edema, decreased vacuolation and hyperplasia /hypertrophy of the zona fasciculate and atrophy of the zona reticularis and zona glomerulosa

Vacuolated macrophages were observed in the aorta, ileum, spleen, mandibular lymph node, and mesenteric lymph node of males and females given 8 or 12 mg/kg and in the liver of females given 8 or 12 mg/kg. An increase in the frequency and severity of vacuolated macrophage infiltrates in the alveoli of the lungs was observed in males given 4, 8, or 12 mg/kg and females given 8 or 12 mg/kg SCH 56592. The vacuolated macrophages observed in various organs were consistent with phospholipidosis.

The following tissues were preserved in 10 % neutral-buffered formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin and examined microscopically.

Table 2: Histopathology Inventory

adrenal (2)	gallbladder	mammary gland	spinal cord (cervical,
aorta	heart	oropharynx	thoracic, and
brain	Ileum	ovary (2)	lumbar)
catheterization site	infusion site	optic nerve(2)	spleen
cecum	jejunum	pancreas	sternum with bone marrow
cervix	kidney (2)	pituitary gland	stomach
colon	lacrimal gland	prostate gland	testis (2)
duodenum	larynx	rib with bone marrow a	thymus
epididymis(2)	lesions	salivary gland [mandibular	thyroid (2 lobes) with
esophagus	liver	(2)]	parathyroid
eye (2)	lungs with large bronchi	sciatic nerve	tongue
femur with bone marrow	lymph node (mandibular)	seminal vesicle	trachea
(articular surface of the distal	lymph node (mesenteric)	skeletal muscle (biceps	urinary bladder
end)		femoris)	uterus
		skin/subcutis	vagina

Adequate Battery: Yes
Peer review: Yes

Toxicokinetics:

Exposure to drug was similar in males and females and mean T_{max} was at the first time point (1 hr) for all animals. C_{max} and $AUC_{(0\text{-}24\ hr)}$ increased in a greater than dose proportional manner on Day 1 and Day 27. A 1:2:3-fold increase in dose resulted in a 1:3:4-fold increase in $AUC_{(0\text{-}24\ hr)}$ values on Day 1 and 1:5:10-fold increase in $AUC_{(0\text{-}24\ hr)}$ values on Day 27. Systemic exposure to SCH 56592 increased with repeated administration in all dose groups, mean R values ($AUC_{(0\text{-}24h)\ Day\ 27} \div AUC_{(0\text{-}24h)\ Day\ 1}$) ranged from 1.93 to 4.23. Blood was collected on Days 1 and 27 at 1, 2, 4, 8 and 24 hours after initiation of infusion in all animals

Table 3. Day 1: Mean posaconazole Toxicokinetic Parameters Following Intravenous Infusion of 4, 8 or 12 mg/kg posaconazole to Cynomolgus Monkeys

Dose	4 mg/kg	8 mg/kg	12 mg/kg
Cmax (ng/mL)	1200	2610	4200
$AUC_{(0\text{-}24h)}$ ng·h/mL	12200	31600	52000

Table 4. Day 27: Mean posaconazole Toxicokinetic Parameters Following Intravenous Infusion of 4, 8 or 12 mg/kg posaconazole to Cynomolgus Monkeys (Males and Females Combined)

Dose	4 mg/kg	8 mg/kg	12 mg/kg
Cmax (ng/mL)	1760	7010	12700
$AUC_{(0\text{-}24h)}$ ng·h/mL	23400	123000	228000
R*	1.9	3.9	4.3

R* = $AUC_{(0\text{-}24h)\ Day\ 27} \div AUC_{(0\text{-}24h)\ Day\ 1}$

Dosing Solution Analysis

All study samples analyzed were within the acceptance criteria of 10.0% of their theoretical concentration values.

Discussion

Female monkeys reach adulthood after 4 years and males reach maturity at 6 years old. The monkeys used in the study (33 to 50 months old) were therefore adolescent or peripubertal. Despite the young age, the adverse events seen were consistent with the current data on posaconazole toxicity.

Daily intravenous dosing with posaconazole for 28 days resulted in monkeys resulted in a single mortality at 12 mg/kg/day. Adrenal changes (single cell necrosis, lymphohistiocytic infiltrates, congestion, hemorrhage, edema and hyperplasia/ hypertrophy of the zona fasciculata) may have contributed to the death.

Consistent with previous studies of posaconazole, dosing was associated with changes in the adrenal and thyroid glands as well as evidence of phospholipidosis in several organs.

Plasma posaconazole levels increased at a rate that was supra proportional to dose. Exposure (as measured by AUC) also increased with repeated dosing. These exposure increases may be related to the fact that, after intravenous dosing, posaconazole is primarily eliminated via the feces [either as drug (or metabolites) secreted directly from the systemic circulation into the gastrointestinal tract or as drug (or metabolites) secreted in bile] and is both an inhibitor and substrate for permeability glycoprotein.

The NOAEL was determined to be 4 mg/kg, which resulted in an exposure of 23,400 ng*h/mL. Since the toxicological significance of phospholipidosis is unclear and the phenomenon is reversible, the vacuolated macrophage infiltrates in the alveoli of the lungs observed in males given 4 mg/kg, was not considered an adverse event.

Patients who received the prescribed regimen of NOXAFIL (posaconazole) Injection, (300 mg taken once a day for 10 or 14 days showed mean AUC values of 36100 ng*h/mL (see Prescribing information). Although this exposure is higher than that at the NOAEL, this finding does not portend serious adverse effects since it is much lower than the exposure at which adverse effects were observed (123,000 ng*h/mL) at 8 mg/kg.

Study title:	An age-targeted 6-week intravenous injection toxicity study of posaconazole (MK-5592) with a five-month postdose period in juvenile beagle dogs
Key Study Findings	Ventricular dilatation in the brain, thinness, serous ocular discharge along with signs typically associated with posaconazole (such as increased adrenal and thyroid weight, neuronal vacuolation [brain, spinal cord, small intestines, large intestines, bladder], histiocytic vacuolation [spleen, lymph nodes, Peyer's patches, thymus], accumulation of macrophages in lung alveoli, atrophy of the zona glomerulosa of the adrenal gland and hyperplasia of the zona fasciculata of the adrenal gland and increased colloid in the thyroid. SBECD-related findings included focal vacuolation of the tubular epithelium in the kidney. Posaconazole-related histological findings were reversible but SBECD-related effects were not completely reversed at the end of the recovery period.
Study report location:	EDR
Sponsor study no.:	TT# 12-9018
Conducting lab Study no:	902700
Conducting laboratory :	(b) (4)
Date of study initiation:	20 August 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, Batch (lot) #:	W-H03455 (CD057) aka Lot WL00046580
% purity:	99.8
Doses:	0 (vehicle control, 5% dextrose in sterile water) 0 (placebo control) 10 mg/kg posaconazole
Frequency of dosing:	Daily
Route of administration:	Intravenous injection (jugular and/or cephalic vein)
Dose volume:	5 mL/kg
Formulation/placebo:	Sulfobutylether-β-cyclodextrin (SBEβCD), edetate disodium (EDTA), 5 % Dextrose for injection, water, [Hydrochloric Acid and Sodium Hydroxide used to adjust pH to 2.6]
Species/Strain:	*Canis lupus familiaris*/beagle dog
Number/Sex/Group:	4
Age:	14 days postpartum
Weight:	923 g at start of dosing
Satellite groups:	3 groups of animals (4/sex/dose group) were dosed like main study animals, then retained for a 5 month recovery period and evaluated for adverse effects.

Male and female (14-day old) beagle pups were dosed intravenously daily for 6 weeks with vehicle, placebo or 10 mg/kg posaconazole after which they were followed for a 5 month recovery period.

Mortality

One female pup from the vehicle control group was euthanized on Day 18 postpartum showing weight loss (-19 %), liquid feces and suspected dehydration. One drug-treated male was euthanized on day 58 due to its poor and deteriorating condition. On day 57, this animal showed vomiting, weakness, suspected dehydration, reduced appetite, decreased activity and was treated for hyperthermia. Postmortem histopathology finding of marked lobar pulmonary inflammation was determined to be the reason for moribundity. This lung finding was not considered to be related to drug.

Clinical Signs

Commencing on Day 54 postpartum, two posaconazole-treated animals showed thinness and a prominent backbone. Other signs such as partly closed eyes and labored breathing affected one or two animals and fur staining and liquid and/or foamy material (affecting up to 3 or 4 animals administered 10 mg/kg/day posaconazole).

Cage side observations were performed daily during the dosing period; prior to dosing, immediately postdose and 1 to 3 hours postdose. The animals were removed from the cage, and a detailed clinical observation was performed daily until weaning as part of the litter checks, and once weekly thereafter.

Body Weights

Body weights gain in placebo and drug-treated animals were slightly lower than vehicle controls starting on Day 38 postpartum for males and females, but these resulted in only slight reductions in bodyweight (<10 %) compared to vehicle controls.

Animals were weighed individually daily from birth until Day 21 postpartum then twice weekly until weaning and weekly thereafter. A non-fasted weight was recorded on the day of necropsy for main study animals. A fasted weight was recorded on the day of necropsy for recovery animals

Feed Consumption

There were no drug-related effects on feed consumption. Food consumption was quantitatively measured daily from weaning or starting the day after weaning and continuing daily thereafter, with the exception of the day of scheduled euthanasia. Weekly values were calculated and reported.

Ophthalmoscopy

At Week 6, a slight, serous ocular discharge was noted in 11/16 dogs treated with posaconazole at 10 mg/kg/day; 3/16 dogs in the placebo group and 5/15 dogs in the vehicle control group (Group 1). The posaconazole-related increase in the incidence of this minor finding was considered to be reversible (generally limited to the dosing period). Animals were subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The examinations were performed during week 6 of the dosing period (before dosing) and between Days 178 and 190 postpartum.

Observational Battery

There were no effects upon the qualitative parameters evaluated for the functional testing of males and females administered the placebo or posaconazole at 10 mg/kg/day.

A qualitative observational battery was performed on all animals during Week 6 of the treatment period (before daily dose administration) and at the end of the recovery period. The qualitative observational battery consisted of the following tests:

Table 5: Qualitative observational battery

Abnormal body position/posture	Respiration rate/pattern	Palpebral closure
Activity level	Urination/defecation	Diarrhea
Bizarre/stereotypic behaviour	Lacrimation	Vocalization
Convulsions	Salivation	Piloerection
Muscle tremors/twitches	Pupil size	

Neurological Examination

There were no effects on neurological evaluations of males and females administered the placebo or posaconazole at 10 mg/kg/day. A neurological examination was performed on all animals during Week 6 of the treatment period (before daily dose administration) and at the end of the recovery period. The neurological examination consisted of the following tests: Gait**,** Muscle Tone, Patellar Reflexes, Flexor Reflexes, Panniculus Reflex, Perineal Reflex, Proprioceptive Positioning, Hemihopping/Hemistanding, Wheel barrowing, Hopping, Placing Reactions-Visual Placing Reactions-Tactile, Righting Reaction, Head – movements/ symmetry, Head Muscle Tone Eye Reactions, Eye Symmetry, Vestibular Nystagmus, Eye Position, Corneal Reflex, Pupillary Light Reflex Nasal Septum Test, Mouth Test, Tongue Test, Pharynx Test.

Clinical Pathology

There were no biologically significant drug related changes in hematology, clinical chemistry and coagulation evaluations. During Week 7 postpartum, there were changes in several parameters (such as increases in alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and globulin, and decreases in creatinine, total protein, albumin, albumin/globulin ratio, and calcium) in the drug-treated animals, but these were not biologically significant since changes were either small or driven by data from one or two animals. Blood was collected for hematology, clinical chemistry and coagulation evaluations from all dose groups during Week 7 postpartum and from recovery animals during the recovery period (Week 28 postpartum)

Urinalysis: Not evaluated

Postmortem evaluations

The only significant drug-related gross pathology finding was dilation of the lateral ventricles of the brain, which was observed in 2/4 female and 3 /4 males. Main study and recovery animals surviving until scheduled euthanasia were sedated with Ketamine HCl for Injection, U.S.P. and Xylazine by intramuscular injection before being transported from the animal room to the necropsy area. There animals were anesthetized by intravenous injection of sodium pentobarbital and then sacrificed by exsanguination via incision of the axillary or femoral artery. Animals were then subjected to a complete necropsy examination.

Organ Weights

Drug related organ weight increases were observed in the adrenals (+75 %) and the thyroids (+27 %, females only). Organs weighed included brain, adrenal gland (pair), pituitary, prostate, thyroid, heart, Kidney (pair) liver, Ovary (pair), Spleen, Testis (pair) Thymus.

Histopathology

Consistent with published data, animals dosed with placebo (containing sulfobutylether-β-cyclodextrin) showed focal vacuolation of the tubular epithelium in the kidney. This change was also noted in the 10 mg/kg posaconazole group and was ascribed to the sulfobutylether-β-cyclodextrin component. At the end of the recovery period, this finding was still present, although at a lesser incidence and severity than at the end of the dosing period.

The following posaconazole-related histological changes were present in all or 7/8 drug-treated animals: neuronal vacuolation of the brain, histiocytic vacuolation (spleen, lymph nodes, Peyer's patches, thymus), accumulation of macrophages in lung alveoli, atrophy of the zona glomerulosa of the adrenal gland and hyperplasia of the zona fasciculata of the adrenal gland. Other findings that were less frequent included ventricular dilatation (5/8 animals) neuronal vacuolation (spinal cord (1/8 animals, small intestines (5/8 animals), large intestines (1/8 animals) urinary bladder (3/4, males only), and increased colloid in the thyroid (4/4 females only).

At the end of the recovery period, there were no posaconazole-related gross or histological findings. A similar incidence of dilatation of the lateral ventricles of the brain was observed histologically in posaconazole -treated and placebo animals following the 5 month treatment-free period; 1/8 posaconazole -treated dogs and in 1/8 dogs from the placebo group.

Sections of tissues in the following list from all dogs, including found dead/early sacrifice dogs, were prepared by routine methods, stained with hematoxylin and eosin, and examined microscopically

Table 6: Histopathology Inventory

Artery, aorta	Gland, mammary	Large intestine, cecum	Nerve, sciatic
Bone marrow smear	Gland, parathyroid	Large intestine, colon	Ovary
Bone marrow, femur	Gland, pituitary	Large intestine, rectum	Pancreas Skin
Bone marrow, sternum	Gland, prostate	Larynx	Spinal cord
Bone, femur	Gland, salivary	Liver	Spleen stomach
Bone, sternum	Gland, thyroid	Lung	Testis
Brain	Gross lesions/masses	Lymph node, mandibular	Thymus
Cervix	Gut associated lymphoid	Lymph node, mesenteric	Tongue
Epididymis	tissue	Small intestine, duodenum	Trachea
Esophagus	Heart	Small intestine, ileum	Urinary bladder
Eye	Injection site	Small intestine, jejunum	Uterus
Gallbladder	kidney	Muscle, skeletal	vagina
Gland, adrenal		Nerve, optic	

Adequate Battery: Yes

Peer Review: Yes

Toxicokinetics

Table 7: Mean plasma posaconazole toxicokinetics parameters in dogs on Day 50 postpartum.

Day	Dose (mg/kg/day)	Sex	AUC_{0-24h} (μM*h)	C_{max} (μM)	T_{max} (h)
50	10	Female	246	13.1	1.0
		Male	286	15.1	1.0
		All	266	14.1	1.0

Posaconazole concentrations were similar in male and female pups and T_{max} occurred at the first postdose timepoint (1 hr). Elimination was slow, with a plasma concentration at 24 hours equal to 64 % of the mean C_{max} The mean overall AUC_{0-24h} corresponded to 172,000 ng*h/mL, which was comparable to the exposure (153,000 ng*h/mL) observed at Week 7 study TT #13-1062, which dosed 31-week old dogs with a slightly lower dose (9 mg/kg/day).

Blood was collected for toxicokinetics evaluations on Day 50, before dosing and at 1, 4, 8, 12 and 24 hours postdose. Plasma samples were analyzed for concentration of posaconazole.

Dosing Solution Analysis

All study samples analyzed were within the acceptance criteria of 10.0% of their theoretical concentration values.

Discussion

Intravenous administration of posaconazole to 14-day old beagle pups resulted in an adverse event profile similar to that obtained in older animals with other posaconazole formulations. This included phospholipidosis (histiocytic vacuolation [spleen, lymph nodes, Peyer's patches, and thymus], accumulation of macrophages in lung alveoli, neuronal vacuolation [brain and spinal cord]) and adrenal effects (including increased adrenal weight and atrophy of zona glomerulosa and hyperplasia of the zona fasciculata).

Animals dosed with the diluent/placebo (containing SBECD) showed focal vacuolation of the tubular epithelium in the kidney, which is a well-known feature of SBECD. There were no posaconazole-related gross or histological findings at the end of the recovery period but the kidney effects of SBECD were not completely reversed.

One unexpected finding was the observed dilatation of the lateral ventricles of the brain, seen in 2/4 females and 3/4 males in the 10 mg/kg posaconazole group. These changes were most likely related to the administration of posaconazole based upon the high incidence relative to concurrent (0/8 in placebo animals and 0/8 in vehicle animals) or historical control animals and the fact that the change was observed in pups from 2 different genetically unrelated dams.

Study title:	Three-Month Intravenous Infusion Toxicity Study in Dogs
Key study findings:	Young beagle dogs receiving daily posaconazole doses of 9 mg/kg/day for 3 months showed no increase in ventricular volume, as measured by MRI.
Study no.:	TT #13-1062
Document location	EDR NDA 205596
Conducting laboratory :	Safety Assessment and Laboratory Animal Resources Merck Research Laboratories, West Point, Pennsylvania, U.S.A.
Date of study initiation:	April 30, 2013
GLP compliance:	Yes
QA report :	Yes
Drug, batch #,	IRQ-PAZ-11-X-134
% purity:	99.8 %
Doses:	0, 9 mg/kg
Species/strain:	*Canis lupus familiaris*/beagle dog
Number/sex/group :	4
Age	31 to 35 weeks old
Weight	Males 8.3 to 9.7 kg Females 5.1 to 7.0 kg
Route	Intravenous (via cephalic/saphenous vein)
Formulation	Sulfobutylether-β-cyclodextrin (SBEβCD), edetate disodium (EDTA), 5 % Dextrose for injection, water, [Hydrochloric Acid and Sodium Hydroxide used to adjust pH to 2.6]
Control/Vehicle	5 % Dextrose for injection, USP
Dose volume	5 mL/kg
Infusion rate	Approximately 3 mL/min

Results

Mortality

There were no unscheduled deaths

Clinical signs:

There were no drug-related clinical signs. Animals were observed daily observation for mortality and physical signs

Body weights:

There were no test article-related body weight changes. Bodyweight was measured pretest and once per week in Study Weeks 1 through 13, on all animals.

Food consumption:

There were no drug-related effects on food consumption. Food consumption was evaluated daily on weekdays.

Magnetic Resonance Imaging

No statistically or biologically significant differences were seen between groups at any time point for any measured ventricle volume. Prior to the initiation of dosing, during study weeks 3, 7, and during study week 12-13, MRI examinations were performed to measure brain ventricle volumes. Dexmedetomidine (Dormitor) was given as a pre-anesthetic, followed by induction of anesthesia with intravenous propofol. Animals were maintained under sedation with isoflurane.

Table 8: Effect of 10 mg/kg posaconazole on mean ventricular volume in mm^3.

		Mean ventricular volume (mm^3)				
	Study week	Left Lateral	Right Lateral	Third	Fourth	Total
Treated	Baseline	448 ± 638	370 ± 607	370 ± 67	195 ± 23	1383 ± 1268
	3	452 ± 641	388 ± 625	351 ± 82	194 ± 23	1384 ± 1294
	7	507 ± 691	433 ± 626	386 ± 100	195 ± 46	1520 ± 1329
	12/13	530 ± 723	462 ± 668	410 ± 103	206 ± 31	1608 ± 1404
Vehicle	Baseline	478 ± 321	362 ± 249	350 ± 91	188 ± 45	1379 ± 546
	3	606 ± 515	461 ± 309	394 ± 88	190 ± 43	1651 ± 792
	7	610 ± 416	356 ± 303	440 ± 94	208 ± 69	1794 ± 736
	12/13	621 ± 419	539 ± 312	441 ± 107	197 ± 51	1798 ±785

At the end of dosing, left lateral ventricles were 15 % decreased in treated animals and the right lateral ventricle was 33 % decreased in treated animals. This is in contrast to the earlier study in younger dogs, which showed that posaconazole treatment as associated with increased ventricular volume. None of these changes were statistically significant.

Gross pathology:

There were multiple pale foci on the lungs of 7 of the 8 dogs treated with posaconazole which were considered likely due to phospholipidosis. There were no test article-related gross changes in the brain. The ventricles of the brain in treated dogs were similar to control dogs when evaluated by gross observation during trimming of the fixed brain and by histomorphology.

Organ weights

There were no drug-related effects on brain or bodyweight. The brain and terminal body weights were recorded from all dogs euthanized at scheduled necropsies.

Histopathology:
There were no remarkable histomorphologic findings in the brain. Sections of brain from all dogs were prepared by routine methods, stained with hematoxylin and eosin, and examined microscopically: brain (including basal nuclei, cerebral cortex, corpus callosum, internal/external capsule, hypothalamus, amygdala, thalamus, hippocampus, optic tract, midbrain, pons, pyramids, cerebellum, medulla oblongata, and choroid plexus)

Peer review: yes (√), no ( )

Ophthalmoscopy: Not evaluated

EKG: Not evaluated

Hematology: Not evaluated

Clinical chemistry: Not evaluated

Urinalysis: Not evaluated

Toxicokinetics:

Blood for toxicokinetics evaluations were taken immediately after completion of dosing [± 2 minutes]) and 30 minutes, 1, 2, 4, 6, and 24 hours after initiation of infusion dosing on Study Day 1 and in Study Week 7. Mean AUC0-24 hr and Cmax values were generally similar between males and females. Plasma elimination of posaconazole was slow with mean trough (24-hour) plasma concentrations that were approximately 28% and 46% of the mean Cmax values on Study Day 1 and in Study Week 7, respectively. Following repeated administration, systemic exposure to posaconazole increased in Study Week 7 compared to Study Day 1. Mean AUC0-24 hr and Cmax values in Study Week 7 were approximately 3.1 and 2.2-fold higher than on Study Day 1, respectively.

Table 9: Day 1: Mean plasma posaconazole toxicokinetics parameters in dogs

Day	Dose (mg/kg/day)	Sex	AUC_{0-24h} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)
1	9	Female	47,900 ± 3760	4380 ± 314	0.25
		Male	51,100 ± 1740	5400 ± 398	0.25
		All	49,500 ± 2010	4890 ± 304	0.25

Table 10. Week 7: Mean plasma posaconazole toxicokinetics parameters in dogs

Week	Dose (mg/kg/day)	Sex	AUC_{0-24h} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)
7	9	Female	139,000 ±16,200	10,100 ± 1360	0.25
		Male	167,000 ± 13,700	11,600 ± 972	0.25
		All	153,000 ± 11,100	10,900 ± 823	0.25

CSF pharmacokinetics:

Toxicokinetics samples of cerebrospinal fluid (1-2 mL) and brain tissue (~100 mg) were collected at the time of necropsy. Brain tissues were homogenized in 3 mL of water per gram of tissue. Drug concentrations were determined by protein precipitation followed by liquid chromatography-tandem mass spectrometry. Results are shown in Table 11, below.

Table 11. Mean CSF and brain posaconazole toxicokinetics parameters in dogs Week 14.

Week	Dose (mg/kg/day)	Sex	CSF (ng/mL)	Brain (ng/mL)
14	9	Female	4.1	1360
		Male	7.4	2442
		All	5.8	1901

Dosing solution analysis

Samples of all dosing formulations were collected for analysis of concentration on Study Days 1 and 2, and in Study Weeks 7, 9 and 13. All dose formulation assay results were within specification (±10% of claim) for the nominal concentration of 1.8 mg/mL (9 mg/kg/day), except for one instance on Study Day 1 which was minimal and had no impact to the results of the study.

Discussion and conclusion

Young (31 week-old) beagle dogs receiving daily, 9 mg/kg doses of posaconazole showed evidence of phospholipidosis (multiple pale foci on the lungs of 7 of the 8 dogs) and AUC values (153,000 ng*h/mL) which were approximately four-fold higher than patients (mean AUC of 36,100 ng*h/mL). An earlier study (TT# 12-9018), had found increased ventricular volume in 14-day old beagle pups, dosed with intravenous posaconazole for six weeks at slightly higher exposures mean (172,000 ng*h/mL). There was no evidence from the present study that posaconazole was associated with increased ventricular volume in these older dogs. This study also provided preliminary evidence that posaconazole injection can distribute into the brain and CSF.

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/s/

OWEN G MCMASTER
02/27/2014

WENDELYN J SCHMIDT
02/27/2014

I concur with Dr. McMaster's assessment that the data is adequate to assess the safety of i.v. posoconazole and to allow clear labeling. I also concur with his interpretation of the data.