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APPLICATION NUMBER:

205053Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

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Date	November 4, 2013
From	Philip M. Colangelo, Pharm.D, Ph.D
Subject	Cross Discipline Team Leader Review
NDA #	205-053
Applicant	Merck, Sharpe, and Dohme, Corp.
Date of Submission	January 25, 2013
PDUFA Goal Date	November 25, 2013
Proprietary Name / Established (USAN) names	NOXAFIL® (Posaconazole) Delayed Release Tablets
Dosage forms / Strength	Posaconazole Delayed Release Tablets , 100 mg
Proposed Indication(s)	Prophylaxis of invasive <i>Aspergillosis</i> and <i>Candida</i> infections in patients 13 years of age and older
Recommended Action:	Approval

1. Introduction

Merck, Sharpe, and Dohme, Corp. submitted an NDA application for NOXAFIL® (Posaconazole) Delayed Release Tablets, 100 mg. Posaconazole (POS) was developed initially as an oral suspension and subsequently approved in 2006 under NDA 22-003 (Schering-Plough Pharmaceuticals) for the prevention of invasive fungal infections (IFI) in immunocompromised patients, specifically neutropenic patients under treatment for acute myelogenous leukemia (AML) or myelodysplasia (MDS), as well as hematopoietic stem-cell transplant (HSCT) patients with graft-versus-host disease (GVHD). Merck is seeking the same indication for the oral tablet and has developed a delayed release POS oral tablet formulation (hereafter referred to as POS Tablets) to improve upon the limitations associated with the dosage and administration of the oral suspension formulation. Namely, POS Oral Suspension needs to be administered multiple times a day (BID or TID, depending on the indication) and also needs to be taken with food, preferably a high fat meal or nutritional supplement, to ensure adequate oral absorption and systemic pharmacokinetic (PK) exposure. (b) (4)

The clinical program for POS Tablets was designed to demonstrate comparable systemic PK exposure and safety among similar patient populations for which the POS Oral Suspension has already been approved (see above). The PK exposure target was based upon the range of POS systemic exposures achieved and the exposure-response relationship established in the earlier efficacy and safety studies of POS Oral Suspension. At the time of the NDA submission for the Oral Suspension, both the FDA and the previous sponsor (Schering-Plough) had agreed upon the range of PK target exposures for posaconazole to achieve an adequate level of efficacy (i.e., prevention of break-through IFI) and safety. In this current NDA submission, the sponsor conducted a Phase 1B/3 safety, tolerability, and PK study (Study P05615) that showed the proposed dosage regimen of POS Tablets (i.e., Loading Dose: 300 mg BID on Day 1; Maintenance Dose: 300 mg QD on Day 2 and thereafter) provided systemic PK exposure to POS within this pre-defined target PK exposure range,

without safety issues, in patients with AML and in HSCT recipients, indicating that the proposed dosage regimen of POS Tablets is acceptable for the prophylaxis of invasive fungal infections.

2. Background

Posaconazole is a triazole antifungal agent available as an immediate release oral suspension or a new delayed release oral tablet. POS blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14 α -demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. The resulting accumulation of methylated sterol precursors and depletion of ergosterol within the cell membrane weakens the structure and function of the fungal cell membrane. This process may be responsible for the antifungal activity of posaconazole.

The proposed indications of POS Tablets are prophylaxis of invasive aspergillus and candida infections in patients, 13 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.

POS Tablets should be swallowed whole, and not divided, crushed, or chewed. (b) (4)

The Clinical Pharmacology review team will recommend in the labeling that POS Tablets should be given with food because it is expected that food intake would increase the systemic bioavailability of POS from the tablet formulation, as was observed with the oral suspension.

Proposed dosage and administration for Noxafil Delayed Release Tablets

Indication:

Prophylaxis of invasive *Aspergillosis* and *Candida* infections in patients 13 years of age and older

Dosage Regimen and Duration of Therapy:

Loading Dose: 300 mg (three 100 mg tablets) twice a day (BID) on the first day (Day 1)

Maintenance Dose: 300 mg (three 100 mg tablets) once a day (QD) on Day 2 and thereafter

Duration of therapy is based on recovery from neutropenia or immunosuppression.

3. CMC/Device

Drug Substance

As per the Chemistry / Quality review of Mark R. Seggel, the POS drug substance chemistry, manufacturing and controls are currently filed under NDA 22-003 for POS oral suspension, 40 mg/mL. The synthesis and characterization of POS are documented therein. The specification for POS, which assures the identity, strength, quality, and purity of the drug substance used in the manufacture of the oral suspension, is also suitable for drug substance used in the manufacture of POS Delayed Release Tablets.

Drug Product

POS Tablets are oblong-shaped and contain (b) (4) 100 mg posaconazole (b) (4) additional (b) (4) microcrystalline cellulose (b) (4), hydroxypropyl cellulose (b) (4) croscarmellose sodium (b) (4), silicon dioxide (b) (4), and magnesium stearate (b) (4). The tablets are debossed on one side with "100", and have a non-functional Opadry II yellow film coating. POS Tablets are packaged in 60-count HDPE bottles with child-resistant closures.

Manufacturing and Stability

Tablet manufacturing involves (b) (4)

This new tablet formulation limits the amount of POS dissolved at low pH in the stomach (b) (4) and enhances the dissolution at neutral pH for maximal absorption in the small intestine (b) (4). As per the CMC reviewer (Mark R. Seggel), the defined product manufacturing processes and controls provide assurance of consistent batch-to-batch quality.

The stability of the drug product was evaluated under long term (25°C/60% RH) and accelerated (40°C/75% RH) conditions. Twelve-month long term data on three primary stability batches and 24-36 month long term data from supporting stability batches shows very little change in drug product quality. No significant changes were observed under accelerated conditions. Overall, the data support a 24-month expiration dating period. This will be confirmed during on-going stability studies.

In summary, the CMC / Quality reviewer finds that this new drug application for POS Tablets contains chemistry, manufacturing and controls (CMC) data and information in sufficient detail to assure the identity, strength, purity, and quality of the drug product. Drug substance CMC is up-to-date, and is adequately documented in NDA 22-003 for POS Oral Suspension. The product description and storage statements, and other CMC-related information, are factually correct and complete. The Office of Compliance has issued an overall recommendation of Acceptable for this application on October 4, 2013. Therefore, from the CMC perspective, NDA 205053 for POS Tablets is recommended for approval. As CDTL reviewer, I concur with this assessment. Refer to the CMC / Quality review by Mark R. Seggel dated October 25, 2013 for more information.

Biopharmaceutics Assessment

The Biopharmaceutics review for POS Tablets focused on evaluation and acceptability of the proposed dissolution method and acceptance criteria, and the in vitro alcohol dose dumping studies.

Dissolution Method and Acceptance Criteria

The sponsor developed a dissolution test method in accordance with USP<711>, Delayed-Release Dosage Forms, using Apparatus II, paddles at 75 rpm. Because of the low solubility of posaconazole, polysorbate 80 is included in the buffer stage dissolution medium. Based on the evaluation of the provided data the following proposed dissolution method was found to be acceptable by the ONDQA-Biopharmaceutics reviewer, Mark R. Seggel.

Apparatus	USP Type-II, Paddle
Medium	Acid Stage: 0.01 N HCl Buffer: 0.2 M phosphate buffer with 1.46% polysorbate 80 Buffer Stage: pH 6.8, 50 mM phosphate with 0.37% polysorbate 80
Volume	Acid Stage: 750 mL Buffer: 250 mL Buffer Stage: 1000 mL
Paddle Rotation Speed	75 rpm
Temperature	37.0°C ± 0.5°C

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The Sponsor agreed to implement FDA's recommended buffer stage acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 145 minutes (5 minutes for pH change plus 20 minutes after pH change). The ONDQA-Biopharmaceutics reviewer found the following acceptance criteria to be acceptable for the dissolution test for batch release and on stability.

Acceptance Criteria	<ul style="list-style-type: none">• Acid Stage: Meets USP <711> criteria for Delayed Release Dosage Form (no individual value exceeds $\frac{(b)}{(4)}\%$ dissolved at 120 minutes at Level 1).• Buffer Stage: $Q = \frac{(b)}{(4)}\%$ at 145 minutes [continuous testing] (120 minutes acid stage + 5 minutes for pH change + 20 minutes after pH change).
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Overall, the ONDQA-Biopharmaceutics reviewer, Mark R. Seggel, determined that the dissolution test method and acceptance criteria will ensure adequate and consistent product performance across batches. It is therefore recommended from the Biopharmaceutics perspective that NDA 205053 for Noxafil (posaconazole) Delayed-Release Tablets be approved. As CDTL reviewer, I concur with this assessment. Refer to the ONDQA-Biopharmaceutics review by Mark R. Seggel dated September 30, 2013 for more information.

4. Nonclinical Pharmacology/Toxicology

The regulatory requirement for Pharmacology and Toxicology studies for this NDA is fulfilled by referring to the nonclinical Pharmacology and Toxicology studies conducted under NDA 22-003 for POS Oral Suspension. The nonclinical data submitted with the current NDA consisted of two nonclinical pharmacokinetics studies conducted to bridge the proposed tablet formulation of POS to the current marketed POS oral suspension. Administration of a single 60 mg oral dose of POS to monkeys as a capsule or tablet increased the systemic PK exposure to POS when compared to the oral suspension. Dosing was well tolerated and was consistent with clinical data; single instances of emesis and soft feces were observed. As per the assessment of the Pharmacology / Toxicology reviewer, Owen G. McMaster, Ph.D, there is no nonclinical pharmacology or toxicology data that preclude the approval of NOXAFIL Tablets, and no additional nonclinical pharmacology or toxicology studies of NOXAFIL Tablets are recommended. As CDTL reviewer, I concur with this assessment. Refer to the Nonclinical Pharmacology / Toxicology review by Owen G. McMaster, Ph.D dated October 9, 2013 for more information.

5. Clinical Pharmacology

There were two main Clinical Pharmacology related issues that needed to be addressed for POS Tablets in this NDA: (1) adequacy of the proposed POS Tablet dosage regimen to attain the same pre-defined target PK exposure range that was shown to be associated with acceptable efficacy and safety for the oral suspension, and (2) the effect of food on POS Tablets (b) (4)

(1). Proposed Dose Justification

The proposed dosing regimen of POS Tablets for the prophylaxis of invasive fungal infections is a loading dose of 300 mg (three 100 mg tablets) BID on Day 1, followed by a maintenance dose of 300 mg (three 100 mg tablets) QD on Day 2, and thereafter. This dosing regimen was evaluated in the Phase 1B/3 safety, tolerability, and PK Study P05615 in 210 immunocompromised patients (mean age 51 yrs.; range 19-78 yrs.) at risk of developing IFI. The POS target PK exposure range for the tablets was based upon the range of exposures achieved with the oral suspension and the exposure-response relationships for efficacy of the oral suspension in the Phase 3 trials of prophylaxis of IFI in NDA 22-003. The following exposure ranges were agreed upon by both the previous sponsor (Schering-Plough) and FDA during the review of the NDA for the oral suspension:

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- Mean steady-state POS C_{min} ≥ 500 ng/mL or AUC ≥ 12,000 hr•ng/mL in at least 90% of subjects;
- Mean steady-state POS C_{min} ≤ 2,500 ng/mL or AUC ≤ 59,000 hr•ng/mL;
- No subject with a mean steady-state POS C_{min} > 3,750 ng/mL or with a steady-state AUC > 90,000 hr•ng/mL.

In Study P05615, the steady state POS C_{min} following administration of POS Tablets at the proposed dosage regimen of 300 mg BID on Day 1, then 300 mg QD on Day 2 and thereafter fell within the pre-defined target exposure (see table below) for greater than 90% of the 186 patients for whom PK data were obtained. The steady state POS C_{min} was ≥ 500 ng/mL in 94.6% of patients (176 out of 186 patients), and was < 500 ng/mL in 5.4% of patients. The mean C_{min} at steady-state in 186 patients treated with the 300 mg QD dose of POS Tablets was ≤ 2,500 ng/mL (i.e., 1716 ng/mL). Although there were 6 patients (3.2%) with a steady state POS C_{min} > 3750 ng/mL, no substantial safety issues were found in these patients (see summary of Clinical review below). Thus, the proposed dosage regimen of POS Tablets is acceptable to the Clinical Pharmacology reviewer, Seong Jang, Ph.D, for the prophylaxis of invasive fungal infections.

Steady-state C_{min} POS plasma concentrations (ng/mL) in immunocompromised patients receiving the proposed clinical POS Tablet dosage regimen of 300 mg QD (Study P05615)

N	Mean	SD	Min	5th	10th	25th	Median	75th	90th	95th	Max
186	1716	1091	210	479	676	1105	1530	2060	2850	3220	9135

No. of Patients with average C_{min} < 500 ng/mL: 10 (5.4%)

No. of Patients with average C_{min} > 3750 ng/mL: 6 (3.2%)

(2). Food Effect

The current sponsor of this NDA (Merck) did not perform a food effect study to evaluate the effect of food on the oral bioavailability of POS Tablets. The protocol for the safety, tolerability, and PK Study P05615 indicated that POS Tablets were to be taken without regard to food intake. During pre-NDA meeting discussions held between the Division (DAIP) and the current sponsor, DAIP requested that the sponsor collect and record information in the case report forms for Study P05615 regarding timing of the patients' food intake in relation to the timing of POS Tablet administration. During the review cycle for this NDA, it was determined that the sponsor did not obtain this information. Based on the lack of this information, the Clinical Pharmacology reviewer, Seong Jang, Ph.D, deemed that it was not acceptable to conclude that POS Tablets were in fact given without regard to food intake in Study P05615 merely because the study protocol indicated that the drug was to be taken without regard to food. (b) (4)

(b) (4)
the proposed labeling to indicate that NOXAFIL Tablets be given with food because it is expected that food intake would increase the systemic bioavailability of posaconazole from the tablet formulation, as was observed with NOXAFIL Oral Suspension.

(b) (4)

The sponsor also evaluated the potential for drug-drug interactions with POS Tablets and medications that affect gastric pH and gastric motility (see table below). There was no effect of gastric pH or gastric motility modifying drugs on the PK of POS after co-administration with POS Tablets. However, POS exposure is substantially reduced by these same drugs after co-administration with POS Oral Suspension.

Mean (%CV) pharmacokinetic parameters of POS following single 400 mg dose of POS Tablets alone or with concomitant medications that effect gastric pH or motility in healthy volunteers (Study P07764)

Treatment	C _{max} (ng/ml)	T _{max} ^a (hr)	AUC _{0-∞} (hr·ng/ml)	t _{1/2} (hr)	CL/F (L/hr)
POS Alone	1090 (43)	4 (2-8)	42406 (49)	27.3 (37)	12.2 (64)
POS + Mylanta	1112 (36)	4.8 (3-12)	42468 (39)	27.7 (29)	11.1 (47)
POS + Ranitidine	1094 (37)	4 (3-5)	39287 (37)	26.9 (35)	11.7 (40)
POS + Esomeprazole	1104 (35)	4.5 (3-24)	41574 (43)	28.0 (30)	11.3 (42)
POS+ Metoclopramide	935 (44)	4 (2-6)	38513 (43)	29.0 (38)	12.9 (59)

^a: Median (range)

The Clinical Pharmacology information provided by the applicant in the NDA submission was deemed acceptable by the Clinical Pharmacology Reviewer, with the exception of the information of the timing of meals / food intake relative to the administration of POS Tablets in Study P05615. As CDTL reviewer, I concur with this assessment. Refer to the Clinical Pharmacology review by Seong Jang, Ph.D dated October 17, 2013 for further information.

6. Clinical Microbiology

No new clinical microbiology data were submitted with this application, and there were no sponsor proposed changes to the Microbiology section of the existing NOXAFIL labeling. As per the Microbiology reviewer, all information regarding the anti-fungal activity of POS was derived from NDA 22-003 for POS Oral Suspension. As CDTL reviewer, I concur with this assessment. Refer to the Microbiology review by Lynette Berkley, Ph.D dated October 29, 2013 for further information.

7. Clinical Efficacy

Study P05615 was a single-arm, uncontrolled, open-label, multicenter study of the safety, tolerability, and PK of POS Tablets used as prophylaxis in adult patients with hematologic malignancies at high risk for IFI. This study was not statistically powered for efficacy; there was no primary efficacy endpoint. Survival outcome at Day 65 was a secondary efficacy endpoint. All subjects were evaluated for safety. As per the Clinical reviewer, Elizabeth O’Shaughnessy, MD, the study was reviewed primarily for safety and tolerability of POS Tablets in the target population of patients with hematologic malignancies at risk for IFI. The treatment duration was 28 days. Study P05615 had a total of 230 evaluable patients (n = 20 who received 200 mg tablet dose; n = 210 who received 300 mg tablet dose), and a majority of subjects (~80%) completed the full 28 days of treatment with POS Tablets.

Clinical Failure and Day 65 Survival

As per the review of Dr. O'Shaughnessy, the survival rate was 91% for the proposed 300 mg dosage regimen of POS Tablets at the Survival Visit on Day 65 in Study P05615. There was one (<1%) patient who failed prophylaxis and developed an IFI (proven or probable) as determined by the investigator. This patient with AML was diagnosed with a fungal infection involving the pleura on Study Day 8 during treatment with POS Tablets. The patient appeared to be colonized with *Candida* as *Candida glabrata* was isolated from feces on Study Day 7. This patient was discontinued from POS Tablets on Study Day 10 and an alternative anti-fungal drug was used. The patient was alive at the Day 65 survival visit. The fungal infection was considered ongoing at the time of reporting. The POS plasma concentrations were above the pre-defined cut-off C_{min} of 500 ng/mL; on Study Day 8, C_{min} was 2530 ng/mL, and on Study Day 11 (1 day after the subject received the last dose), C_{min} was 2930 ng/mL. There were an additional nine cases of possible IFI who were analyzed as clinical failures which resulted in a breakthrough fungal infection rate of 10/210 (4.7%).

Deaths occurred in approximately 9% (18/210) of the treated patients by Study Day 65. The most common cause of death were due to infections (including sepsis and septic shock), reported in eight patients. Two cases of renal failure associated with drug-drug interactions with a calcineurin inhibitor resulted in death. There was one patient, post HSCT, who died from multi-organ failure including renal failure, and the immediate cause of death was reported as hepatic insufficiency. POS Tablets might have contributed to the hepatic injury in this patient, however it is more likely that death was due to complications post HSCT, including CMV reactivation, and hepatotoxic effects associated with myelosuppressive drugs. Two additional subjects died after the survival visit on Day 65 (>70 days). These 2 patients died from progression of their underlying hematologic malignancy, sepsis, fungal pneumonia, viral hepatitis, cardiac disorders, and complications post HSCT due to graft-versus-host disease.

8. Clinical Safety

Study P05615 was a single-arm study and therefore there were no comparative safety data for POS Tablets. The safety database included 230 patients who received at least one dose of POS Tablets. The most common adverse reactions (> 25%) were diarrhea and nausea. Other adverse reactions included elevation of hepatic transaminases, QTc interval prolongation, and drug-drug interactions, all of which are known adverse reactions associated with triazole antifungal drugs, including posaconazole.

Dr. O'Shaughnessy evaluated the patients in this study for safety issues that are associated with the triazole class of antifungal drugs, which included hepatotoxicity, QTc interval prolongation, adrenal insufficiency, and clinical drug-drug interactions. There was one subject (300mg dose cohort) who met the protocol pre-specified criteria for significant QTc interval prolongation (QTc >500 msec). The patient was asymptomatic, and the study drug was discontinued and the event resolved. Elevation of hepatic transaminases and hyperbilirubinemia were reversible in most cases. Five subjects (2%) had hepatic treatment related adverse events that were considered related to study drug and led to discontinuation of study drug. Two patients (<1%) had hepatic function test results that met the criteria for Hy's Law during their treatment; hepatic transaminases and bilirubin levels returned to normal ranges in one patient and had improved in the other patient before the end of the study period. Many of the cases with elevated hepatic transaminases were confounded by adverse reactions associated with myelosuppressive regimens for treatment of leukemia or HSCT and GVHD.

The attribution of adverse reactions to POS Tablets was confounded by having no comparative safety data and by adverse reactions related to the patients' underlying hematologic malignancies and concomitant

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myelosuppressive drug regimens. The adverse reactions in patients with high and low exposures to POS tablet were compared and did not appear to be different. Dr. O'Shaughnessy determined that, within the range of exposures that have been observed in this study, there did not appear to be an association of higher POS concentration with a higher incidence of a treatment-related adverse events following administration of POS Tablets.

In summary, POS tablets were reasonably well tolerated and had a similar safety profile to the marketed POS Oral Suspension. Based on the safety information provided in Study P05615 and the known safety profile of posaconazole, the potential benefit of POS Tablets in preventing life-threatening invasive fungal infection outweighs the risk of adverse reactions in immunocompromised patients with hematologic malignancies. As CDTL reviewer, I concur with this assessment. At the time of writing of this CDTL memo, the Clinical review by Elizabeth O'Shaughnessy, MD was not entered into DARRTS.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held for this NDA.

10. Pediatrics

POS Tablets are not suitable for young children because young pediatric patients are unable to consistently swallow tablets or capsules. The formulation of the tablet also does not permit the tablet to be crushed or split. The sponsor plans to develop an age-appropriate oral powder for suspension formulation using the same manufacturing process as for POS Tablets (b) (4) and thus, is proposed to have similar absorption properties to that of POS Tablets.

In their pediatric plan, the sponsor proposes to conduct a study to evaluate the safety, tolerability, and PK of two new formulations of posaconazole (IV solution, followed by sequential use of the new age-appropriate oral formulation) in immunocompromised pediatric patients with known or expected neutropenia. The dosing regimens for the IV and new age-appropriate oral formulations in pediatrics will be determined based on attaining the same target POS PK exposure ranges (i.e, steady-state C_{min} and steady-state AUC) as that which has already been agreed upon by DAIP and the sponsors for POS Oral Suspension (Schering-Plough) and POS Tablets (Merck).

The sponsor is requesting a waiver for pediatric patients < 2 years of age and a deferral for studies in pediatric patients > 2 to < 13 years of age. The adult studies for POS Oral Suspension included patients 13 years and older. A meeting was held with the Pediatric Review Committee (PeRC) on October 2, 2013. PeRC recommended that a waiver be granted for patients < 1 year of age, instead of < 2 years, because cases of hematological malignancies do occur in children between the ages of 1 to 2 years of age. PeRC also recommended that an efficacy study be requested if an appropriate pediatric dosage regimen cannot be determined for the IV and new age-appropriate oral formulation of POS in the PK study proposed by the sponsor. As CDTL reviewer, I concur with this assessment by PeRC.

11. Other Relevant Regulatory Issues

There are no outstanding regulatory issues for this NDA application.

12. Labeling

The sponsor has modified the approved labeling for NOXAFIL Oral Suspension to include information relevant to POS Tablets in physician's labeling rule (PLR) format. The most notable issue with the labeling is the revision of the Dosage and Administration section (b) (4)

DAIP's revision that POS Tablets should be taken with food. As CDTL reviewer, I concur with this labeling revision. (b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

As the CDTL reviewer, I concur with the assessments made by the review team and recommend approval of this NDA for POS Tablets.

- Risk Benefit Assessment

NOXAFIL is currently marketed as an oral suspension for the prophylaxis of invasive fungal infections in immunocompromised patients, specifically neutropenic patients undergoing treatment for acute myelogenous leukemia (AML) or myelodysplasia (MDS), as well as hematopoietic stem-cell transplant (HSCT) patients with graft-versus-host disease (GVHD). The oral suspension formulation has several limitations that render administration to these patients potentially problematic, i.e, highly variable oral absorption, the need to administer with a high fat meal or nutritional supplement, and the need for frequent daily dosing because of dose limited absorption. POS Tablets employ a formulation and manufacturing process that allows POS to be delivered to the more basic pH of the small intestine that enhances the oral absorption of POS. POS Tablets have greater oral bioavailability than the oral suspension and is given QD (vs. BID or TID for the oral suspension). (b) (4)

Overall, as the CDTL reviewer, I feel that the benefit of POS Tablets outweigh the risks.

- Recommendation for Post-Marketing Risk Management Activities

There are no recommendations for post-marketing risk management activities.

- Recommendation for other Postmarketing Study Commitments

There are no recommendations for post-marketing commitments.

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- Recommended Comments to Applicant

There are no comments for the applicant.

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/s/

PHILIP M COLANGELO
11/04/2013