Official Protocol Title:	A Study of the Safety, Tolerability, and Pharmacokinetics of Intravenous (IV) and Powder for Oral Suspension Formulations of Posaconazole (POS) in Immunocompromised Pediatric Subjects with Neutropenia
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TITLE:

A Study of the Safety, Tolerability, and Pharmacokinetics of Intravenous (IV) and Powder for Oral Suspension Formulations of Posaconazole (POS) in Immunocompromised Pediatric Subjects with Neutropenia

IND NUMBER: 75,061
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
1.0; 2.1; 2.2; 4.2.1; 4.2.2; 4.2.2.1; 4.2.2.2; 5.2; 8.1.4; 8.2.5	Trial Summary; Trial Design; Trial Diagram; Rationale for the Trial and Selected Subject Population; Rationale for Dose Selection/Regimen; Starting Dose for This Trial; Maximum Dose/Exposure for This Trial; Trial Treatments; Power and Sample Size; Power and Sample Size	Addition of a third dose cohort (6 mg/kg) based on review of the PK data from Dose Cohort #1 (3.5 mg/kg) and Dose Cohort #2 (4.5 mg/kg) which have completed enrollment.	Based on interim analysis of the first 2 enrolled dose cohorts, the 4.5 mg/kg dose cohort (currently the highest dose cohort in the protocol) achieved exposures (as measured by mean Cavg concentrations) that were significantly lower than the exposure seen in adult studies of the POS IV and tablet formulations. Therefore, in an effort to achieve systemic POS exposure more closely aligned with the exposure profile in adults, a third dose cohort (6 mg/kg, Dose Cohort #3) is being added to the study.

1.0; 2.1; 8.2.5	Trial Summary; Trial Design; Power and Sample Size	Addition of 36 subjects to the study to be enrolled in the newly added third dose cohort (6 mg/kg).	The number of subjects enrolled in this cohort is being increased from a minimum of 24 subjects, as was enrolled in the initial two dose cohorts, to a minimum of 36 in order to generate a more robust safety database at the likely dose that will achieve sufficient PK exposures.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title (s)	Description of Change (s)	Rationale
Note: a few grammar edits were included throughout the protocol to enhance readability.			
4.2.2.2	Maximum Dose/Exposure for This Trial	Additional description of 300 mg/day as maximum dose.	Clarification of reasoning of the maximum dose choice.
5.1.2	Subject Inclusion Criteria	The following text was deleted from inclusion criterion #5: "Sexually active females of childbearing potential must have a negative urine pregnancy test which must be followed up with a confirmed negative serum pregnancy test (β-HCG) within 48 hours following the screening visit."	A serum pregnancy test is no longer required at Screening. Pregnancy is listed as an exclusion criterion, and details of serum and urine test requirements are now clarified in Section 6.1, Trial Flow Chart Part 1, footnote e, and in Section 7.1.3, Laboratory Procedures/Assessments.

6.1 (Part 1)	Trial Flow Chart Part 1: (Visits 1-14)	Footnote e, addition of the following language: If a serum pregnancy test is performed at screening and the baseline visit occurs more than 2 days after screening, the serum pregnancy test should be repeated at the baseline visit. If the baseline visit occurs 2 days or less from the screening visit, serum pregnancy test is sufficient and a pregnancy test does not need to be repeated at the baseline visit. A urine pregnancy test may be substituted for a serum pregnancy test at the screening visit; however, if a urine pregnancy test is used for screening, it must be followed up with a confirmed negative serum pregnancy test within 48 hours.	To provide clarification of pregnancy testing requirements at screening and baseline visits. And to clarify that negative serum pregnancy test results are required before treatment.
6.1 (Part 1)	Trial Flow Chart Part 1: (Visits 1-14)	Addition of total protein to footnote f to align with Laboratory Tests in Table 8. In Section 7.1.3.1.	Correction of a typographical error; total protein was inadvertently left out of footnote f in the prior protocol version.

6.2 (Part 2)	Trial Flow Chart Part 2: (Visits 15-28)	Addition of a check mark in the prior/concomitant medications row in the column for the Follow-up 14 Days after End of Therapy (Visit 27).	Correction of a typographical error. The collection of concomitant medications is a required part of the safety follow-up per Section 7.1.1.5.2 of the protocol and the Data Entry Guidelines.
6.2 (Part 2)	Trial Flow Chart Part 2: (Visits 15-28)	Addition of total protein to footnote h to align with Laboratory Tests in Table 6.	Correction of a typographical error, total protein was inadvertently left out of footnote f in the prior protocol version.
7.1.2.7	IV Study Drug Administration/ Infusion Site Examination	Clarification of IV dosing: loading dose (BID) versus subsequent dosing (once daily dosing).	IV drug administration needed to be described with additional details.
7.1.3.1	Laboratory Safety Evaluations, Table 8	Deletion of Urinalysis column and addition of pregnancy test footnote. Footnote added to state when urine pregnancy test may be used, and the need for a follow-up serum pregnancy test.	Clarification that urine pregnancy tests could be substituted for serum pregnancy tests at screening.
7.1.3.1	Laboratory Safety Evaluations, Table 8	Addition of magnesium testing as part of chemistry testing.	Correction of a typographical error. Magnesium testing is included in the chemistry testing in Sections 6.1 and 6.2 on the Trial Flow Chart (in footnotes f and h, respectively), but was inadvertently excluded from Table 8.

7.1.5.1	Visit Requirements/Screening Electrocardiogram	Addition of the following text for clarification: A single ECG or telemetry may be used to evaluate QTc for eligibility at the screening visit, however two 12 lead ECGs performed 5 minutes apart must be done at the Baseline Visit to confirm QTc criteria for study eligibility before study drug dosing occurs.	To provide clarification of the ECG testing requirements at the baseline and screening visits.
7.1.5.2	Baseline Visit	Addition of the following text for clarification: Two 12 lead ECGs performed 5 minutes apart must be done at the Baseline Visit to confirm QTc criteria for study eligibility before study drug dosing occurs.	Additional ECG information, including number and criteria.
7.1.5.2	Baseline Visit	Explanation of repeat pregnancy test.	Rationale for repeated pregnancy tests needed to be included in repeated laboratory tests.

8.2.6	Interim Analysis	Description of interim analysis that was performed on first 2 dose cohorts, and statement that no formal interim analysis is planned for the third dose cohort.	The interim analysis was the basis for the addition of the 6 mg/kg dose cohort.
9.2	Packaging and Labeling	Text revised for clarification. The text in Section 9.2 in the first amendment states that on Day 1 subjects will be dispensed two vials for their dose of POS IV solution. The new text is as follows: On Day 1 of POS IV solution, subjects will be dispensed 2 vials which are to be taken as 2 separate doses to be administered 12 hours apart (BID). This will be followed by 1 vial daily on days 2-10, or until IV treatment is completed.	The text is being updated in order to clarify that on Day 1 subjects will receive 2 vials meant to be taken as 2 separate doses 12 hours apart and they are not to be taken together as one dose. Additional text added for clarification.

1.0 TRIAL SUMMARY

Abbreviated Title	Safety, tolerability, & PK of IV & oral POS in immunocompromised children.
Trial Phase	1B
Clinical Indication	Prophylaxis of invasive fungal infections in immunocompromised pediatric subjects with neutropenia or expected neutropenia.
Trial Type	Interventional
Type of control	No treatment control
Route of administration	IV and oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Two treatment groups by age (which will enroll simultaneously): • Age Group 1 (Young Children): 2 to < 7 years of age, and • Age Group 2 (Adolescents/Older Children): 7 to 17 years of age Three dosing cohorts within each Age Group (which will enroll sequentially): • 3.5 mg/kg/day (a minimum of 24 subjects across both age groups) • 4.5 mg/kg/day (a minimum of 24 subjects across both age groups) • 6 mg/kg/day (a minimum of 36 subjects across both age groups) The maximum dose is 300 mg in all dose cohorts. Subjects that would receive >300 mg based on weight based dosing will receive 300 mg. Note that earlier versions of the protocol (MK-5592-097-00 and 01), included the first dose cohorts (3.5 and 4.5 mg/kg daily). These dose cohorts have completed enrollment. The third dose cohort (6 mg/kg daily) is a new addition with this version of the protocol (MK-5592-097-02).
Number of trial subjects	Approximately 84 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 32 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for approximately 120 days, from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 7 days, each subject will receive study drug for a maximum of 28 days. The last study visit will be 14 days +/- 2 days after administration of the last dose of study drug. A survival assessment will be also performed anytime between Days 90 to 110.
Randomization Ratio	Non-randomized

A list of abbreviations used in this document can be found in Appendix 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a nonrandomized, multicenter, open-label, sequential dose-escalation study of the safety, tolerability, and PK of 2 posaconazole (POS, MK-5592) formulations in pediatric subjects: (1) an intravenous (IV), sulfobutylether-beta-cyclodextrin-containing (SBEβCD) formulation which is currently approved in adults (hereafter referred to as "POS IV solution") and (2) powder for oral suspension prepared as a single-use powder for reconstitution (which has the same components contained within the adult-approved POS oral tablet; hereafter referred to as "POS PFS"). In this study, these 2 formulations will be administered to immunocompromised children and adolescents ages 2 years to 17 years with neutropenia or expected neutropenia (absolute neutrophil count $\leq$500/mm^3). The study will be conducted in conformance with Good Clinical Practices.

All subjects will be administered POS IV solution for a minimum of 10 days. Those subjects who are still neutropenic will then switch to oral treatment with the POS PFS for a minimum of 10 days; however, subjects may continue on POS IV solution beyond Day 10, if a subject cannot tolerate or refuses to take oral medication. Transition to POS PFS, rather than remaining on POS IV solution, is preferred.

Those subjects who complete at least 10 days of POS IV solution and are both willing and able to tolerate oral treatment will start on oral treatment the next day and will be administered POS PFS for a minimum of 10 days. Those subjects who continue on POS IV solution beyond Day 10 may transition to POS PFS at any time through Day 18 that they are able to tolerate oral medication, or they may complete study treatment with POS IV solution only. POS PFS may also be continued beyond 10 days of treatment if the subject remains neutropenic. However, the maximum total duration of POS, administered as either IV solution or POS PFS, is 28 days.

There will be two age groups in this study. Both age groups will enroll simultaneously. The original protocol, MK-5592-097-00, outlined the study of two dose cohorts, 3.5 mg/kg and 4.5 mg/kg. At the time of this amendment, these dose cohorts, 3.5 mg/kg and 4.5 mg/kg, have completed enrollment. This protocol amendment, MK-5592-097-02, adds a third dose cohort, 6 mg/kg, based on the observed PK in Dose Cohort 1 and 2. See the Study Rationale in Section 4.2.2. Dose cohorts will enroll sequentially. Each POS formulation (IV and POS PFS) will be assessed separately within each dose cohort. If a dose cohort within a specific age group has an acceptable safety profile and does not achieve the target exposure for both formulations, dosing will be escalated to the next dose cohort within that same age group.

The two age groups (Young Children [ages 2 - < 7 years; Age Group 1]; Adolescents/Older children [7 to 17 years; Age Group 2]) will enroll simultaneously:

- **Age Group 1: Young Children (minimum of 36* subjects, age 2 to <7 years)**
  - Dose Cohort #1: A minimum of 12 subjects will receive POS IV solution at 3.5 mg/kg (maximum 300 mg/dose, 3.5 mg/kg IV BID on Day 1, then 3.5 mg/kg IV once daily on Days 2-10). Thereafter, subjects will either proceed to POS PFS at 3.5 mg/kg (maximum 300 mg/dose) once daily or continue on POS IV solution, if they are unwilling or unable to tolerate POS PFS.
  - Dose Cohort #2: A minimum of 12 subjects will receive POS IV solution at 4.5 mg/kg (maximum 300 mg/dose, 4.5 mg/kg IV BID on Day 1, then 4.5 mg/kg IV once daily on Days 2-10). Thereafter, subjects will either proceed to POS PFS at 4.5 mg/kg (maximum 300 mg/dose) once daily or continue on POS IV solution, if they are unwilling or unable to tolerate POS PFS.
  - Dose Cohort #3: A minimum of 12 subjects will receive POS IV solution at 6 mg/kg (maximum 300 mg/dose, 6 mg/kg IV BID on Day 1, then 6 mg/kg IV once daily on Days 2-10), Thereafter, subjects will either proceed to POS PFS at 6 mg/kg (maximum 300 mg/dose) once daily or continue on POS IV solution, if they are unwilling or unable to tolerate POS PFS.
- **Age Group 2: Adolescents/Older Children) (minimum of 36* subjects, age 7 to 17 years)**
  - Dose Cohort #1: A minimum of 12 subjects will receive POS IV solution at 3.5 mg/kg (maximum 300 mg/dose, 3.5 mg/kg IV BID on Day 1, then 3.5 mg/kg IV once daily on Days 2-10). Thereafter, subjects will either proceed to POS PFS at 3.5 mg/kg (maximum 300 mg/dose) once daily or continue on POS IV solution, if they are unwilling or unable to tolerate POS PFS.
  - Dose Cohort #2: A minimum of 12 subjects will receive POS IV solution at 4.5 mg/kg (maximum 300 mg/dose, 4.5 mg/kg IV BID on Day 1, then 4.5 mg/kg IV once daily on Days 2-10). Thereafter, subjects will either proceed to POS PFS at 4.5 mg/kg (maximum 300 mg/dose) once daily or continue on POS IV solution if they are unwilling or unable to tolerate POS PFS.
  - Dose Cohort #3: A minimum of 12 subjects will receive POS IV solution at 6 mg/kg (maximum 300 mg/dose, 6 mg/kg IV BID on Day 1, then 6 mg/kg IV once daily on Days 2-10). Thereafter, subjects will either proceed to POS PFS at 6 mg/kg (maximum 300 mg/dose) once daily or continue on POS IV solution if they are unwilling or unable to tolerate POS PFS.

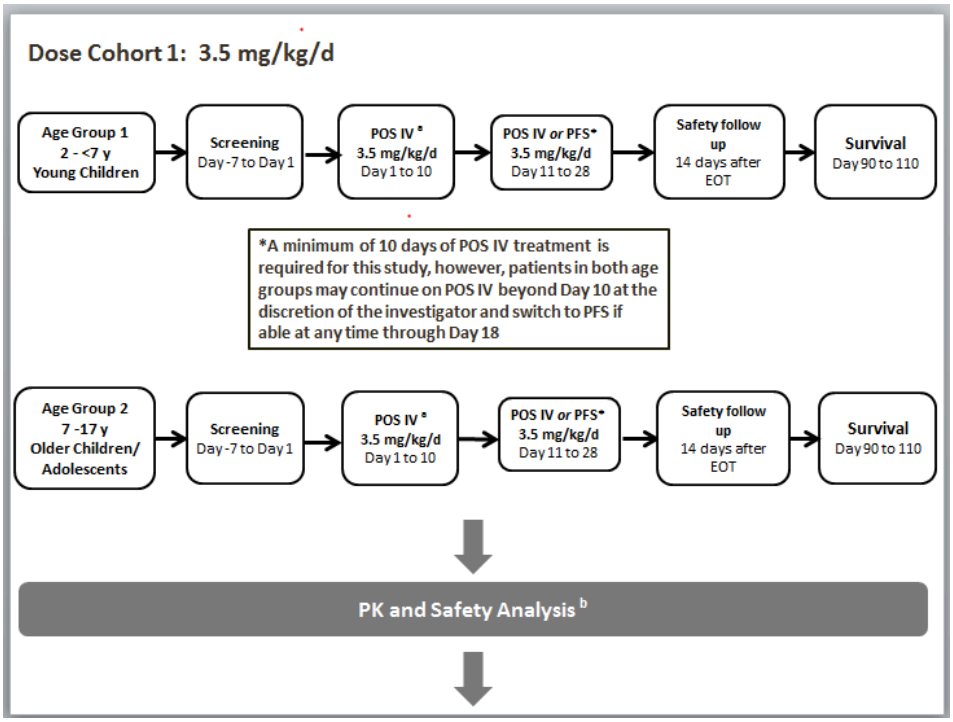
*NOTE: In addition to the minimum of 72 subjects required to complete each of the 3 dose cohorts in the 2 age groups, for Dose Cohort #3, an additional 12 subjects will be enrolled

without regard to age group in Dose Cohort #3. Therefore, in total, a minimum of 84 subjects will be enrolled for the entire study.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1 below.



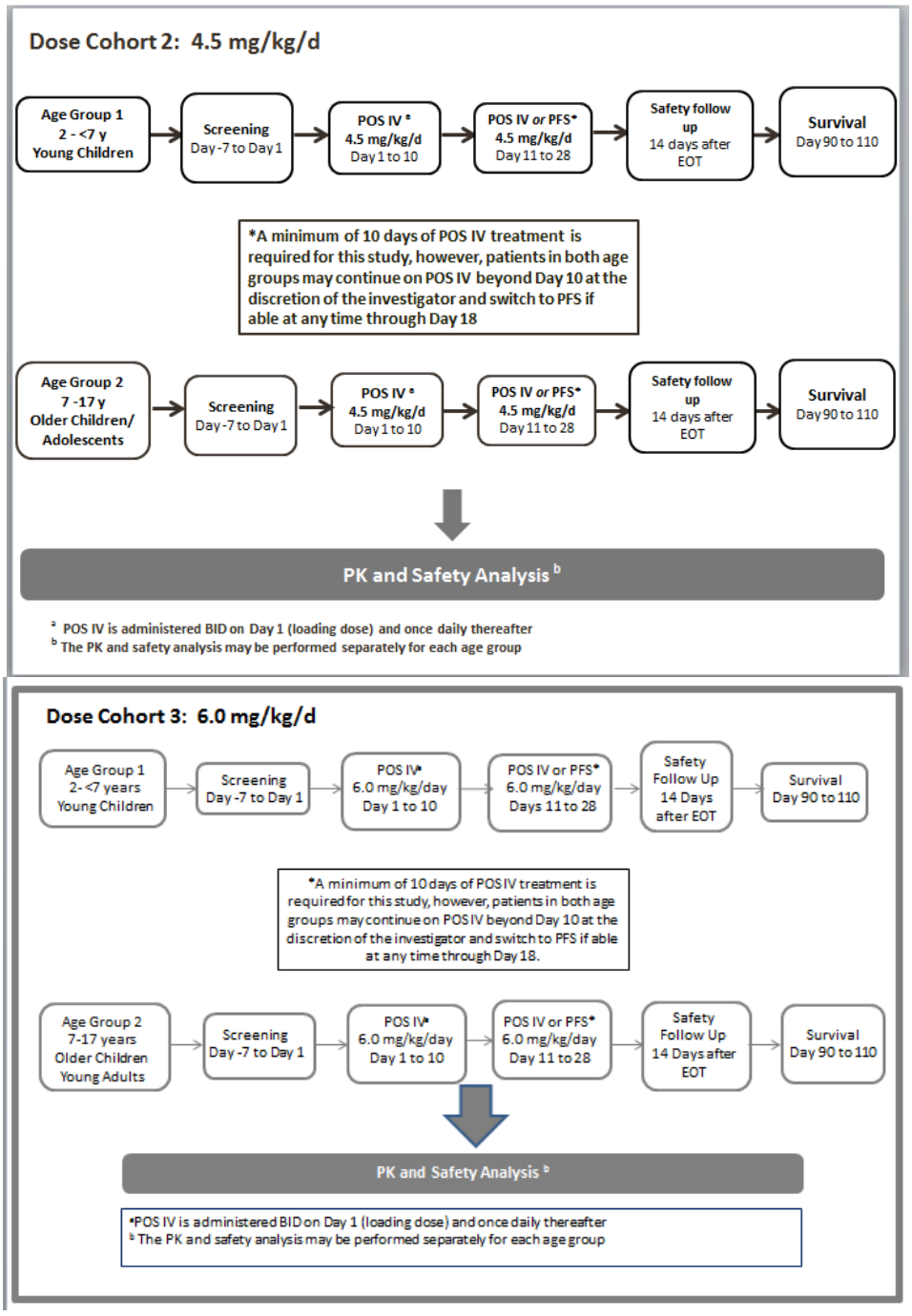


Figure 1 Study Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate the pharmacokinetics (PK) of POS IV solution and POS PFS administered to immunocompromised pediatric subjects (ages 2 years to 17 years) with neutropenia or expected neutropenia.

   Estimation: The plasma pharmacokinetics profile [AUC, C_{max}, C_{min}, and C_{avg}] following administration of POS IV solution and POS PFS will be summarized by age group and dose cohort.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate the safety and tolerability of POS IV solution and POS PFS administered to immunocompromised pediatric subjects (ages 2 years to 17 years) with neutropenia or expected neutropenia

   Estimation: Safety parameters will be summarized for each age group and dose cohort.

3.3 Exploratory Objectives:

1) **Objective:** To evaluate the palatability and acceptability of POS PFS

2) **Objective:** To evaluate the PK of sulfobutylether-beta-cyclodextrin (SBEβCD)

4.0 BACKGROUND & RATIONALE

4.1 Background

Posaconazole (POS) is a broad-spectrum triazole antifungal compound which exhibits potent antifungal activity against a variety of yeasts and molds, including strains that are resistant to amphotericin B (AMB), fluconazole (FLZ), voriconazole (VOR), or itraconazole (ITZ).

POS has shown excellent in vitro activity when compared with ITZ, FLZ, VOR, and AMB against most of the more than 25,000 strains of yeasts and molds including FLZ-resistant (FLZ-R), VOR-resistant (VOR-R), ITZ-resistant (ITZ-R), and amphotericin B-resistant (AMB-R) strains. A global surveillance study focusing on *Candida* and *Aspergillus* isolates was conducted for an eight year period spanning 2001 to 2009: no major changes in susceptibility to POS were observed. Results in clinically relevant animal models of aspergillosis, candidiasis, and other serious fungal infections demonstrated the potential benefit of therapeutic and prophylactic administration of POS.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on POS.

4.1.1 Pharmaceutical and Therapeutic Background

POS is a triazole antifungal compound for the treatment of serious fungal infections. POS, like other azoles, blocks the synthesis of ergosterol, a key component of the fungal membrane, through the inhibition of the enzyme lanosterol 14α–demethylase (CYP51).

Several POS formulations have been developed for both oral and intravenous (IV) administration in adults. The current oral formulations for adults include the POS oral suspension (approved by the FDA in 2006) and the POS oral tablet (approved by the FDA in 2013). POS oral suspension, an aqueous suspension containing 40 mg/mL of POS, was initially approved for use in adults for the prophylaxis and treatment of invasive fungal infections (IFI). The indications for POS oral suspension vary by country. POS oral suspension is commercially available in United States (US), the European Economic Area (EEA), Switzerland, and other regions of the world.

The current IV formulation of POS, the POS IV solution, is an aqueous injectable cyclodextrin-based solution containing 18mg/ml of POS to be diluted with either 0.9% saline or 5 % dextrose solution prior to IV administration. It includes the solubilizer, sulfobutylether-beta-cyclodextrin (SBEβCD). POS IV solution has completed Phase III trials in adults. The IV formulation was granted approval for use in adults in the US in March 2014 and was granted approval for use in adults by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in September 2014.

The POS oral tablet, which contains 100 mg of POS per tablet interspersed with a pH-resistant polymer hypromellose acetate succinate (HPMCAS), has completed Phase III trials in adults and was granted approval for use in adults in the US in November 2013 and in the EU in April 2014. The current POS oral tablet is too large to be easily swallowed by young children. The Sponsor does not believe that a smaller strength tablet (e.g., 20 mg) will address the needs for the pediatric patient population for two key reasons: 1) a single-strength tablet that cannot be divided will not allow for weight-based dosing, which is the most appropriate means of dosing pediatric patients, and 2) such tablets would still need to be swallowed whole, which is a formidable task, particularly for younger children. However, an oral equivalent, such as a pediatric oral formulation containing POS (interspersed with HPMCAS polymer as a single-use powder for reconstitution (wherein the powder is mixed with liquid and then administered as an oral drink to the patient), could potentially fulfill the need. To this end, the Sponsor plans to utilize the same POS/HPMCAS intermediate developed for the POS tablet in a single-use powder for reconstitution (i.e., POS PFS) for use in pediatric patients. This represents a more age-appropriate and dose-flexible formulation platform to support pediatric clinical trials, while potentially offering similar benefits of improved absorption and PK as the POS tablet used in adults.

The Sponsor has evaluated a prototype of the PFS formulation, a powder for oral suspension formulation, in an initial trial in adult healthy volunteers (PN106), comparing the PK of the POS oral powder formulation with the POS tablet. The trial completed in 4Q2012 and the Clinical Study Report (CSR) was finalized in June 2013. Final results demonstrate that this pediatric oral formulation has favorable pharmacokinetics (with plasma levels comparable to

those of the adult oral tablet), is well tolerated, and is not associated with major taste issues. Pediatric dosing of the POS PFS was informed by results from this study based on the top potency of 300 mg.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Rationale for Current Trial

IFIs are a leading cause of infectious disease morbidity and mortality in immunocompromised patients. As in adults, the pediatric population at risk for developing IFI, primarily due to neutropenia and T-cell dysfunction, includes, but is not limited to allogeneic stem cell transplant (SCT) recipients, patients with acute leukemias, myelodysplasia, severe aplastic anemia, and advanced stage non-Hodgkin's lymphoma. The incidence of IFI in pediatric patients with cancer ranges from 5% to 20%, but this incidence is higher in certain subgroups such as recipients of stem cell transplants (up to 16%), subjects with acute leukemia (10% to 20%), and subjects with acute myelogenous leukemia (9%) [1], [2], [3], [4].

As a potent triazole antifungal agent with a wide spectrum of activity against both pathogenic yeasts and molds, POS may be useful in pediatric patients who are at risk for developing IFI. The decision to initiate prophylaxis for IFI is dependent on the underlying disease and the degree of immunosuppression of the patient. Currently, there is no standard of care for prophylaxis in this patient population. In the current Infectious Diseases Society of America (IDSA) *Clinical Practice Guidelines for the Management of Candidiasis,* POS is included in the list of agents recommended for prophylaxis of candidiasis in neutropenic patients; however, there are no specific recommendations for pediatric patients. Furthermore, exposure to POS appears to be correlated with efficacy. Based on the available clinical efficacy data, the fact that candidiasis is the most common pediatric IFI and that the spectrum of activity of POS includes *Aspergillus*, the next most common pediatric IFI, the use of POS in the immunocompromised patient population is justified.

For pediatric patients, two new formulations of POS are under development: the POS IV solution (same formulation as in adults) and the POS powder for oral suspension (PFS) formulation (containing similar components to those employed in the adult oral tablet). Both new formulations will potentially benefit the pediatric population. The POS IV solution may be used in hospitalized patients who are unable to tolerate oral intake or in whom there is concern for poor oral drug absorption. The POS PFS is anticipated to have a more favorable PK profile than the currently available POS oral suspension, based on data from adult studies evaluating the solid oral tablet. Given the potential benefit to pediatric patients, the new formulations merit study in this population. The study of both formulations is combined into one trial for two principal reasons. First, the transition of therapy from IV to oral administration when patients are able to tolerate oral therapy while still requiring antifungal prophylaxis reflects current clinical practice. Second, given the substantial challenges of enrolling trials in this pediatric patient population, evaluating both formulations in one study

may provide information beneficial to patients earlier than if the formulations were evaluated in 2 separate trials which would be competing for the same population.

The intention of this study is to collect pharmacokinetics (PK), safety, and tolerability information on POS administered as POS IV solution, followed by POS PFS to neutropenic pediatric subjects, or pediatric subjects who are expected to become neutropenic, and who are at risk of developing IFI. The subjects will range in age from 2 years to 17 years of age. This age range represents the pediatric population at risk of developing IFI for which data are lacking. The study design includes an assessment of safety for all treated subjects at each dose level for each age group employing rapid data collection and centralized analysis.

Rationale for Age Groups in this Study

As noted above, the intention of this study is to characterize the PK, safety, and tolerability of the POS IV solution and the POS PFS in a prophylactic setting (namely, in neutropenic pediatric subjects who are at risk for developing IFI).

Presently there is no oral formulation of POS approved for pediatric patients <13 years of age. Therefore, the POS PFS (containing similar components to those employed in the adult oral tablet) is under investigation.

The subjects in this study will range in age from 2 years to 17 years. The subject population will be divided into two age groups.

- Young Children (Age Group 1) will be subjects 2 years to < 7 years,
- Adolescents/Older Children (Age Group 2) will be subjects 7 years to 17 years.

Three dosage levels of POS are planned for each Age Group (3.5 mg/kg daily, Dose Cohort #1; 4.5 mg/kg daily, Dose Cohort #2; 6 mg/kg daily, Dose Cohort #3). Note that the original protocol, MK-5592-097-00, had Dose Cohorts #1 and #2, 3.5 and 4.5 mg/kg daily, respectively. The third dose cohort, 6 mg/kg daily, was added in amendment, MK-5592-097-02.

The study design includes an assessment for safety for all treated subjects at each dose level for each age group employing rapid data collection and centralized analysis.

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

4.2.2 Rationale for Dose Selection/Regimen

Rationale for dose cohorts 1 and 2 included in original protocol version, MK-5592-097-00

The starting dose of 3.5 mg/kg/day for the POS IV solution and POS PFS formulation was projected via modeling and simulation to achieve the pharmacokinetic (PK) target of an average concentration (C_{avg}) of between 500 and 2500 ng/mL in approximately 90% of patients 2 to 17 years of age (see Section 4.2.3 for details regarding the PK target). In this

study, if at least 10 out of 12 PK-evaluable patients in a dose cohort achieve a C_{avg} in the specified range the PK exposure target will be considered to have been met.

Specifically, utilizing population PK models developed for the POS IV solution and the POS PFS formulation based on observed adult PK data, simulations were conducted to project the exposure in the pediatric population. The PK profile of the POS PFS formulation is expected to be comparable to the POS tablet, based on results of a biocomparison study conducted in adults. The PK concentration versus time profile in the pediatric population was projected by allometrically scaling model parameters by body weight, and simulating the resulting profiles, then calculating the distribution of projected C_{avg} values for each formulation for young children (2 to <7 years) and adolescents (7 to 17 years).

For the POS IV solution, a dose of 3.5 mg/kg/day was expected to result in 91% of young children (2 to <7 years) and 96% of adolescents/older children (7 to 17 years) with C_{avg} values within the target range of 500 and 2500 ng/mL. For the POS PFS formulation, 85% of young children (2 to <7 years) and 90% of adolescents (7 to 17 years) were expected to achieve the PK target.

For the POS IV solution, a dose of 4.5 mg/kg/day was expected to result in 94% of young children (2 to <7 years) and 88% of adolescents/older children (7 to 17 years) with C_{avg} values within the target range of 500 and 2500 ng/mL. For the POS PFS formulation, 90% of young children (2 to <7 years) and 86% of adolescents/older children (7 to 17 years) were expected to achieve the PK target.

Rationale for the addition of third dose cohort (6 mg/kg) in Amendment MK-5592-097-02

At the time of this amendment, MK-5592-097-02, the 3.5 mg/kg and 4.5 mg/kg dose cohorts have completed enrollment. Based on interim analysis, although the 4.5 mg/kg dose cohort achieved the primary PK target of ~90% of subjects having a steady state C_{avg} POS concentration between 500 and 2500 ng/mL for both the IV solution and oral PFS formulations in both age groups (see Table 1), the overall exposures (as measured by mean C_{avg} concentrations) were markedly lower than the exposure seen in adult studies of the POS tablet (see Table 2). Specifically in Age Group 1, mean C_{avg} values were approximately 30-40% lower than what was seen in an adult study of the oral tablet (1080 ng/mL and 976 ng/mL for the IV and PFS, respectively, compared with 1580 ng/mL for the tablet). Therefore, in an effort to achieve systemic POS exposure more closely aligned with the exposure profile in adults, a third dose cohort (6 mg/kg, up to a maximum of 300 mg) is being added to the study.

The selection of the 6 mg/kg/day for Dose Cohort #3 was supported by a modeling and simulation analysis, which predicted the geometric mean C_{avg} and the fraction of subjects with C_{avg} falling within the target range of 500-2500 ng/mL at higher doses for each formulation and age group. Specifically, a population PK model was developed for the IV and PFS formulation based on observed pediatric PK data in Dose Cohorts 1 and 2 (3.5 and 4.5 mg/kg, respectively) and simulations were conducted to project the exposure in the same pediatric age groups for each formulation at doses of 6 and 7.5 mg/kg.

For the POS IV solution, a dose of 6 mg/kg/day is expected to result in 97% of subjects in Age Group 1 (2 to <7 years) and 87% of subjects in Age Group 2 (7 to 17 years) with C_{avg} values within the target range of 500 and 2500 ng/mL Geometric mean C_{avg} values for IV are predicted to be 1343 ng/mL and 1651 ng/mL for Age Groups 1 and 2, respectively. For the POS PFS formulation, 83.5% of Age Group 1 (2 to <7 years) and 82% of Age Group 2 (7 to 17 years) are expected to achieve the PK target. Geometric mean C_{avg} values for PFS are predicted to be 847 ng/mL and 1083 ng/mL for Age Group 1 and 2, respectively.

A dose of 7.5 mg/kg/day is predicted to result in less than 80% of Age Group 2 (7 to 17 years) having C_{avg} values within the target range of 500 and 2500 ng/mL for either formulation. This is because a substantial fraction will have C_{avg} values above 2500 ng/mL indicating that this dose would result in too many subjects exceeding the PK target for this Age Group. Taken together, the simulations support that 6 mg/kg/day is the most appropriate dose to be used for both formulations across both age groups in Dose Cohort 3.

The primary PK driver for the addition of the third dose cohort (6 mg/kg, up to a maximum of 300 mg per administration) is the low C_{avg} values seen in Age Group 1 (2 years to <7 years) (see Table 1). Age Group 2 (7 years to 17 years) will be included in Dose Cohort #3 in order to determine if it is possible to identify a single dose for both formulations that achieves adequate exposure across both Age Groups, since a single weight-based dose across all ages is preferable. Because the maximum dose is capped at the adult dose of 300 mg (BID Day 1 and once daily each successive day), the increase in exposure in Age Group 2 will be limited because any subject 50 kg or heavier (most prevalent in the Adolescents/Older Children group) will receive a maximum dose of 300 mg/d.

Table 1 Number of Subjects per Cavg Range by Age group and Formulation for PK Evaluable Subjects in Dose Cohort #1 (3.5 mg/kg/d) and Dose Cohort #2 (4.5 mg/kg/d) of MK-5592-097

Dose	Age Group	*Dose Type*	N	<200	200 - <500	500 - <2500	2500 - <3650	>3650
3.5 mg/kg	1 (2 to <7 yrs old)	IV	11	0	2 (18%)	9 (82%)	0	0
		PFS	5†	0	3 (60%)	2 (40%)	0	0
	2 (7 to 17 yrs old)	IV	19†	0	0	18 (95%)	1 (5%)	0
		PFS	10	0	1 (10%)	9 (90%)	0	0
4.5 mg/kg	1 (2 to <7 yrs old)	IV	13	0	0	13 (100 %)	0	0
		PFS	7†	0	1 (14%)	6 (86%)	0	0
	2 (7 to 17 yrs old)	IV	14	0	0	13 (93%)	1 (7%)	0
		PFS	8†	0	0	8 (100%)	0	0

†Due to subjects being at steady state, the predose value was assumed to be equal to C24hr for the 2 subjects (for 3.5 mpk PFS), 1 subject (for 3.5 mpk IV) and 2 subjects (for 4.5 mpk PFS) missing the 24 hour PK sample and this value was used to replace the missing C24hr in order to calculate Cavg.

Table 2 Summary of Posaconazole Plasma Steady State Pharmacokinetic Parameters for Dose Cohort #1 (3.5 mg/kg/d) and Dose Cohort #2 (4.5 mg/kg/d) by Age Group and Dose Formulation in PK Evaluable Subjects from MK-5592-097

Dose Cohort	Age Group	Dose Type	N	C_{max} (ng/mL)†	T_{max} (hr)‡	AUC_{0-24} (hr*ng/mL)†	C0 (ng/mL)†	C_{min} (ng/mL)†	Cavg (ng/mL)†
1: 3.5 mg/kg	1 (2 to <7 yrs old)	IV§	11	1590 (43.1)	1.78 (1.67 - 5.53)	17800 (55.0)	424 (82.4)	400 (81.3)	743 (55.0)
		PFS§	5	884 (44.4)	3.83 (1.92 - 4.25)	12300 (36.0)	262 (40.4)	256 (45.4)	511 (36.0)
	2 (7 to 17 yrs old)	IV	19	2450 (72.7)	1.77 (0.00 - 3.50)	27300 (49.7)	802 (90.4)	670 (65.1)	1140 (49.7)
		PFS	10	1340 (30.8)	2.20 (1.92 - 6.03)	20700 (33.7)	629 (46.5)	579 (44.9)	861 (33.7)
2: 4.5 mg/kg	1 (2 to <7 yrs old)	IV	13	2350 (41.1)	1.75 (1.42 - 5.90)	25900 (29.7)	536 (62.9)	492 (59.0)	1080 (29.7)
		PFS§	7	1590 (43.5)	3.92 (1.88 - 5.92)	23400 (64.4)	615 (174.3)	557 (163.7)	976 (64.4)
	2 (7 to 17 yrs old)	IV	14	2380 (40.1)	1.75 (1.52 - 1.80)	31500 (38.1)	882 (57.3)	813 (57.9)	1310 (38.1)
		PFS	8	1670 (28.5)	6.14 (1.98 - 7.98)	28700 (33.9)	827 (54.3)	790 (48.2)	1190 (33.9)

†Geometric mean (%GCV); ‡median (min - max).
§ Due to subjects being at steady state, the predose value was assumed to be equal to C24hr for the 2 subjects (for 3.5 mpk PFS), 1 subject (for 3.5 mpk IV) and 2 subjects (for 4.5 mpk PFS) missing the 24 hour PK sample and this value was used to replace the missing C24hr in order to calculate C_{avg}.

4.2.2.1 Starting Dose for This Trial

In this study, 3 different doses will be evaluated in 3 sequential cohorts, 3.5 mg/kg (Dose Cohort #1), 4.5 mg/kg (Dose Cohort #2), and 6 mg/kg (Dose Cohort #3). The starting dose is 3.5 mg/kg.

All doses administered of the POS IV solution will be calculated based on the subject's weight at Baseline. All doses administered of POS PFS will be calculated based on a subject's body weight as measured within 3 days prior to the first day of POS PFS treatment.

Starting Dose for POS IV Solution:

The IV starting dose for this trial is 3.5 mg/kg in both age groups. For each subject, the IV solution will be given for the first 10 days, with a BID loading dose on Day 1, followed by once daily on Days 2-10. Thereafter, subjects should preferably switch to POS PFS (see below).

For subjects who are unable or unwilling to tolerate a transition to oral medication at Day 10 of POS IV solution, the subjects may continue on POS IV solution and switch to POS PFS up through Day 18 at the discretion of the investigator or complete study treatment with POS IV solution.

Starting Dose for POS PFS:

The oral PFS starting dose for this trial is 3.5 mg/kg in both age groups (after the subject completes at least 10 days of treatment with POS IV solution). For each subject, the POS PFS will be given once daily for 10-18 days. POS PFS may be continued beyond 10 days of treatment if the subject remains neutropenic.

In this study, the total maximum duration of POS, administered as either IV solution or PFS, is 28 days.

No comparator will be used in this trial. The primary goal of this study is to evaluate the PK of POS IV solution and POS PFS.

4.2.2.2 Maximum Dose/Exposure for This Trial

In this study, 3 different doses are to be studied. Two dosing cohorts have completed evaluation (3.5 mg/kg/day Dose Cohort #1, and 4.5 mg/kg/day Dose Cohort #2). A third Dose Cohort of 6 mg/kg/day (Dose Cohort #3), is to be the final dose cohort to be evaluated in this study.

Maximum dose by formulation:

POS IV solution:

- 6 mg/kg/day (up to a maximum of 300 mg) of POS administered as an IV solution on Days 1-10 (given BID on Day 1). Subjects may receive up to 28 days of POS IV solution if they are unable to transition to oral therapy (POS PFS).

POS PFS:

- 6 mg/kg/day POS (up to a maximum of 300 mg) after the subject completes at least 10 days of treatment with POS IV solution. For each subject, the POS PFS will be given once daily for 10-18 days. POS PFS may be continued beyond 10 days of treatment if the subject remains neutropenic.
- In this study, the total maximum duration of POS, administered as either IV solution or PFS, is 28 days.

For a given subject, the maximum dose for an individual subject of either formulation is 300 mg/day (following BID dosing on Day 1). No subjects will receive more than 300 mg/day dosing (after 300 mg BID dosing on Day 1). The maximum total daily dosing established for this study reflects the approved adult dose for POS tablet and POS IV solution formulations, which is 300 mg BID on Day 1 followed by 300 mg once daily. Daily dosages above 300 mg/day will not be evaluated in this trial.

4.2.2.3 Rationale for Dose Interval and Trial Design

The dose interval and trial design were chosen based on target doses and PK profiles identified for adults enrolled in the POS IV solution and oral tablet studies. The duration of study therapy administration for each formulation is based on the minimum duration of POS required to achieve steady state (i.e., 7 – 10 days).

4.2.3 Rationale for Pharmacokinetic Targets

The minimum desired target level of the steady-state POS plasma concentration for this study is based on observations from earlier registration clinical trials conducted with the POS oral suspension in adult patients (Table 3).

Table 3 Posaconazole Exposures at Steady State During Treatment with Posaconazole Oral Suspension from Pivotal Trials Supporting Safety and Efficacy in Adult Patients

	Mean C_{avg} ng/mL	Lower Bound 2nd Quartile ng/mL	99th Percentile ng/mL
Prophylaxis of IFIs (600 mg/day)			
Neutropenic subjects (AML/MDS)	583	322	1920
GVHD subjects	1130	557	3260
Treatment of IFIs (800 mg/day)	808	290	2990

C_{avg} = average plasma concentration; GVHD = graft-versus-host disease; IFI= invasive fungal infections; AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome

In a controlled trial involving neutropenic adult subjects (study P01899), POS oral suspension was superior to standard azoles (fluconazole and itraconazole) in reducing the incidence of IFI, including aspergillosis and candidiasis, and in reducing 100-day all-cause mortality; in this study, the mean plasma concentration at steady state was 583 ng/mL. POS oral suspension was also found to be effective for the treatment of adult subjects with refractory IFI, including aspergillosis, and for the treatment of IFI in adult subjects who were intolerant to certain antifungals (study P00041). POS oral suspension showed a better response rate and survival benefit when compared to historical control cases; in this study, the mean plasma concentration was 808 ng/mL.

There appeared to be an association between POS plasma concentration achieved with POS oral suspension at steady state and efficacy in these pivotal clinical trials. In general, adult subjects with POS steady state exposures in the second quartile or higher had higher response rates than control (Table 4). Using these data and following receipt of regulatory guidance, a mean steady state C_{avg} exposure of approximately 1200 ng/mL with approximately 90% of subjects with values between 500 and 2500 ng/mL has been proposed as a target exposure for the POS pediatric program.

Since there is evidence that efficacy is correlated to exposure, with lower exposures being associated with poor outcomes, and the cumulative data to date does not suggest any toxicities are associated with C_{avg} >2500 ng/mL, the primary goal is to ensure that most pediatric subjects achieve a steady-state C_{avg} that is >500 ng/mL.

Table 4 Clinical Response Rates by C_{avg} Quartile Analyses from Pivotal Trials of POS Oral Suspension Supporting Safety and Efficacy in Adult Patients

	CI98-316 Prophylaxis in GVHD		**P01899 Prophylaxis in Neutropenia (AML/MDS)**		**P00041 Treatment - Aspergillosis**	
Quartile	***C_{avg} Range***	***Clinical Failure***	***C_{avg} Range***	***Clinical Failure***	***C_{avg} Range***	***Clinical Success***
Q1	21.5 – 557	44.4% 28/63	89.6 – 322	54.7% 29/53	55 – 277	24% 4/17
Q2	557 – 915	20.6 % 13/63	322 – 490	37% 20/54	290 – 544	53% 9/17
Q3	915 – 1563	17.5% 11/63	490 – 734	46.3% 25/54	550 – 861	53% 9/17
Q4	1563 – 3650	17.5% 11/63	734 - 2200	27.8% 15/54	877 – 2010	71% 11/16
Control	--	35%	--	42%	--	26%

Shaded area = Targeted exposure in 90% of subjects
C_{avg} = average plasma concentration; GVHD = graft-versus-host disease; AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome

4.2.4 Rationale for Endpoints

4.2.4.1 Efficacy Endpoints

There are no efficacy endpoints for this study.

4.2.4.2 Safety Endpoints

Safety will be assessed based on adverse events, physical examinations, vital signs, clinical laboratory test results, and electrocardiogram (ECG) results. All subjects who receive at least one dose of study treatment will be included in the safety analysis.

The occurrence of azole-associated toxicity will be evaluated.

An external Data Monitoring Committee (eDMC) will be assembled at the onset of the study and will evaluate the accumulating available data for safety at the completion of Dose Cohort #1 for each age group, prior to each age group starting the next dosing group and at other time points as determined by the study team and eDMC.

4.2.4.3 Pharmacokinetic Endpoints

The primary endpoint will be C_{avg} for both the POS IV solution and POS PFS. The C_{avg} will be calculated by dividing the AUC with dosing interval. Additionally, C_{min}, C_{max}, T_{max}, and AUC will also be calculated for patients in each age group per dose cohort.

4.2.4.4 Additional Endpoints

Palatability and acceptability parameters for the new POS PFS formulation will be assessed in all subjects (refer to Section 7.1.2.9 for further details of palatability assessment).

In addition, the PK of sulfobutylether-beta-cyclodextrin (SBEβCD) will also be assessed as an exploratory objective while on POS IV solution. This objective is included in support of a regulatory authority request to contribute data on pediatric cyclodextrin use, for which pediatric clinical trial data are lacking.

4.2.4.5 Planned Exploratory Biomarker Research

4.2.4.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on buccal swab DNA specimens collected during this clinical trial). Importantly, a subject may participate in the main trial without participating in the Future Biomedical Research portion of the study.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male or female immunocompromised subjects who are between the ages of 2 years to 17 years (inclusive) and have documented or anticipated neutropenia (ANC<500/mm^3 [0.5 x 10^9/L]) which is expected to last for at least 7 days following start of study treatment will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1) Be a child or adolescent of either sex and of any race, 2 to 17 years of age at the time of screening.

2) Have a parent/guardian or legally authorized representative who is willing to give written informed consent. Assent will be obtained from minors according to institutional practices. The guardian/subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

3) Have documented or anticipated neutropenia (ANC < 500/mm^3 [0.5 x 10^9 /L]) expected to last for at least 7 days following start of study treatment in at least one of the following clinical situations:
    a. Acute leukemia,
    b. Myelodysplasia,
    c. Severe aplastic anemia,
    d. Recipients of Autologous HSCT,
    e. High risk neuroblastoma,
    f. Advanced stage non-Hodgkin's lymphoma (NHL),
    g. Recipients of allogeneic HSCT during the pre-engraftment (neutropenic) period,
    h. Hemophagocytic lymphohistiocytosis

4) Must have a central line (e.g. central venous catheter, peripherally inserted central catheter, etc.) in place or planned to be in place prior to beginning IV study therapy.

5) If the subject is of reproductive potential and is not surgically sterile (or their partner is not surgically sterile), must agree to remain abstinent* or use (or have their partner use) a medically accepted method of birth control starting from the time of consent through 1 month after the completion of the study. Acceptable methods of birth control‡ are: intrauterine device (IUD) with spermicide, diaphragm or cervical cap (if acceptable to local standard of care) with spermicide, contraceptive sponge with spermicide, condom with spermicide, and any registered and marketed hormonal contraceptive that contains an estrogen and/or progestational agent, including oral, subcutaneous, intrauterine or intramuscular agents that is used with a barrier method.

* Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡ If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1) Has a proven or probable IFI, as defined by the 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) consensus group criteria, at the time of screening.

2) Has received POS (any formulation) within the past 10 days prior to screening.

3) Is receiving prohibited drugs (has not met the required washout periods as listed in Section 5.5.1) at the time of randomization or is expected to receive such prohibited medications during the course of study therapy.

4) Has laboratory results that are outside of normal limits at screening, as follows:
   a) Moderate or severe liver dysfunction, as defined as:
      - Aspartate aminotransferase (AST) > 5 times the upper limit of normal (ULN),

        OR

      - Alanine aminotransferase (ALT) > 5 times the ULN, **OR**
      - Serum total bilirubin >2.5 times the ULN, **OR**
      - AST or ALT > 3 times ULN with total bilirubin > 2 times ULN,

b) Calculated creatinine clearance <30 mL/min. Creatinine clearance will be calculated using the following equation:

Creatinine clearance = $\frac{k \times \text{height (cm)}}{\text{Serum creatinine (mg/dL)}}$

Where k = 0.55 for male and female children 1-13 years old; k = 0.7 for adolescent males 13-18 years old, k= 0.55 for adolescent females 13-18 years old; (Schwartz equation)

5) Has QTc prolongation (either based on Fridericia or Bazett's correction) at screening defined as :

a) Symptomatic QTc prolongation >450 msec (males) or >470 msec (females)

OR

b) Any QTc prolongation of >500 msec

6) Is pregnant or intends to become pregnant during the course of the study, or is breastfeeding at screening.

7) Has a history of anaphylaxis attributed to the azole class of antifungal agents.

8) Has any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the study, evaluations or optimal participation in the study including:

a) Not expected to receive a minimum of 10 days of POS IV solution

9) Has previously participated in this study

10) Has participated in any Phase 1 clinical study for a medication classified as an Investigational New Drug (IND) within 30 days prior to enrollment or is expected to participate in such a study within 60 days following randomization. Participation in non-IND studies is permitted.

11) Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

POS study drug will be administered to patients with neutropenia associated with chemotherapy given for a diagnosis of acute leukemia (newly diagnosed or relapsed), myelodysplasia, severe aplastic anemia, high risk neuroblastoma, advanced NHL, or hemophagocytic lymphohistiocytosis. In addition, recipients of an autologous HSCT or recipients of autologous HSCT during the pre-engraftment (neutropenic) period are eligible.

The subject population will be divided into 2 age groups. Age Group 1 will be Young Children, who are aged 2 years to <7 years of age, and Age Group 2 will be Adolescents/Older Children, who are aged 7 to 17 years of age.

The two formulations will be studied in all subjects in a sequential manner (POS IV solution, followed by POS PFS formulation). There will be three pre-specified dosage cohorts in this study. The decision to move to the next higher dose cohort may be done independent of complete enrollment of the other age group.

The first dosage cohort (Dose Cohort #1) will receive 3.5 mg/kg (up to a maximum of 300 mg) BID of POS IV solution on Day 1, followed by 3.5 mg/kg/day (up to a maximum of 300 mg) of POS IV solution administered once daily from Day 2 through Day 10; thereafter, treatment with the POS PFS formulation at a dose of 3.5 mg/kg/day will be initiated and administered for at least 10 additional days. Subjects who are unwilling or unable to tolerate a transition to oral therapy after Day 10 may continue on POS IV solution at the discretion of the investigator. Subjects who continue on POS IV solution beyond Day 10 may (a) transition to POS PFS at any time up through Day 18 that they are able to tolerate oral medication, or (b) complete study treatment with POS IV solution only. POS PFS may also be continued beyond 10 days of treatment if the subject remains neutropenic. The total maximum duration of POS, administered as either IV solution or PFS, is 28 days. Preliminary PK data for each formulation will be reviewed upon completion of the first dosage cohort. If the PK exposure target is achieved in an age group in Dose Cohort #1, and an appropriate pediatric dose can be determined for both formulations, then the second dosage cohort may not be enrolled for that age group.

The second dosage cohort (Dose Cohort #2) will receive 4.5 mg/kg (up to a maximum of 300 mg per administration) BID POS IV solution on Day 1, followed by 4.5 mg/kg/day of POS IV solution administered once daily from Day 2 through Day 10; thereafter, treatment with the POS PFS formulation at a dose of 4.5 mg/kg/day will be initiated and administered for at least 10 additional days. Subjects who are unwilling or unable to tolerate a transition to oral therapy after Day 10 may continue on POS IV solution at the discretion of the investigator. Subjects who continue on POS IV solution beyond Day 10 may (a) transition to POS PFS at any time up through Day 18 that they are able to tolerate oral medication, or (b) complete study treatment with POS IV solution only. The total maximum duration of POS, administered as either IV solution or PFS, is 28 days. The dose chosen for Dose Cohort #2 may be modified prior to enrollment based on preliminary review of PK data from the Dose Cohort #1 in order to optimize the achievement of the desired PK target.

The third dosage cohort (Dose Cohort #3) will receive 6 mg/kg (up to a maximum of 300 mg) BID POS IV solution on Day 1, followed by 6 mg/kg/day (up to a maximum of 300 mg) of POS IV solution administered once daily from Day 2 through Day 10; thereafter, treatment with the POS PFS formulation at a dose of 6 mg/kg/day will be initiated and administered for at least 10 additional days. Subjects who are unwilling or unable to tolerate a transition to oral therapy after Day 10 may continue on POS IV solution at the discretion of the investigator. Subjects who continue on POS IV solution beyond Day 10 may (a) transition to POS PFS at any time up through Day 18 that they are able to tolerate oral

medication, or (b) complete study treatment with POS IV solution only. The total maximum duration of POS, administered as either IV solution or PFS, is 28 days.

The POS study treatments to be used in this trial are outlined below in Table 5.

Table 5 Trial Treatment

		POS IV Solution Treatment Period (minimum 10 days)		POS PFS Oral Treatment Period (minimum 10 days)
		Day 1	**Day 2 through end of IV dosing**	
Age Group 1 **Young Children** (2 to < 7 years old)	**Dose Cohort # 1**	3.5 mg/kg BID POS IV solution*	3.5 mg/kg once daily POS IV solution*	3.5 mg/kg once daily POS PFS *
	Dose Cohort # 2	4.5 mg/kg BID POS IV solution*	4.5 mg/kg once daily POS IV solution*	4.5 mg/kg once daily POS PFS*
	Dose Cohort # 3	6 mg/kg BID POS IV solution*	6 mg/kg once daily POS IV solution*	6 mg/kg once daily POS PFS*
Age Group 2 **Adolescents/Older Children** (7 to 17 years old)	**Dose Cohort # 1**	3.5 mg/kg BID POS IV solution*	3.5 mg/kg once daily POS IV solution*	3.5 mg/kg once daily POS PFS*
	Dose Cohort # 2	4.5 mg/kg BID POS IV solution*	4.5 mg/kg once daily POS IV solution*	4.5 mg/kg once daily POS PFS*
	Dose Cohort # 3	6 mg/kg BID POS IV solution*	6 mg/kg once daily POS IV solution*	6 mg/kg once daily POS PFS*

*Maximum dose of 300 mg per administration

- Young children (Age Group 1, ages 2 to <7 years) and adolescents/older children Age Group 2, (ages 7-17 years) will be enrolling in parallel.
- The duration of POS IV solution treatment may be extended beyond 10 days if subjects are unwilling or unable to transition to POS PFS.
- The combined duration of POS treatment, either as POS IV solution or POS PFS, for each subject cannot exceed 28 days
- Safety and PK data will be assessed separately for each dose cohort in 2 age groups.
- Potential modifications to dosing based on preliminary study data are outlined in Section 4.2.2.

Trial Treatment should begin within 7 days of the screening visit. Subjects will receive a minimum of 10 days of POS IV solution. POS will be administered intravenously over approximately 1.5 hours via a central line.

All supplies indicated in Table 5 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

All doses of POS IV solution will be based on the subject's age and the actual body weight as measured at Baseline (prior to receiving the first IV dose of POS). The IV dose will remain the same for all subsequent IV doses (through Day 10, or beyond Day 10, for subjects unable or unwilling to transition to POS PFS).

All doses of POS PFS will be based on the subject's age and the actual body weight as measured on the first day of oral treatment (prior to receiving the first dose of POS PFS) or the subject's weight within 3 days prior to the first dose of PFS. The oral dose will remain the same for all subsequent oral doses.

Doses should be continued through each treatment period as outlined in Table 5.

The rationale for the selection of doses to be used in this trial is provided in Section 4.2.2.

5.2.1.2 Dose Escalation

There is no dose escalation in this study for individual subjects. Dose escalation will be performed at the completion of each age group and dose cohort, for the subsequent dose cohort as outlined in Table 5.

5.2.2 Timing of Dose Administration

- Each dose of POS IV solution will be administered approximately 12 hours apart on Day 1 and every 24 hours thereafter during IV treatment.
- Each dose of POS PFS will be administered every 24 hours during the oral treatment period. POS PFS will be administered without regard to food intake; however, information about food intake will be recorded in a food diary as outlined in Section 7.1.2.8.
- Serial PK samples will be obtained prior to dosing or within 24 hours after the last dose of study drug administration for early discontinuation.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the study treatment administered.

5.3 Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

Treatment allocation will be stratified according to the following factors:

1. Age Group 1 (Young Children): 2 years to < 7 years of age
2. Age Group 2 (Older Children/Adolescents): 7 years to 17 years of age

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

All prior medication taken by the subject 14 days prior to study treatment initiation and all medications (including chemotherapeutic medications) taken during study treatment, or during the 14 day safety follow-up period following therapy will be recorded on the appropriate electronic Case Report Form (eCRF). The identity of the therapy, the dates started or stopped (or notation of continuing if that is the case), and the reason for use must be recorded. The use of any concomitant medication must relate to an AE or the subjects medical history.

Patients receiving other systemic (PO or IV) antifungal agents as prophylactic therapy must discontinue those treatments prior to study drug administration. No other systemic antifungal agents may be administered during the POS treatment phase without Sponsor approval.

In addition, nasal sprays of amphotericin B (AMB) and aerosolized AMB are viewed as systemic regimens and are prohibited during IV/oral POS study therapy (treatment phase). If subjects are on such treatment before study entry, such drugs must be discontinued prior to study drug administration.

Topical non-absorbable antifungals may be used for the prophylaxis or treatment of oropharyngeal candidiasis, vaginal candidiasis, or cutaneous fungal infection. These include the following medications: oral AMB, miconazole (oral or topical), nystatin (oral or topical), and clotrimazole (oral or topical). All other antifungal therapies must be approved by the Sponsor prior to use.

Investigational drugs under an IND (i.e., other drugs not yet approved for marketing by the FDA or local health authorities) administered in the 30 days prior to randomization are prohibited. Such investigational agents are also prohibited for 60 days following randomization.

Subjects should be monitored for 14 days after the last dose of POS for AEs, and all AEs should be reported in the eCRF.

5.5.1 Medications Prohibited Prior to Study Drug Administration and During the Study Treatment Phase

The medications prohibited prior to study drug administration and during the treatment phase of the study are listed in Table 6. This table also lists the recommended washout periods to be

observed for these prohibited medications prior to initiation of POS treatment. The washout period for POS after discontinuation is approximately 7 days.

Table 6 Prohibited Medications Prior to Study Drug Administration and During the Study Treatment Phase

Prohibited Medications During the Study Treatment Phase and Prior to Study Drug Administration	**Minimum Washout Period[a]**
Other systemic antifungal therapy (oral, intravenous or nasal/inhaled) for the treatment of invasive fungal infections (IFI)	30 days
Other systemic antifungal therapy (oral, intravenous, or nasal/inhaled) for the prophylaxis of IFI	No washout required
Medications that are known to interact with azoles and may lead to life-threatening side effects: astemizole, cisapride, ebastine, halofantrine, pimozide, quinidine, and terfenadine	10 days (astemizole) 24 hours (others)
Medications known to lower the serum concentration/efficacy of azole antifungals: barbiturates, carbamazepine, cimetidine, isoniazid, phenytoin, rifabutin, rifampin, and St. John's Wort (hypericum perforatum)	24 hours
Vinca alkaloids (vincristine, vinblastine, or other licensed or investigational members of this class)	48 hours
Ergot alkaloids (ergotamine, dihydroergotamine or other licensed or investigational members of this class)	2 days
Sirolimus (CYP3A4 substrate)	48 hours
Anthracycline-based chemotherapy	24 hours
Investigational drugs (new chemical or biological entities as part of an IND)	30 days
Trisenox (arsenic trioxides)	30 days
Disopyramide	4 days
Bepridil	10 days
Ibutilide	3 days
Haloperidol	10 days
HMG-CoA reductase inhibitors metabolized via CYP3A4 (e.g., simvastatin, lovastatin and atorvastatin)	24 hours
Cyclophosphamide	24 hours
Specific antiretroviral agents for the treatment of HIV including atazanavir, efavirenz, fosamprenavir, or ritonavir	24 hours
Kayexalate (sodium polystyrene sulfonate) [b]	No washout required

CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; QTc = QT interval corrected for rate; TdP = torsades de pointes.

[a] These waiting times should be observed prior to study drug administration in subjects receiving a prohibited drug as prior therapy. No concurrent use of prohibited medications is permitted. Deviations from these washout periods must be approved by the Sponsor prior to use of study drug or prohibited agent.

[b] Administration of Kayexalate prohibited during oral (PFS) treatment phase only

5.5.2 Medications Allowed During the Study

All medications not listed in Table 6 are permitted in the study. Specific medications that are allowed with caution and/or monitoring are presented in Table 7.

5.5.3 Medications Allowed With Caution and Clinical Monitoring

Clinical and/or QTc monitoring is recommended when the study drug is coadministered with one of the following drugs that have reported a potential risk of torsades de pointes:

- Antiarrhythmics (amiodarone, dofetilide, procainamide, sotalol)
- Chlorpromazine
- Clarithromycin
- Domperidone
- Droperidol
- Levomethadyl
- Mesoridazine
- Methadone
- Erythromycin
- Sparfloxacin
- Thioridazine

Medications that are allowed with caution and/or monitoring are presented in Table 7. These drugs are permitted, although their efficacy and safety should be clinically monitored and/or serum levels followed with appropriate dosage adjustments as necessary at the initiation of study drug, periodically during treatment, and after discontinuation of study drug:

Table 7 Medications Allowed During the Study that Require Monitoring

Medication Class	Medication Name*	Recommendation
Anticoagulants	Coumadin-type	Coumadin-type anticoagulants are permitted, although their efficacy and safety should be clinically monitored and/or serum levels followed with appropriate dosage adjustments as necessary at the initiation of study drug, periodically during treatment, and after discontinuation of study drug.
Antiretroviral Therapy	Tenofovir	As HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are CYP3A4 substrates, it is expected that POS will increase plasma levels of these antiretroviral agents. Patients should be carefully monitored for any occurrence of toxicity during the coadministration of POS and these agents. NOTE: Coadministration of POS with atazanavir, efavirenz, fosamprevanir, or ritonavir is not permitted during the treatment phase of the study.

Medication Class	Medication Name*	Recommendation
Benzodiazepines	Alprazolam Midazolam Triazolam	POS 200 mg orally once daily increased the AUC of midazolam by 83% following intravenous (IV) administration. Due to the inhibition of intestinal CYP3A4 by POS, an even greater effect of POS on the AUC of midazolam is expected following oral administration. Dose adjustments should be considered for all benzodiazepines that are metabolized through CYP3A4. POS interferes with the hepatic clearance of triazolam and midazolam, and thus, may enhance the sedative effects of these agents. Therefore, these agents should not be used unless monitoring is provided for excessive sedation
Calcium Channel Blockers	Diltiazem Nifedipine Nisoldipine Verapamil	For calcium channel blockers metabolized through CYP3A4 (e.g., diltiazem, nifedipine, nisoldipine, verapamil), frequent monitoring for AEs and toxicity related to calcium channel blockers is recommended during co-administration with POS. Dose adjustment of calcium channel blockers may be required.
Cardiac Glycosides	Digoxin	Administration of other azoles has been associated with increases in digoxin levels. Digoxin levels should be monitored when initiating or discontinuing POS treatment
Immunosuppressive	Cyclosporine	In heart transplant patients on stable doses of cyclosporine, POS 200 mg once daily increased cyclosporine concentrations requiring dose reductions of up to 29%. Cases of elevated cyclosporine concentrations resulting in SAEs, including nephrotoxicity were reported in clinical efficacy studies. Monitoring of cyclosporine blood levels should be performed upon initiation, during coadministration, and upon discontinuation of POS treatment, with adjustment of cyclosporine doses as necessary.
	Tacrolimus	POS increased C_{max} and AUC of tacrolimus (0.05 mg/kg body weight single dose) by 121% and 358%, respectively. Clinically significant interactions resulting in hospitalization and/or POS discontinuation were reported in clinical efficacy studies. When initiating POS treatment in patients already receiving tacrolimus, the dose of tacrolimus dose should be reduced (e.g., to about one third of the current dose). Thereafter, blood levels of tacrolimus should be monitored carefully during coadministration, and upon discontinuation of POS, and the dose of tacrolimus should be adjusted as necessary.
Oral Hypoglycemic Agents/Sulfonylureas	Glipizide	Glucose concentrations decreased in some healthy subjects when glipizide was coadministered with POS. Monitoring of glucose concentrations is recommended in diabetic patients.
Xanthine Derivatives	Theophylline	Theophylline is permitted, although its efficacy and safety should be clinically monitored and/or serum levels followed with appropriate dosage adjustments as necessary at the initiation of study drug, periodically during treatment, and after discontinuation of study drug.
* Not all medications from a specific medication class may be listed here.		

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

There are no diet or activity restrictions for this study. Information on food intake relative to dose administration will be collected during the oral (PFS) phase of the study in a study medication/food diary. The data collected will include the time the dose was administered, the type of meal that was consumed (if any) and the timing of the meal relative to study medication administration.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Death;

In this trial, a subject may discontinue from treatment, but continue to participate in the regularly scheduled activities of the study as long as the subject does not withdraw consent.

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- Serious adverse experience related to study therapy or the occurrence of an adverse experience (clinical or laboratory) that, in the judgment of the investigator, warrants withdrawal of study therapy;
- Failure to comply with the dosing, evaluations, or other requirements of the study;
- Request of the subject or subject's parent or legally authorized representative (subjects have the right to discontinue treatment or the study at any time for any reason);
- The subject has a confirmed positive serum pregnancy test;
- Initiation of other systemic (IV, oral, or nasal/inhaled) antifungal agents for empiric, pre-emptive or definitive therapy of IFI, including agents containing amphotericin B

(AMB), echinocandins, azole and triazole antifungal agents, or other investigational antifungal drugs;

- Subjects who, following Baseline require any of the prohibited medications listed in Table 6 of Section 5.5.1;
- Any situation or condition which may threaten the subject's health or well-being by continuing on study treatment;
- Administrative (e.g. study termination);
- An AST or ALT value that is greater than or equal to 3 X the ULN and an elevated total bilirubin value that is greater than or equal to 2 X the ULN and, at the same time, an alkaline phosphatase value that is less than 2 X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. **NOTE**: Patients will be discontinued from study therapy but followed for safety until the abnormal value(s) has/have normalized, stabilized, or returned to baseline;
- If the QTc interval change from Baseline is greater than 60 msec or the QTc interval is $\geq$500 msec (refer to Section 7.1.2.5 for details on ECG testing).

A subject who develops a superficial fungal infection (e.g., cutaneous fungal infection, thrush or candidal vaginitis) may be treated with topical antifungal agents (nystatin and/or azole formulations) and continued on study drug if in the judgment of the investigator there is no evidence of systemic involvement or more extensive mucosal involvement that would require more specific systemic antifungal therapy. Superficial candidiasis (including signs and symptoms and supportive laboratory findings) must be noted on the eCRF. It is the right and duty of the investigator or subinvestigator to interrupt treatment of any subject if he/she feels that study discontinuation is necessary to protect the subject, or that there are unmanageable factors, that may interfere significantly with the study procedures or interpretation of the results.

If a subject discontinues prior to completion of the study, the reason for the discontinuation will be obtained. The date of the last dose of study medication and the date of the last assessment and/or contact will be obtained. This information will be documented in the appropriate section of the eCRF. A follow-up contact (telephone or visit) will be arranged as appropriate.

At the time of discontinuation, every effort should be made to ensure all procedures and evaluations scheduled for the final study visit are performed (see Section 6.0, Trial Flow Chart). For all discontinued subjects, a trough sample should be collected within 24 hours of the last dose, AEs should be recorded and followed to outcome and medication compliance should be assessed.

5.9 Subject Replacement Strategy

If a subject in a given dose cohort and age group fails to complete 7 days of IV study therapy, a replacement subject will be entered at that dose cohort and age group. Subjects will not be re-enrolled in this study.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

The Trial Flow Chart for this study has been split into two parts:

Part 1: Screening and POS IV solution treatment phase of the study (Visits 1-14)

Part 2: POS PFS and Follow-up Phases of the study (Visits 15-28)

6.1 PART 1: (Visits 1-14) SCREENING, BASELINE & POS IV SOLUTION VISITS

			POS IV SOLUTION TREATMENT PHASE												
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Visit Title:	**Screening**	**Baseline**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Optional Use of POS IV Solution Day 11-28**	**Last Day of POS IV Solution[a]**	
Scheduling window	**Day -7 to < Day -1**	**Day-1**													
Administrative Procedures															Visits 15 - 28 Continue on next table (Part 2)
Obtain Informed Consent/Assent	X														
Informed Consent for Future Biomedical Research (optional)	X														
Review Inclusion/Exclusion Criteria	X	X													
Issue Subject Identification Card	X														
Medical History	X														
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Screening Number Assignment	X														
Randomization Number Assignment		X													
Clinical Procedures/Assessments															Visits 15 - 28 Continue on next table (Part 2)
Complete physical examination	X	X													
Focused physical examination[b]			X		X		X		X		X		X[b]	X	
Body Weight (kg)	X	X													
Height (cm)	X														
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram[c]		X								X[c]					
Chest Radiograph[d]		X													
IV Study Drug Administration			X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	

			POS IV SOLUTION TREATMENT PHASE											
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Visit Title:	**Screening**	**Baseline**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Optional Use of POS IV Solution Day 11-28**	**Last Day of POS IV Solution[a]**
Scheduling window	**Day -7 to < Day -1**	**Day-1**												
Laboratory Procedures/Assessments														
Pregnancy Test (Serum) [e]	X	X												
Hematology/Serum Chemistry [f, g]	X	X[f]			X[g]			X[g]				X[g]	X[g]	X
Absolute Neutrophil Count [h]	X	X[h]			X[h]			X[h]				X[h]	X[h]	X
POS PK Trough Sampling [i, J]								X[i]					X[j]	
POS Full PK Sampling [k]									X[k]					
Cyclodextrin (SBEβCD) PK sampling[l]									X[l]					
DNA/Buccal swab for Future Biomedical Research (optional)[m]			X											

a. The last day of POS IV solution can occur anytime between the 10th and the 18 day of treatment with POS IV solution.
b. After Day 1, the focused physical exam should be performed 3 times per week until the last day of POS IV
c. ECG may be performed on Day 6, 7, or 8
d. As clinically indicated to rule out fungal infection.
e. Pregnancy test will be done on females of childbearing potential. If a serum pregnancy test is performed at screening and the baseline visit occurs more than 2 days after screening, the serum pregnancy test should be repeated at the baseline visit. If the baseline visit occurs 2 days or less from the screening visit, serum pregnancy test is sufficient and a pregnancy test does not need to be repeated at the baseline visit. A urine pregnancy test may be substituted for a serum pregnancy test at the screening visit; however, if a urine pregnancy test is used for screening, it must be followed up with a confirmed negative serum pregnancy test within 48 hours.
f. Hematology: complete blood count (CBC) with differential; serum chemistry: BUN, calcium, serum creatinine, potassium, sodium, glucose, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, magnesium, chloride, and bicarbonate. At Baseline, only repeat hematology, chemistry & ANC if > 2 days since screening labs.
g. Hematology and chemistry testing must be performed 2 times per week with at least 2 days in between samples.
h. Collect ANC 2 times per week while on POS IV solution with at least 2 days in between samples.
i. **Plasma TROUGH sampling** (POS only; 0.35 mL of blood per sample) pre-dose (0 hr) on Day 6 of IV treatment. The Day 6 sample may be collected on Day 5 to coincide with other labs. For premature discontinuations (prior to Day 7), a trough level sample will be taken approximately 24 hours post start of infusion of the last dose, and all other safety assessments will be performed according to the Last Day of POS IV solution schedule.
j. For subjects continuing POS IV solution beyond Day 10 collect troughs once per week.
k. **POS PK sampling during POS IV solution administration**: Full PK sampling may be performed on any day from Day 7-10. Perform PK sampling at pre-dose (0 hour), within 15 minutes after the end of infusion, and at approximately 4, 6, 12 and 24 hours post start of infusion.
l. **Cyclodextrin (SBEβCD) PK sampling during POS IV solution administration**(0.35 mL of blood per sample): PK sampling at pre-dose (0 hour), within 15 minutes after the end of infusion, and at approximately 4, 6 and 12 hours post start of infusion. May be performed on any day from Day 7-10 and should coincide with POS full PK.
m. Participation in future biomedical research is optional. Informed consent for future biomedical research must be obtained before the DNA Buccal swab samples. The DNA buccal swab should be collected on Day 1 on randomized subjects only or at a later date, as soon as the informed consent is obtained.

6.2 PART 2: (VISITS 15-28) ORAL (PFS) TREATMENT AND FOLLOW-UP VISITS

	POS PFS TREATMENT											FOLLOW-UP		
Visit Number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit Title:	**1st Day of POS PFS[a]**	**2nd Day of POS PFS**	**3rd Day of POS PFS**	**4th Day of POS PFS**	**5th Day of POS PFS**	**6th Day of POS PFS**	**7th Day of POS PFS**	**8th Day of POS PFS**	**9th Day of POS PFS**	**10th Day of POS PFS**	**Optional POS PFS Day 11-18[b]**	**EOT/ Last Day of POS PFS[b]**	**FOLLOW-UP 14 Days after End of Therapy (EOT) (POS IV solution or POS PFS)**	**Survival Assessment[n]**
Scheduling window	**Day after last IV Dose**												**EOT +14 DAYS**	**Day 90-110**
Administrative Procedures														
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Medication/Food Diary Assessment [c]	X	X	X	X	X	X	X	X	X	X	X	X		
Provide or collect Study Medication/Food Diary (outpatients)[d]	X[d]					X[d]				X[d]		X[d]		
Clinical Procedures/Assessments														
Focused physical exam [e]	X		X			X				X	X	X		
Body Weight (kg)[f]	X													
Vital Signs[e]	X		X			X				X	X	X		
Electrocardiogram[g]										X[g]				
Oral Study Drug Administration	X[a]	X	X	X	X	X	X	X	X	X	X	X		
Assessment of Palatability	X				X							X		
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival Assessment[n]														X
Laboratory Procedures/Assessments														
Hematology/Serum Chemistry[h,i]			X[h i]			X[h i]				X[h i]	X[h i]	X[h i]		
Absolute Neutrophil [j]			X[j]			X[j]		X[j]			X[j]	X		
POS PK Trough Sampling[k,l]						X[k]					X[k, l]	X[k]		
POS Full PK Sampling[m]										X[m]				

a. The first day of POS PFS formulation can occur any day after Day 10 of POS IV solution.
b. The last day of POS PFS can occur anytime between the 10th through the 18th day of POS PFS (combined treatment with POS IV and POS PFS cannot exceed 28 days).
c. Food information will be collected in study medication diaries for subjects receiving PFS. The timing and characteristics of food taken will be recorded for each dose. Outpatients will maintain the daily dosing record and will record the actual time of dosing at the time of administration and the timing and characteristics of meals.
d. The SM/Food diary should be provided to outpatients and the completed diaries collected at least once a week at a scheduled outpatient visit.
e. For inpatients, perform focused physical exam and record vital signs 2 times per week, at least 2 days apart while on POS PFS. For outpatients, perform focused physical exam, and record vital signs once per week while on POS PFS.
f. The subject's weight as measured within 3 days prior to the first dose of oral treatment (PFS) will be used to calculate the first and all subsequent doses of PFS.
g. ECG may be performed on Day 8, 9, or 10 of PFS
h. Hematology: complete blood count (CBC) with differential; Serum Chemistry: BUN, calcium, serum creatinine, potassium, sodium, glucose, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, magnesium, chloride, and bicarbonate. The first sample after the first day of POS PFS should be collected no later than the 5th dose of POS PFS.
i. For inpatients, hematology and chemistry testing must be performed 2 times per week with at least 2 days in between samples. For outpatients, lab testing must be performed once per week while on POS PFS
j. ANC must be drawn a minimum of twice a week for inpatients and once per week for outpatients while on POS PFS and during periods of neutropenia (ANC <500/mm3). The first sample after the first day of POS PFS should be collected no later than the 5th dose of POS PFS.
k. **POS plasma trough sampling** during POS PFS administration (0.35 mL of blood per sample): Collect trough sample pre-dose (0 hr) on the 6th day of POS PFS and at the end of POS therapy. For premature discontinuations, a trough level sample will be taken approximately 24 hours after administration of the last dose, and all other safety assessments will be performed according to the Last Day of POS PFS schedule. The trough may be collected at either the 5th or 6th day of POS PFS to coincide with other labs.
l. For subjects continuing for more than 7 days of POS PFS treatment, POS trough samples should be collected once per week with other required labs.
m. **PK full sampling during POS PFS administration** (0.35 mL of blood per sample)**:** If an inpatient, perform PK sampling at pre-dose (0 hour), and 2, 4, 6, 8, and 24 hours post-dose; if an outpatient, perform PK sampling at predose (0 hour) 2, and 4 hours post-dose. Full PK sampling may be performed anytime between the 7th through the 10th day of POS PFS treatment.
n. Survival Assessment, if the subject is alive or dead, will be recorded on the electronic case report form (eCRF). If the subject dies, the cause and date of death will be recorded. This assessment can be made by telephone or by medical records.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

7.1.1.4 Medical History

A detailed medical history will be obtained by the investigator or qualified designee and recorded in the eCRF. The medical/disease history should include:

- Identify the specific medical condition listed in Inclusion criteria #3 that qualified the subject for the study
- Details regarding any ongoing or prior cancer diagnoses, immunosuppressive conditions (including HIV), and transplant procedures (BMT and solid organ)
- Details of previous surgeries or trauma
- Details of previous arrhythmias
- Details regarding recent or ongoing bacterial infections
- Detail of any prior history of fungal infection
- Any history of hepatitis
- Any significant signs or symptoms related to underlying medical conditions
- Results of any abnormal chemistry, hematology lab or imaging results performed within 7 days of starting the trial.

Any medical conditions found at the Screening and Baseline exams will be recorded on the eCRF in the Medical History module. The status of the condition will be evaluated as "resolved", "stable" or "unstable". Any unstable medical condition will require a comment.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirements, and prohibited medications for the 14 days prior to initiation of POS treatment as outlined in Section 5.5.1 and listed in Table 6.

- Record prior medication (prescription or over the counter) taken by the subject within 14 days before starting the trial. It is important to also record any protocol-specified prohibited medications, as outlined in Section 5.5.1 (Table 6), received during the 14-day period prior to enrollment.
- The identity of the therapy, the dates started and stopped (or notation of "continuing" if that is the case), and the reason for use must be recorded for all medications.
- Patients receiving other systemic antifungal agents (IV, oral or nasal/inhaled) as prophylactic therapy must discontinue these treatments prior to study drug administration. No other systemic antifungal agents may be administered during the study treatment phase (i.e., POS IV solution/PFS) without sponsor approval.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record all medications and therapeutic procedures taken by the subject during POS treatment and for the 14 days of safety follow-up. Of note, any protocol-specified prohibited medications (see Section 5.5.1 and Table 6) received during the 14-day follow-up period after POS had ended should also be recorded.

- Parenteral nutrition products should be recorded as concomitant medication.

The identity of the therapy, the dates started and stopped (or notation of "continuing" if that is the case), and the reason for use must be recorded for all medications. The use of any concomitant medication must relate to an AE or the subject's medical history.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Randomization Number

All eligible subjects will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 randomization number.

7.1.1.8 Trial Compliance (Medication)

Study medication compliance will be monitored by ongoing data review during the IV treatment phase (POS IV solution) of the study. Compliance during the oral treatment phase (POS PFS) will be verified by review of the study medication/food diary.

Interruptions from the protocol specified treatment (defined as missing one or more doses) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

The shifting of the timing of a dose (within the window provided to accommodate a subject's schedule) is not considered an interruption.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

The principal investigator or designee will perform a complete physical exam at the Screening & Baseline Visits and will perform directed (focused) physical exams at least two times a week thereafter as indicated in the Trial Flow Chart (Section 6.0). Any medical conditions found at the Screening and Baseline exams will be recorded on the eCRF in the Medical History module. The status of the condition will be evaluated as "resolved", "stable" or "unstable". Any unstable medical condition will require a comment. An exacerbation of a pre-existing condition or any new finding that occurs during the study will be captured as an adverse event and recorded in the Adverse Event module of the eCRF.

7.1.2.2 Body Weight (kg)

Body weight at Baseline will be used to calculate the subject's dose for the IV treatment phase of the study. The subject's weight measured within three days prior to the first dose of oral treatment should be used to calculate all oral treatment (PFS) doses. The actual weight measured should be recorded. Body weight should be obtained without shoes. At each required visit, it is preferred that the weight should be measured on the same scale for the same individual. Measurements should be recorded to the nearest tenth of a kg.

7.1.2.3 Height (cm)

Height measurements should be taken without shoes and be recorded to the nearest cm.

7.1.2.4 Vital Signs

The pretreatment vital signs will be considered the Baseline values.

Vital signs will be obtained by the principal investigator or designee. Systolic and diastolic blood pressure (mm Hg), heart rate (bpm) and body temperature (°C or °F) will be obtained according to the local standard procedure and will be recorded.

If the scheduled time for vital sign measurements coincides with a blood collection, the vital signs should be performed prior to the blood collection or at least 5 minutes afterwards. The same timing for obtaining the vital signs (before or after blood collection) should be used for all vital sign measurements.

Body temperatures obtained within one hour of blood product transfusions should not be included on the eCRF. On the required days, the maximum daily temperature (outside of blood transfusions) will be collected and recorded on the eCRF.

7.1.2.5 Electrocardiogram

Two baseline ECGs must be performed at least 5 minutes apart at the Baseline Visit for purposes of protocol eligibility.

Prior to study drug administration, all ECGs should be reviewed for clinically significant abnormalities and reported as normal (or with findings that are not clinically significant).

ECGs should also be performed on Day 6, 7 or 8 of POS IV solution treatment and on Day 8, 9, or 10 of POS PFS treatment and as clinically indicated for the evaluation of AEs.

ECGs performed after the Baseline Visit should be done at approximately the same time of day (AM or PM) that baseline ECGs were performed.

A standard 12-lead ECG, reporting ventricular rate, PR, QRS, QT, and QTc intervals, will be performed. Any clinically significant abnormality must be followed until stabilization or return to baseline.

Any change in the QTc interval of greater than 30 msec post Baseline (when compared to Baseline) will require a repeat ECG, and a determination of serum potassium (K), calcium (Ca), magnesium (Mg), and electrolyte replacement, if necessary. Additional evaluation may be required, and the principal investigator should determine if discontinuation of study drug or other evaluation is required in consultation with the project physician.

If the QTc interval change from Baseline is greater than 60 msec, study drug should be interrupted while evaluation and treatment of other etiologies is ongoing (Section 5.8, Subject Discontinuation Criteria).

During the Treatment Phase, if a QTc interval is found to be abnormal (symptomatic QTc intervals greater than 450 msec [males] or 470 msec [females]) after repeated ECG for

confirmation a cardiology consultation is to be requested to determine possible etiologies in addition to or other than study drug should also be performed at the same time (e.g., review of other concomitant drugs, and determination of serum Mg, Ca, and K levels). The investigator will determine if discontinuation of study drug is warranted after clinical examination of the subject and pertinent laboratory evaluation, and discussion of the case with the Sponsor's project physician.

ECGs performed will be transferred to a blinded third party for an evaluation of QT, QTc (Fredericia and Bazett), PR, and QRS intervals and ventricular rate, as well as an overall clinical interpretation. The final results of the third-party analysis will be considered the definitive ECG data and will be the only ECG data used in the analysis.

Note: When the collection of vital signs, ECGs, and PK samples coincide, the blood samples for PK determination should be collected first (so that the PK samples are collected on time), followed by the vital signs, and then the ECG. It is preferred that the ECG be performed at the same time each day (e.g., morning) to reduce diurnal variation.

7.1.2.6 Chest Radiograph

A chest radiograph will be performed, as clinically indicated, to evaluate for fungal infection.

7.1.2.7 IV Study Drug Administration/Infusion Site Examination

- The collection of blood specimens for safety labs and PK trough levels should preferably occur prior to the administration of POS IV solution.
- The subject's body weight at Baseline will be used to calculate all IV doses
- IV infusions should be administered via a central line at approximately the same time each day. On the first day of IV dosing there is a loading period during which 2 doses are given, separated by 12 hours. Subsequently, a single dose is given once daily. For the third dose, the dose should be timed to be given approximately 24 hours after the initial loading dose (i.e., approximately 12 hours after the second loading dose). All subsequent IV doses should be administered approximately 24 hours apart. If for any reason the timing of the medication needs to be adjusted after the first dose, the dose time may be adjusted by +/-3 hours.
- The infusion site should be examined prior to and at the end of the infusion according to local standard of care. Any adverse events observed at the infusion site or during the infusion will be recorded on the eCRF.

7.1.2.8 Oral Study Drug Administration (PFS)

- The collection of blood specimens should preferably occur prior to the oral administration of POS PFS.

- A subject's body weight should be measured within 3 days prior to the first day of POS PFS treatment. The weight measured will be used to calculate all subsequent doses of POS PFS treatment.
- The POS PFS dose may be administered by oral syringe or via a feeding tube and should be prepared and administered using the Sponsor supplies as outlined in the Pharmacy Manual. Refer to the Pharmacy Manual for additional details on allowed dosing devices.
- Doses of POS PFS should be administered 24 hours apart at approximately the same time each day. If for any reason, the timing of the medication needs to be adjusted after the first dose, the dose time may be adjusted by +/- 3 hours.
- The Study Medication/Food Diary must be completed for every dose of PFS. If treatment is given as an outpatient, the subject or the subject's guardian or caretaker will complete the study medication/food diary on a daily basis. The diary will be collected and entered by site study staff at the visits outlined in the trial flow chart (Section 6.0).
- Subjects who vomit within 30 minutes of POS PFS administration should be given a replacement dose as soon as possible. Repeated episodes of vomiting should be recorded on the Adverse Event (AE) eCRF and the Dosing eCRF.
- Subjects should be observed for approximately 30 minutes after the first dose of PFS for tolerance. During this time, a palatability assessment should be performed as outlined in Section 7.1.2.9.

7.1.2.8.1 Outpatient Administration of Oral Study Medication (PFS)

It is preferred that the subject be administered their first dose of PFS before leaving the hospital so the patient and caregiver have an opportunity to observe or be observed preparing the first oral dose (PFS) for administration. If the investigator determines that the subject is able to be discharged from the hospital and will be able to continue treatment with POS PFS at home, the investigator should take the following steps:

- Refer to the Trial Flow Chart and determine the number of days until the next PK collection timepoint and schedule the out-patient appointment (allowing enough time to perform PK blood sampling predose (0 hour), 2, and 4 hours post-dose).
- Direct IVRS to dispense enough doses (including replacement doses if the subject is at risk of vomiting) for the subject to take home with them to last until their next clinical visit.
- Instruct the subject not to take their daily dose of POS PFS prior to their scheduled appointment on clinic visit days. On the clinic visit days, doses of PFS should be administered in the clinic after the pre-dose PK blood sample is collected and recorded in the study medication/food diary.
- Provide the subject/parent/caregiver with the study medication/food diary and the Palatability Assessment form and instruct them on how to complete both forms.

- Instruct the subject/parent/caregiver to bring all medication (including empty packages), the palatability assessment form and the study medication/food diary with them to all office visits.

These steps need to be repeated at every outpatient visit.

7.1.2.9 Assessment of Palatability (Taste)

All subjects will rate the palatability of the PFS formulation at three times during the PFS treatment phase of the study:

- Immediately after the first oral dose (POS PFS).
- Approximately 3-5 days later immediately after the subject has taken their oral dose.
- At the End of Treatment (EOT), immediately after the last dose of oral treatment.

The palatability assessment questionnaire that will be used can be found in the Administrative Site Binder.

The palatability assessment should be completed for all subjects regardless of age or condition. The paper form may be completed by the subject, reported by the patient to an observer (caregiver or parent), or completed as observed by a parent/primary caretaker, nurse or member of the trial staff.

7.1.2.10 Adverse Event Monitoring

The monitoring for Adverse Events will occur at the visits outlined in the Trial Flow Chart following the guidelines in Section 7.2.

7.1.2.11 Survival Assessment

A survival assessment (if the subject is alive or dead) will be performed between Day 90 and Day 110 and will be recorded on the eCRF. In the event of death, the cause and date of death will also be recorded. This assessment can occur by telephone or by using medical records.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Appendix 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry, Urinalysis & Other

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 8. These safety lab tests will be performed locally. The timing for these assessments are outlined in the Trial Flow Chart (Section 6.0).

- If the Baseline and Day 1 visits are combined, clinical lab tests should be drawn prior to the administration of study treatment.
- Blood specimens may be drawn either peripherally or via central venous catheter.
- If during the trial any laboratory result is outside the reference range and is considered clinically significant by the investigator, the test should be repeated at appropriate time intervals until it returns to baseline or becomes a clinically insignificant finding.
- If clinically indicated, safety lab tests may be repeated more often to evaluate clinical symptoms of AEs and must be followed until stabilization or return to baseline.

Table 8 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Albumin	Serum β-human chorionic gonadotropin (β-hCG)[1]
Hemoglobin	Alkaline phosphatase	
Platelet count	Alanine aminotransferase (ALT)	
WBC (total and differential)	Aspartate aminotransferase (AST)	
Absolute neutrophil count (ANC)	Bicarbonate	
	Calcium	
	Chloride	
	Creatinine	
	Glucose	
	Potassium	
	Sodium	
	Total Bilirubin	
	Direct bilirubin, if total bilirubin is elevated above the upper limit of normal	
	Total protein	
	Blood urea nitrogen	
	Magnesium	

If possible, lab samples should be collected in the fasting state (after an overnight fast for morning sample).

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

Plasma posaconazole concentration data will be used to estimate the following PK parameters:

- C_{avg}: Average steady-state plasma concentration
- C_{min}: POS trough level immediately before a subject receives the dose on the day specified in the protocol
- C_{max}: Maximum plasma concentration
- T_{max}: Time of maximum plasma concentration
- AUC: Area under the plasma concentration versus time curve
- CL: Total body clearance
- CL/F: Apparent total body clearance

The current blood sampling schedule is an optimized schedule based on the adult steady-state PK data. For patients receiving IV therapy, if all blood samples can be collected at steady-state as scheduled, the steady-state AUC will be calculated using the non-compartmental trapezoidal method. The C_{avg} will be calculated by dividing the AUC with dosing interval. For patient receiving PFS, since sparse PK samples are collected for outpatients, a population PK analysis will be conducted and model-predicted plasma concentration-time profiles will be used to determine $C_{avg.}$

Plasma sulfobutylether-beta-cyclodextrin-containing (SBEβCD) concentration data will be used to estimate the following PK parameters:

- C_{max}: Maximum plasma concentration
- T_{max}: Time of maximum plasma concentration
- AUC: Area under the plasma concentration versus time curve

7.1.3.2.1 Blood Collection for Plasma Posaconazole Levels of MK-5592

Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

7.1.3.3 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Buccal swabs for genomics use

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit (EOT) should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. A PK trough sample should be collected approximately 24 hours after the last dose, and all other safety assessments will be performed. The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial. If a subject discontinues for any reason at any time during the course of the trial, the subject may be asked to return to the clinic (or be contacted) for the End of Trial (EOT) approximately 72 hours after the last dose of trial drug is administered) to have the applicable procedures conducted. However, the investigator may decide to perform the End of Trial procedures at the time of discontinuation or as soon as possible after discontinuation.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be

suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained with the study documentation as source documentation at the trial site.

Critical Equipment for this trial includes:

- ECG machine
- Refrigerated centrifuge
- Freezer for storage of samples
- Refrigerator

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

All screening procedures outlined in Section 6.0 must be performed within 7 days of enrollment into the study. Prior to randomization, potential subjects must be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Only subjects with clinically acceptable results from all screening criteria are to be enrolled in the study. Screening procedures may be repeated after consultation with the Sponsor.

At the Screening visit the following procedures will be performed:

- The investigator or qualified designee shall discuss with the parents(s) or legal guardian of each subject, and with each subject as appropriate, the nature of the study, its requirements, and its restrictions.
- Written informed consent will be obtained from the parent or legal guardian of each subject prior to any study procedures being performed, and a signed copy will be given. Assent will be obtained from minors according to institutional practices.
- The inclusion/exclusion criteria will be reviewed
- A subject identification card will be issued
- Demographic profile
- Complete medical history
- Record all medications taken within the last 14 days
- Screening number will be assigned (after signing of study-specific informed consent)
- Complete physical exam
- Body weight
- Height

- Vital signs (blood pressure, heart rate and temperature)
- Electrocardiogram. A single ECG or telemetry may be used to evaluate QTc for eligibility at the screening visit, however two 12 lead ECGs performed 5 minutes apart must be done at the Baseline Visit to confirmQTc criteria for study eligibility before study drug dosing occurs.
- Blood samples will be collected for evaluation of eligibility criteria and for safety assessments (e.g., pregnancy test, hematology, chemistry & absolute neutrophil count)

7.1.5.2 Baseline Visit

At the Baseline visit the following procedures will be performed:

- Review the inclusion/exclusion criteria
- Record all medications taken within the last 14 days.
- A complete physical examination
- Body Weight
- Vital signs
- 12-lead electrocardiogram (ECG). Two 12 lead ECGs performed 5 minutes apart must be done at the Baseline Visit to confirm QTc criteria for study eligibility-before study drug dosing occurs.
- A chest radiograph (as clinically indicated for fungal infection)
- Adverse Event Monitoring
- Laboratory tests (including a pregnancy test on females of child-bearing potential, hematology, chemistry & absolute neutrophil count). Only repeat hematology, chemistry & ANC if it has been more than 2 days since the screening labs were performed. Only repeat pregnancy test if it has been more than 2 days since the screening pregnancy test was performed, or if a urine pregnancy test was conducted at screening.

7.1.5.3 Treatment Day(s)

Eligibility will be confirmed at Day -1 or pre-dose on Day 1 through review of pregnancy testing (females), a physical examination, ANC, vital signs, and concomitant medication/adverse event monitoring (see Section 6.0).

All subjects will be administered POS IV solution for a minimum of 10 days. Those subjects that are still neutropenic will then switch to oral treatment with the POS PFS for a minimum of 10 days; however, subjects may continue on POS IV solution beyond Day 10, if a subject cannot tolerate or refuses to take oral medication. Transition to POS PFS, rather than remaining on POS IV solution, is preferred.

Blood samples for POS PK testing will be drawn prior to study treatment and as close as possible to the time points listed in the Trial Flow Chart (Section 6.0). The exact date/time of dosing and blood sampling will be recorded.

Procedures performed during POS IV solution and POS PFS treatment are outlined separately below and should be performed as outlined in The Trial Flow Chart (Section 6.0):

7.1.5.3.1 POS IV Treatment Days

On IV treatment days the following procedures will be performed:

Day 1:

- On Day 1 of IV treatment, POS IV solution will be administered twice. Each dose will be administered approximately 12 hours apart.
- The exact date and time of each dose administration will be recorded on the appropriate eCRF.
- Review prior and concomitant medications
- Perform a focused physical exam
- Vital signs
- Adverse event monitoring (examine the infusion site on a daily basis, prior to and at the end of infusion, according to local standard of care, for local adverse reactions).
- A buccal swab will also be collected (If elected, the informed consent for future biomedical research but must be obtained before the DNA /Buccal swab is collected on Day 1 on randomized subjects only or at a later date, as soon as the informed consent is obtained)

Day 2 to Day 28:

- Review concomitant medications
- Vital signs
- Perform a focused physical exam 3 times per week until the end of IV treatment as outlined in the Trial Flow Chart (Section 6)
- Electrocardiogram (may be performed on Day 6, 7 or 8 of treatment)
- Monitor for adverse events
- Collect blood for laboratory safety tests (e.g., hematology, blood chemistries, ANC), according to the Trial Flow Chart (Section 6)
- Administer study medication once daily at approximately the same time each day; each dose should be administered approximately 24 hours apart
- Record the exact date and time of each dose administration on the appropriate eCRF

POS PK sample collection

- Collect POS C_{min} or trough samples (0.35 mL of blood per sample) prior to dosing (pre-dose (0 hr) on the 6th day of POS IV solution treatment; the Day 6 sample may be collected on Day 5 to coincide with other labs
- Collect POS trough samples once per week for subjects continuing POS IV solution beyond Day 10
- Perform full POS PK sampling on any day from Day 7-10 at pre-dose (0 hour), within 15 minutes after the end of infusion, and at approximately 4, 6, 12 and 24 hours post start of infusion
- Record the exact date and time that each sample is collected on the appropriate eCRF

Cyclodextrin PK sample collection

- Cyclodextrin (SBEβCD) PK sampling should coincide with POS full PK on any day from Day 7-10 at pre-dose (0 hour), within 15 minutes after the end of infusion, and at approximately 4, 6, and 12 hours post start of infusion
- Record the exact date and time that each sample is collected on the appropriate eCRF

For Premature Discontinuations:

- Collect a POS trough level sample approximately 24 hours after administration of the last dose
- Perform all other safety assessments according to the Last Day of POS IV schedule.
- Update IVRS system with subject status.

7.1.5.3.2 POS PFS Treatment Days

Note: If the subject will be an outpatient during PFS treatment, the investigator staff should provide the subject with enough PFS to ensure study medication compliance until the next clinic visit and instruct the subject/caregiver in how to complete the Study Medication/ Food Diary Assessment form and the Assessment of Palatability form. Clinic Visits should be scheduled to coincide with lab safety and PK collection times.

On PFS treatment days the following procedures will be performed:

- During POS PFS administration, administer each dose approximately 24 hours apart, at the approximately the same time each day
- Record the exact date and time of each dose administration on the appropriate eCRF.
- Review concomitant medications
- Vital signs
- Perform a focused physical exam according to the Trial Flow Chart (Section 6)
- Electrocardiogram (may be performed on Day 8, 9 or 10 of treatment)

- Monitor for adverse events
    - Examine the infusion site on a daily basis, prior to and at the end of infusion, according to local standard of care, for local adverse reactions
- Collect blood for laboratory safety tests (e.g., hematology, blood chemistries ANC), according to the Trial Flow Chart (Section 6).
- Study Medication/Food Diary Assessment
- Assessment of Palatability

POS PK sample collection:

- Collect POS C_{min} or trough samples prior to dosing on the 6th day of oral treatment (PFS) and at EOT; the Day 6 trough sample may be collected at either the 5th or 6th day of POS PFS to coincide with other labs
- Collect POS trough samples once per week for subjects continuing POS PFS beyond Day 7
- Perform POS full PK sampling at pre-dose (0 hour), and 2, 4, 6, 8, and 24 hours post-dose on any day from Day 7-10 for an inpatient
- PK sampling for an outpatient will be performed on any day from Day 7-10 during oral treatment (PFS) at predose (0 hour), 2, and 4 hours post-dose of POS PFS treatment
- Record the exact date and time that each sample is collected on the appropriate eCRF.

For Premature Discontinuations:

- Collect a POS trough level sample approximately 24 hours after administration of the last dose.
- Perform all other safety assessments according to the End of Treatment (EOT)/Last Day of POS PFS schedule.
- Update IVRS system with subject status.

7.1.5.4 Post-Trial/14 Day Follow-up

Subjects will be required to return to clinic approximately 14 days after the last dose of trial drug for the post-trial visit. If the post-trial visit occurs less than 14 days after the last dose of trial drug, a subsequent follow-up phone call should be made at 14 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit.

7.1.5.5 Survival Assessment

A survival assessment, if the subject is alive or dead, will be performed any day from Day 90-110. If the subject dies, the date of death will be recorded. This assessment can be performed by telephone or by medical records.

7.1.5.6 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, collection of blood samples for POS PK sampling is the critical procedure.

At any post-dose time point, the blood sample for POS needs to be collected as close to the specified time point as possible.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose occurs when the subject has taken (accidentally or intentionally) any drug administered as part of the protocol that exceeded the dose as prescribed by the protocol. All reports of overdose must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 9 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

The following will not be considered SAEs in this study.

1. An event that results in hospitalization or prolongs an existing hospitalization will not be considered a serious adverse event if the only reason for the hospitalization was:
   a. administration of chemotherapy
   b. transfusion of blood products
   c. administration of study procedures
   d. placement of a permanent intravenous catheter

e. hospice placement for terminal care

f. outpatient hospitalization for procedures such as elective day surgery or hospitalization due to convenience purposes (e.g., transportation difficulties)

2. Any Grade 3 or 4 leukopenia, absolute neutropenia, or thrombocytopenia (regardless of baseline value) will not be considered a serious adverse event, even in the event of medical intervention to prevent medically significant sequelae.
3. Any Grade 1, 2, or 3 decrease in hemoglobin will not be considered a serious adverse event.

If an abnormal laboratory value included in item numbers 2 or 3 resulted in a clinical event, then the clinical event and not the abnormal laboratory value must be recorded as an AE in the eCRF. This clinical event must be reviewed to determine if it meets the criteria for an SAE.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 9. The investigator's assessment of causality is required for each adverse event. Refer to Table 9 for instructions in evaluating adverse events.

Table 9 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the External Data Monitoring Committee (eDMC)] regarding the trial.

7.3.1 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (eDMC) will monitor the ongoing, accumulating safety data from this trial. The voting members of the committee are external to the Sponsor. The members of the eDMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The eDMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the eDMC will review ongoing trial safety results, consider the overall risk and benefit to trial participants and recommend to the EOC if the trial should continue in accordance with the protocol. The eDMC will evaluate the accumulating available data for safety at the completion of Dose Cohort #1 for each age group, prior to each age group starting the next dosing group (Dose Cohort #2), and at other time points as determined by the study team and eDMC.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of eDMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The eDMC will monitor the trial at an appropriate frequency, as described in the detailed eDMC charter. The eDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

8.1.1 Pharmacokinetic Analyses

The primary PK population for POS IV solution will be all treated subjects who receive at least 7 days of POS IV solution therapy and complete the full POS PK sampling while on POS IV solution. The non-compartmental PK analysis will be used for the primary PK population.

For POS PFS therapy, a population PK analysis will be conducted to determine the individual PK exposure since sparse PK samples will be collected for patients who are outpatients during the POS PFS treatment period. Model-predicted individual concentration-time profiles will be used to determine C_{max}, C_{min}, C_{avg}, and AUC.

PK parameters (C_{max}, T_{max}, C_{min}, C_{avg}, AUC, CL and CL/F) for both POS IV solution and POS PFS will be summarized using descriptive statistics as described in Section 8.2.1 below.

A non-compartmental PK analysis will be performed to determine the PK exposure of sulfobutylether-beta-cyclodextrin-containing (SBEβCD).

8.1.2 Safety Analyses

The All-Subjects-as-Treated (ASaT) population will be employed for safety analyses, and consists of all subjects who took at least one dose of POS study therapy.

8.1.3 Efficacy Analyses

There are no efficacy analyses planned for this study.

8.1.4 Power and Sample Size

A total of approximately 120 subjects will be screened to obtain a minimum of 72 PK-evaluable subjects in the PK analysis.

8.2 Statistical Analysis Plan

8.2.1 Pharmacokinetic Analysis Plan

Only subjects who receive at least 7 days of POS IV solution therapy and complete the full POS PK sampling while on POS IV solution will be included in the non-compartmental PK analysis for the primary patient population.

PK parameters for POS (C_{max}, C_{min}, $C_{avg,}$ CL) will be listed and summarized by POS formulation, dose cohort, and age group using descriptive statistics.

For POS PFS therapy, a population PK analysis will be conducted to determine the individual PK exposure. A population PK model will be developed using the plasma data collected from this study in combination with the adult PK data. Model-predicted individual concentration-time profiles will be used to determine C_{max}, C_{min}, $C_{avg,}$ AUC and CL/F for patients receiving POS PFS. Covariates of age group and dose cohort will be explored in the model.

Comparison of the exposure from previous experience in adults (from P05520 for the POS IV formulation; P05615 for the tablet formulation) will be conducted at steady state using graphics. Additionally, the proportion of subjects in PN097 with steady-state C_{avg} greater than or equal to 500 ng/mL (as well as the proportion of subjects with C_{avg} between 500-2500 ng/mL) will be compared to the previous studies using descriptive statistics.

A non-compartmental PK analysis will be performed to determine the PK exposure of sulfobutylether-beta-cyclodextrin-containing (SBEβCD). PK parameters for POS (C_{max}, T_{max} and AUC) will be listed and summarized by POS dose cohort, and age group using descriptive statistics.

8.2.2 Safety Analyses

All subjects who receive at least one dose of study drug will be included in the safety analysis.

Adverse events (AEs) will be tabulated by age (2 to <7 years, 7 to 17 years) and POS treatment (IV solution, PFS). The number and percent of each event will be computed and summarized by body system organ class. Severity, duration, relationship to POS, and outcome of the events will also be recorded. ECGs and clinical safety laboratory values, such as hematology and serum chemistry, will be tabulated by age and treatment group and compared to baseline using summary statistics. Vital signs will be listed by date and time. Key toxicities, including hepatotoxicity and nephrotoxicity, will be tabulated by age and dose cohorts.

Additionally, survival at Day 100 (allowed range Day 90 -110) and Day 65 (allowed range Day 60-70) will be tabulated by age group and dose cohort.

8.2.3 Efficacy Analyses

There are no efficacy analyses planned for this study.

8.2.4 Other Analyses

Compliance with study medication, including palatability/acceptability of the POS PFS formulation, will be summarized by age and treatment group.

8.2.5 Power and Sample Size

The sample size is not based on any formal power calculation.

The total sample size for the study is a minimum of 84 subjects (72 PK-evaluable subjects) distributed across the 3 dose cohorts as follows:

Dose cohort #1 (a minimum of 24 PK evaluable subjects, divided 12 per Age Group).

Dose cohort #2 (a minimum of 24 PK evaluable subjects, divided 12 per Age Group).

Dose cohort #3 (a minimum of 36 subjects, divided as 12 PK evaluable subjects per Age Group and an additional 12 distributed across either Age Group).

The actual total number of enrolled subjects may be greater than 84 in order to ensure a minimum of 72 subjects that meet PK evaluability criteria.

At the time of this amendment (MK-5592-097-02), enrollment in Dose Cohorts #1 and #2 is complete. Therefore, the remaining target enrollment for this amendment is a minimum 36 subjects in Dose Cohort #3 (12 PK evaluable subjects per age group and an additional 12 distributed across either age group).

If successful dose selection is defined as at least 10 out of 12 (82.2%) patients per age/dose group achieving a C_{avg} >500 ng/mL, the chance of achieving success is at least 89%, based on a sample size of 12 patients in each age/dose cohort using a binomial distribution (n=12, p=0.90), where p = probability of success.

8.2.6 Interim Analysis

Interim Analysis for Dose Cohorts #1 and #2

For the 2 dose cohorts (3.5 mg/kg and 4.5mg/kg) which have completed enrollment at the time of this amendment, a pre-planned interim summary of PK and safety data was conducted in order to inform the decision to advance to the next higher dose cohort. Because these data summaries did not involve formal tests of hypotheses, they did not affect type I error.

Interim Analysis for Dose Cohort #3

There is no formal interim analysis planned for the third dose cohort (6 mg/kg).

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 10.

Table 10 Product Descriptions

Product Name & Potency	Dosage Form
Posaconazole 300 mg	IV Solution (sterile)
Posaconazole 300 mg	Powder for Oral Suspension
Ora-Blend® SF	Oral Suspension

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open label posaconazole vials (IV solution) or posaconazole sachets (PFS). On Day 1 of POS IV solution, subjects will be dispensed 2 vials which are to be taken as 2 separate doses to be administered 12 hours apart (BID). This will be followed by 1 vial daily on days 2-10, or until IV treatment is completed. Vials will not be kitted. Subjects switching to POS PFS will receive kitted sachets to allow for daily dosing until the end of treatment. In addition, Ora-Blend® SF will be provided for the purposes of reconstituting the POS PFS.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study

Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the

authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to

submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

1. Rosen GP, Nielsen K, Glenn S, Abelson J, Deville J, Moore TB. Invasive fungal infections in pediatric oncology patients: 11-year experience at a single institution. J Pediatr Hematol Oncol 2005; 135-40.

2. Hovi, L, Saarinen-Pihkala UM, Vettenranta K, Saxen H. Invasive fungal infections in pediatric bone marrow transplant recipients: single center experience of 10 years. Bone Marrow Transpl 2000;26:999-1004.

3. Dvorak CC, Steinbach WJ, Brown JM, Agarwal R. Risks and outcomes of invasive fungal infections in pediatric patients undergoing hematopoietic cell transplantation. Bone Marrow Transpl 2005;36:621-9.

4. Castagnola E, Cesaro S, Giacchino M, Livadiotti S, Tucci F, Zanzazzo G, et al. Fungal infections in children with cancer. A prospective, multicenter surveillance study. Ped Inf Dis J 2006;25:634-9.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.2

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.2

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The DNA (buccal swab) specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA (buccal swab) specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced

to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Buccal swab specimens for DNA isolation will be obtained at a time when the subject is having other trial procedures conducted. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or

key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Buccal swab specimens will be collected inside the cheek with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.

Merck has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it

be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

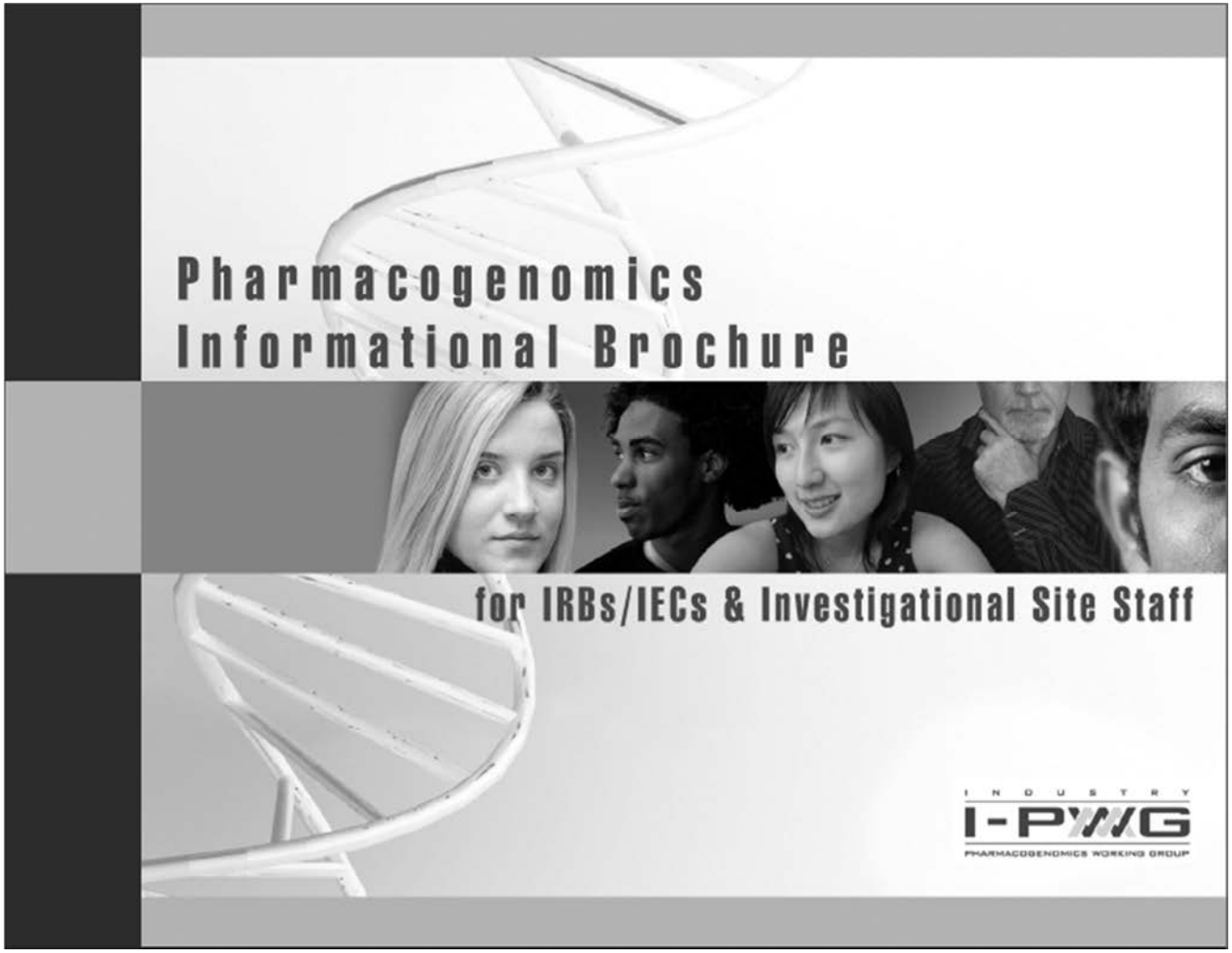
13. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



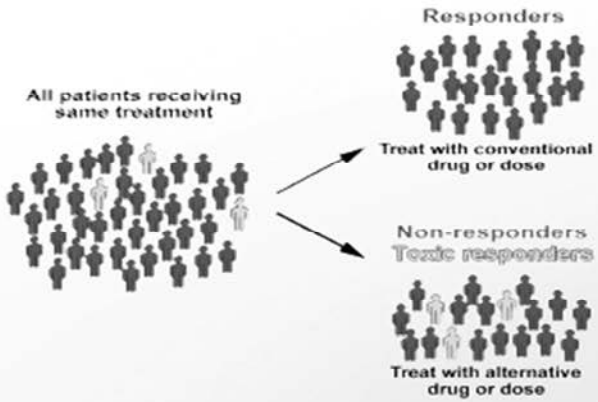
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid (DNA)**. DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

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Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:

www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-Identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Trial Visit:	Screening & Baseline	POS IV Solution Treatment	POS Oral (PFS) Treatment	Post Treatment Follow-up	Total Collections	mL per collection	Total mL/test
	Visits 1-2	Visit 3-14	Visits 15-26	Visits 27-28			
	Approximate Blood Volume						
Lab Safety Tests							
Hematology/Chemistry	2	4	5	0	11	4	44
ANC	2	4	5	0	11	4	44
Serology							
Serum β-Human Chorionic Gonadotropin (β-hCG)[a]	1	0	0	0	1	1	1
Study Drug							
POS Full PK *(0 hour), , within 15 minutes after the end of infusion, and at approximately 4, 6, 12 and 24 hours post start of infusion.)	0	6*	6*	0	12	.35	4.2
POS PK Trough (0.35 ml /sample)	0	3	3	0	6	0.35	2.1
SBEβCD Cyclodextrin PK (0.35ml /sample)	0	5	0	0	5	.35	1.75

[a] Serum pregnancy tests only applies to sexually active females of childbearing potential

12.5 List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AMA	American Medical Association
AMB	Amphotericin B
AMB-R	Amphotericin B Resistant
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Asia Pacific
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
AUC(tf)	Area under the plasma concentration versus time curve from time 0 to the time of the final quantifiable sample
β-hCG	Serum β-human chorionic gonadotropin (β-hCG)
BID	*bis in die*; twice a day
BMT	Bone Marrow Transplantation
BPM	Beats Per Minute
BUN	Blood urea nitrogen
°C	Celsius
C_{avg}	Average steady-state plasma concentration
CBC	Complete Blood Count
CHMP	Committee for Medicinal Products for Human Use
CFR	Code of Federal Regulations
CL/F	Apparent total body clearance
cm	Centimeter
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
CRU	Clinical Research Unit
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Minimum observed plasma concentration
CYP	Cytochrome P450
DBS	Dried Blood Spot
DILI	Drug Induced Liver Injury
dL	Deciliter
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram

ECI	Event of Clinical Interest
eCRF	Electronic Case Report Form
eDMC	External Data Monitoring Committee
EEA	European Economic Area
EEMEA	Eastern Europe, Middle East and Africa
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment/Last Study Visit
ERC	Ethics Review Committee
EU	European Union
°F	Fahrenheit
F	Female
FDA	Food and Drug Administration, USA
FLZ	Fluconazole
FLZ-R	Fluconazole Resistant
GCP	Good Clinical Practice
GVHD	Graft versus host disease
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPMCAS	hypromellose acetate succinate
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSA	Infectious Disease Society of America
IEC	Independent Ethics Committee
IFI	Invasive fungal infection
IND	Investigational New Drug Application; legal instrument in the USA that allows study of unapproved, investigational new drugs in human subjects
IRB	Institutional Review Board
ITZ	Itraconazole
ITZ-R	Itraconazole resistant
IUD	Intrauterine Device
IV	Intravenous
IVRS/IWRS	Interactive Voice Response System
kg	Kilogram
L	Liter
LA	Latin America
M	Male

MDS	Myelodysplastic syndrome
mg	Milligram
min	Minute
mL	Milliliter
mm^3	Cubic millimeter
MSG	Mycoses Study Group
NHL	Non-Hodgkin's Lymphoma
NNRTI	Non-nucleoside reverse transcriptase inhibitors
OGS	Oral granules for suspension
PD	Pharmacodynamic
PFS	Powder for oral suspension
PGt	Pharmacogenetic
PK	Pharmacokinetics
PO	Per OS (by mouth)
POS	Posaconazole
QTc	QT interval corrected for rate
RBC	Red blood cell
RNA	Ribonucleic Acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBEβCD	Sulfobutylether-beta-cyclodextrin
SCT	Stem cell transplantation
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SOP	Standard Operating Procedure
TdP	Torsade de pointes
T_{max}	Time to maximum observed plasma concentration
ULN	Upper limit of normal
US	United States
VOR	Voriconazole
VOR-R	Voriconazole Resistant
WBC	White blood cell

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	