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1.0 TITLE PAGE

Title	A Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis in Adults and Adolescents (Phase 3; Protocol No. MK-5592-069)
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C O N F I D E N T I A L

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT: This amendment has clarified aspects of the planned protocol and statistical analyses for the study. Key elements of the analyses for the study that have been modified include approximate sample size and power calculation, time windows allowed for the assessment of all-cause mortality and global clinical response, and the elimination of some secondary objectives for which data analyses are no longer planned.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.0, 2.2	Synopsis, Trial Flow Chart	Oral tablet acceptability text in adolescent subject exploratory analysis has been deleted. A footnote was added under the trial flow chart: [t] Visit 7 window (Week 6, Day 30-54) is slightly different from the window for the Global Clinical Response assessment at Week 6 (± 2 weeks)	Removal of text to align with final planned protocol analyses as an insufficient number of adolescent subjects have been enrolled to conduct sub-analysis. The footnote was added to clarify the flow chart Week 6 visit window is different from the window for the Week 6 Global Clinical Response assessment
2.0, 5.2	Synopsis, Subject Population Rationale	Following text deleted: ~~At least 30 FAS-evaluable adolescents will be enrolled in this study~~	Text removed as it is no longer planned to have enrollment of at least 30 adolescents in the study.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.0, 8.7.2	Synopsis, Sample Size and Power for Efficacy Analyses	Added underlined text: This sample (approximately 300 randomized subjects in each azole arm) will have ~ 82.7% power (with 1-sided alpha=0.025) to show non-inferiority of POS compared to VOR using a 10% margin assuming an all-cause mortality through Day 42 of 23% for both treatment groups.	Text updated to clarify sample size and related power calculation statements
2.2	Trial Flow Chart	Underlined text from footnote 'u' was modified: All subjects randomized and treated are to be followed for mortality assessment throughout the study period until ~~Visit 9~~Day 114, regardless of whether the subject discontinues study therapy prior to Visit~~9~~ 8 ~~D85~~ Day 84	Text updated to clarify the specific study day through which mortality analyses will be planned to be conducted.
2.0, 6.2, 8.2.2, 8.5.1	Synopsis, Secondary Objectives, Secondary Trial Objectives, Statistical Methods for Efficacy Analyses	Removed the word Key from Secondary Objectives/Endpoints	Done for simplification purposes and to align with the planned endpoint analysis.
2.0, 8.2.2	Synopsis, Secondary Objectives	The secondary objective to evaluate the all-cause mortality for POS vs. VOR through Day 84 was separated into 2 objectives, one in the ITT and the other in the FAS population	Update text to align with the planned endpoint analyses

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.0, 6.2, 8.2.2, 8.5.1	Synopsis, Other Secondary Trial Objectives, Secondary Objectives, Other Secondary Objectives, Statistical Methods for Efficacy Analyses	Other secondary objectives (previously Sections 6.3 and 8.2.3) were merged with Secondary objectives. Table 13, Analysis Strategy for Key Efficacy Variables, in Section 8.5.1 was updated	Merged the 2 sets of secondary objectives for simplification purposes
7.7.1.2, 7.7.1.3	Secondary Endpoints, Other Endpoints	Other Endpoints merged with Secondary Endpoints	Merged other endpoints with secondary endpoints for simplification purposes
2.0, 6.2, 7.7.1.3, 8.2.3	Synopsis, Secondary Trial Objectives, Other Endpoints, Secondary	Following text deleted: • ~~To evaluate the time to global clinical response for POS versus VOR in the FAS population~~ • ~~Time to global clinical response at Weeks 2, 4, 6, and 12 in the FAS population.~~ • ~~To evaluate the global clinical response at Weeks 6 and 12 in subjects with a diagnosis of possible, probable, or proven IA receiving POS vs. VOR in the ITT population~~	Modified text to align with the planned endpoint analyses

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.0, 6.2, 8.2.3	Synopsis, Secondary Trial Objectives, Secondary	Added underlined text: To evaluate, <u>in the subset of subjects that have pharmacokinetic data and food intake records,</u> the pharmacokinetic profile of POS and VOR, including an evaluation of the effect of food intake on the POS tablet steady state pharmacokinetic profile, and to evaluate the exposure-response (efficacy and safety endpoints) relationships of POS and VOR in a subset of subjects <u>with available data.</u>	Modified the text to align with the planned study analysis
2.0, 6.1, 6.2, 7.1, 7.7.1.1, 7.7.1.2, 8.2.1, 8.2.2, 8.5.1	Synopsis, Primary Trial Objective, Secondary Trial Objectives, Overall Trial Design, Primary Endpoint, Key Secondary Endpoints, Primary Objective, Secondary Objectives, Statistical Methods for Efficacy Analyses	Added “through Day 42 and Day 84” as replacement text for “Week 6 and Week 12,” for mortality endpoint analysis throughout the protocol.	Added, to specifically indicate the actual endpoint for mortality analysis

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
7.4.1.5.8, 8.10,	Investigational Medicinal Product Accountability, Compliance (Medication Adherence)	Following text was modified in Investigational Medicinal Product Accountability and Compliance sections: In this study, as part of the routine recording of the amount of study treatment taken by each patient, at each site, the volume of infusion administered and the number of tablets/capsules dispensed and returned will be counted, reviewed, and recorded at regular intervals at the local level. Pharmacy records of dispensing and return of study medication will be recorded using local documentation records and will be monitored and reviewed by unblinded study monitors throughout the study period. Pharmacy records will be retained at the local pharmacy and available for Sponsor review. Site records will be used to ensure and document study medication compliance. Study medication dosing will be recorded in the electronic case report for each study medication component (IV or oral, placebo or active drug) based upon local documentation records.	Text was modified to clarify the procedures followed to assess drug accountability and compliance in the study
7.7.1.2	Secondary Endpoints	Modified the following text primary: For the ~~primary~~ global clinical response endpoint (6 weeks) the assessment would ~~need to~~ be ± 2 weeks.	Text modified to align with study endpoints and to clarify that the secondary endpoint of clinical response would include study windows of +/- 2 weeks.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
7.7.3.1	Pharmacogenetics Endpoints	Following text deleted: • ~~Any significant PGt relationships to outcome will require validation in future clinical trials~~ Added underlined text: • Exploratory analysis genetic testing of the CYP2C19 polymorphisms and PK/PD, safety and efficacy relationships may be conducted as the data allow.	Modified text to align with the planned study analyses, and to omit the requirement for future clinical trials to further assess PGt relationship.
7.7.4	Other Endpoints	Added underlined text: These PK samples should be collected via peripheral venipuncture and not be drawn from the central catheter. PK/PD correlation tests assessing achievable serum drug levels of POS and VOR vs. minimum inhibitory concentrations for *Aspergillus* isolates and global clinical response will be conducted on all randomized subjects with available data. Exposure/response assessments will be conducted including an exploration of the relationship between PK/PD indices with efficacy and safety timepoints as available data allow.	Text added to clarify the scope of the PK/PD data analyses as the data allow

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
8.2.3	Exploratory Objectives	Added underlined text regarding exploratory objectives: Please note: The analyses to test the above three exploratory objectives may be conducted at a later date, as data allow	Added the text, to clarify that the analysis of pharmacogenomic data may be conducted at a future date as data allow.
8.4.1	Efficacy Analysis Populations	Added the following underlined text: The FAS population consists of all randomized subjects who have been classified as having proven or probable IA (based upon independent adjudication assessment) using the modified 2008 EORTC/MSG definitions, and receive at least one dose of study drug	Language updated to clarify the FAS study population for analysis purposes
8.5.1	Statistical Methods for Efficacy Analyses	Added the following underlined text: • Mortality will be evaluated through Day 42 and through Day 84 with no time window applied either before or after the target day. • Global clinical response at Week 6 and Week 12 will be evaluated to include the completion of the response components within the visit windows, ±2 weeks for Week 6 and ±4 weeks for Week 12. Modified Table 13 to align with the planned endpoint analyses.	Text updated to align with the planned endpoint analyses

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
8.5.2	Statistical Methods for Safety Analyses	Added the underlined text: • Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints <u>prior to database lock</u> will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. • CNS and visual safety: Treatment-emergent adverse events (TEAEs) of visual abnormalities (including: terms related to visual hallucination, diplopia, nystagmus, photophobia, photopsia, <u>dyschromatopsia</u>, scotoma, hemianopia, optic neuritis, uveitis, optic disc disorder, visual impairment, vision blurred, visual acuity reduced, blindness, optic atrophy, papilledema, and optic neuropathy); confusion, hallucination, altered mental status, <u>cognitive disturbance, dizziness, altered level of consciousness, depressed level of consciousness, asterixis, tremor</u>, seizures, or encephalopathy.	Text modified to indicate that a final review of the reported AE terms will be conducted prior to database lock to determine additional related terms that may be added to the Tier 1 evaluations

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
8.5.3	Summaries of Baseline Characteristics, Demographics, and Other Analyses	Deleted Population PK Analyses	Deleted population PK analyses section as these analyses will not be conducted as a part of the planned study analysis
8.7.2	Sample Size and Power for Efficacy Analyses	Modified the following underlined text: Table 17 summarizes the study power for assumed VOR mortality rates ranging between 18% and 28%, for different numbers of subjects in each arm, with the POS mortality rate ranging from -2% to +2% from the VOR rate. • For example, if the VOR mortality is assumed to be 18% and the POS mortality is assumed to be 19% with 600 subjects (300/arm) in ITT population, then this ~~current~~ study design has 80.4% power to demonstrate non-inferiority with a 10% margin. • Alternatively, if the VOR mortality is assumed to be 22% and the POS mortality is assumed to be 21% with 540 subjects (270/arm), then this study design has 87.2% power to demonstrate non-inferiority with a 10% margin. • If an all-cause mortality rate of 23% is observed in 270 VOR patients (23%=62/270), the largest observed all-cause mortality rate that could be observed among POS patients and still meet the non-inferiority criterion would be 26% (69/270). In this	Text modified to provide supportive information and to clarify sample size and power calculation for the statistical analysis

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		instance, the observed difference in mortality rates would be again 3.0 percentage points (POS minus VOR) with a 95% CI of (-4.7, 9.8). Modified Table 17 to include 570 (285/arm) and 540 (270/arm) subjects.	
8.7.3	Sample Size and Power for Safety Analyses	Added underlined text: Table 18 gives the difference in percentage points (POS minus VOR) that can be ruled out with different power levels and 95% confidence when there are 300 or 285 or 270 randomized subjects in each treatment group. The true frequency of subjects experiencing an AE on POS arm is assumed the same as that in the VOR arm. For a reasonably common adverse experience which occurs in 20% of subjects receiving either POS or VOR, the study with 300 randomized subjects in each arm has 90% power to declare, with 95% confidence that the true difference between group proportions is no more than 12.7 percentage points. Modified Table 18 to include 570 (285/arm) and 540 (270/arm) subjects.	Text added to provide supportive information for the statistical analysis

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
8.8	Subgroup Analyses and Effect of Baseline Factors	Following text deleted: • ~~Adolescents (≥13 years to <18 years) and Adults (≥18 years)~~ • Patients population: (1) proven vs. probable IA; ~~(2) probable IA due to galactomannan EIA vs. all other probable/proven IA;~~ (3) site of IA infection (lung, sinus, multiple sites, etc.); (4) underlying disease; (5) neutropenic status at baseline [ANC <500 vs. >500]	Text modified to remove the subgroups that will no longer be included in the planned study analyses
8.10	Compliance (Medication Adherence)	Modified section with underlined text: For IV study therapy, on each day, each patient should take a certain number of infusions/injections encompassing both the assigned treatment and any matching placebo (sham infusions). A day within the study will be considered an "On-therapy" day if the patient receives at least one infusion. For oral therapy, on each day, each patient should take a certain number of tablets and capsules encompassing both the assigned treatment and any dummy placebo tablets or capsules. A day within the study will be considered an "On-Therapy" day if the patient takes one capsules/tablet.	Text was modified to clarify how drug accountability and compliance will be evaluated in the study analyses

2.0 SYNOPSIS

TITLE OF TRIAL: A Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis in Adults and Adolescents (Phase 3; Protocol No. MK-5592-069).

OBJECTIVES:

Primary Trial Objective: To compare the all-cause mortality for posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) through Day 42 in all randomized subjects who received at least one dose of study treatment (in the ITT [Intention to Treat] population). The hypothesis to be tested is that the all-cause mortality at through Day 42 in the POS treatment group is non-inferior to that in the VOR treatment group.

Secondary Trial Objectives:

- To evaluate the all-cause mortality for POS vs. VOR through Day 42 in the FAS population.
- To evaluate the all-cause mortality for POS vs. VOR through Day 84 in the ITT populations.
- To evaluate the all-cause mortality for POS vs. VOR through Day 84 in the FAS populations.
- To evaluate the adjudicated global clinical response for POS vs. VOR at Week 12 in the FAS population.
- To evaluate the adjudicated global clinical response for POS vs. VOR at Week 6 in the FAS population.
- To evaluate the time to death (all causes) for POS vs. VOR in the FAS population.
- To evaluate mortality due to IA through Day 42 and through Day 84 for POS vs. VOR in the FAS population.
- To evaluate the safety and tolerability of POS and VOR by analyzing Tier 1 Safety events and all adverse events.
- To evaluate the safety of POS compared to VOR therapy in the All-Patients-as-Treated (APaT) population.
- To evaluate, in the subset of subjects that have pharmacokinetic data and food intake records, the pharmacokinetic profile of POS and VOR, including an evaluation of the effect of food intake on the POS tablet steady state pharmacokinetic profile, and to evaluate the exposure-response (efficacy and safety endpoints) relationships of POS and VOR.

Exploratory Objectives:

- To explore the effects of CYP2C19 polymorphisms and predicted metabolic enzyme activity on POS and VOR plasma concentration.
- To explore pharmacogenetic endpoints and their association with key efficacy and safety parameters.
- To explore the effect of treatment on serological biomarkers (e.g., serum galactomannan EIA, beta-D-glucan).

Rationale:

Current guidelines for the treatment of IA recommend the use of VOR as primary therapy [10], [23]. Early initiation of antifungal therapy is recommended while the definitive diagnostic evaluation is in process. The duration of azole treatment is not yet well defined; current recommendations call for a minimum duration of 6 to 12 weeks in immunocompromised subjects. These recommendations are based upon the findings of controlled clinical studies that found initial treatment with VOR to be superior to amphotericin B deoxycholate (AmB) in the treatment of acute IA. In an open-label controlled study after 12 weeks of therapy, the global clinical response to therapy was 53% in subjects who were randomized to receive VOR with a survival rate of 71% compared to a response rate of 32% for AmB and a survival rate of 58% [2] Invasive aspergillosis is a serious, life-threatening disease that occurs among patients with prolonged and/or severe impairment of the immune system. Without the initiation of antifungal therapy, the acute mortality rate has been shown to exceed 85% (Appendix 2). With early diagnosis and the prompt initiation of therapy, the mortality rate of patients treated with a mold-active antifungal agent has improved. A meta-analysis of all-cause mortality at through Day 42 based on historical data of VOR treatment of IA found a mortality rate of 23% [27]. In 2015, a recently completed prospective clinical study of isavuconazole(ISA) vs VOR given to patients with invasive aspergillosis reported through Day 42 all-cause mortality rate of 18.6% and 20.2, ISA and VOR treatment arms, respectively. In the same clinical study, with the use of the 2008 EORTC/MSG guidelines for the evaluation of clinical response among subjects with proven or probable IA, a successful clinical response at the end of therapy was noted to be 35% and 38.9%, ISA and VOR treatment arms, respectively [27].

More effective or safer antifungal therapy is sought for patients with IA. POS is a highly active triazole with the potential to have at least similar efficacy to VOR based on animal model data, and some potential advantages in terms of tolerability and drug interactions. POS was shown to be effective in an open label, externally controlled salvage therapy trial of 107 patients with proven/probable aspergillosis. The global clinical response rate (complete and partial response) at the end of therapy was 42% in POS treated subjects, compared to 26% in external controls receiving standard therapy [5]. In addition, POS has activity against *Aspergillus* spp. other than *A. fumigatus*, and importantly, against Zygomycetes, which can mimic the clinical presentation of aspergillosis in high risk patients. In this study of refractory IA, there was an exposure response association; subjects in the highest quartile with the highest POS exposure (mean Cavg of 1250 ng/mL) had a higher response (approximately 75%) compared to lower concentration quartiles.

This study will investigate two extended spectrum azoles (POS and VOR) in subjects with proven, probable or possible IA based on modified EORTC/MSG definitions [1, 10]. Subjects with proven invasive fungal infection (IFI) will have confirmed infection based upon detection of the fungus by histological analysis or culture of a specimen taken from sterile material from a site of infection. Subjects with probable IFI will require the presence of appropriate host factors, clinical criterion, and a mycological criterion including both direct tests and indirect tests including galactomannan antigen detection. Subjects with possible IA will meet the criteria for a host factor and a clinical criterion, but without confirmatory mycological criterion. Subjects who are enrolled with a diagnosis of possible IA will undergo additional diagnostic work-up to confirm proven or probable IA post-randomization. Subjects with possible IA diagnosis will continue in the study, and all randomized subjects who receive at least one dose of study drug will be evaluated as the ITT study population. Subjects with a diagnosis of proven or probable IA (based on modified EORTC/MSG definitions) will be considered part of the FAS population. By enrolling subjects as early as possible, it is hoped that better outcomes overall will be achieved, based on data indicating that early intervention improves survival [11, 26]. Subjects enrolled into this study may be randomized to treatment with either POS IV or POS tablet formulations. Merck has developed and registered IV and oral tablet formulations of POS that are able to achieve a higher exposure target with reduced variability compared to POS oral suspension [6, 29]. Phase 1B/3 studies have been conducted in patients treated with POS IV solution and POS oral tablet given as antifungal prophylaxis. In patients, the mean steady state Cavg exposure for POS IV solution 300 mg QD was 1430 ng/ml; the mean steady state Cavg exposure for POS tablet 300 mg QD was 1460 ng/ml [29]. With these new formulations, the desired exposure target for the treatment of invasive

aspergillosis (Cavg at least 1250 ng/mL) will be more rapidly and more consistently achieved. In the strategy employed by this protocol, a sufficient number of subjects with well documented IA can be enrolled within a reasonable time, following treatment paradigms which reflect clinical practice and provide data to support the safety and efficacy of POS versus VOR in the treatment of patients who have suspected or documented aspergillosis.

Trial Design

Overview: This is a Phase 3, randomized, double-blind study of POS versus VOR in subjects with IA as defined by modified EORTC/MSG consensus criteria. Subjects with features consistent with proven, probable, or possible IA will be enrolled. All randomized subjects who receive at least one dose of study drug will be included in the primary ITT population. Subjects who are enrolled with a diagnosis of possible IA will undergo additional diagnostic work-up to confirm proven or probable IA post-randomization are to be included in the secondary FAS population.

At the time of study enrollment, subjects will be randomized to receive one of two possible treatment arms: POS or VOR for a maximum total duration of therapy of 12 weeks. In general, most subjects should receive the full 12 weeks of study therapy. Subjects will be randomized to POS or VOR in a 1:1 ratio. Overall, approximately 600 subjects will be enrolled, randomized and treated in the study will comprise the primary ITT population (approximately 300 ITT-eligible subjects per treatment arm). The study will also evaluate subjects whose diagnosis of proven or probable IA as confirmed by an independent Clinical Adjudication Committee (CAC) will comprise the secondary FAS study population. The FAS further requires subjects to have received at least one dose of study drug and have at least one post-randomization observation for the analysis endpoint subsequent to at least one dose of study treatment (and have baseline data for those analyses requiring baseline data).

Most subjects will begin antifungal azole (VOR or POS) therapy via the IV route; however, some may begin therapy via the oral route. Azole therapy will be switched from IV route to the oral route when the subject is considered clinically stable and able to take oral medication. The assigned azole treatment (POS or VOR) will be provided in a double-blind manner. All subjects will be treated with study drug for up to 12 weeks. The primary study objective is to evaluate mortality through Day 42 in the ITT study population. The final study visit (follow-up evaluation) will be done 1 month (Day 114 following randomization) after the end of treatment visit. Ultimately, subjects who complete 12 weeks of study treatment will participate in the study for a total of approximately 16 weeks post-randomization.

Overview of Active Study Drug Dosing by Treatment Arms

Treatment Arms	IV Therapy[a]	Oral Therapy
Arm 1 – Posaconazole (POS)	POS IV: Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD	POS oral: Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD
Arm 2 – Voriconazole (VOR)	VOR IV: Day 1[b]: 6 mg/kg per body weight administered BID Day 2-84[c]: 4 mg/kg per body weight administered BID	VOR oral: Day 1[b]: 300 mg BID Day 2-84[c]: 200 mg BID

[a] Subjects will begin IV study drug and then step down/transition to oral study drug. If clinically indicated, some subjects may begin study drug with oral therapy instead of IV therapy.
[b]Day 1 refers to the first day of subject taking either IV or Oral therapy. Subjects will only take one formulation, either IV or oral at a time
[c] The planned duration of study therapy is 12 weeks (84 days) with a maximum allowable duration of up to 98 days. IV=intravenous; POS=posaconazole; VOR=voriconazole

Diagnostic and efficacy data from all subjects will be reviewed by an independent Clinical Adjudication Committee (CAC) who will be blinded to the assigned treatment arm. The CAC will determine acceptability of the diagnostic criteria according to modified MSG/EORTC consensus criteria [9]. Subjects who are randomized and receive at least one dose of study drug will

comprise the ITT dataset. In addition, subjects whose diagnosis of proven or probable IA is confirmed post-randomization by the CAC will comprise the FAS dataset. The CAC will adjudicate classification of the global clinical response to treatment (as per modified 2008 EORTC/MSG guidelines) at 6 weeks and at 12 weeks/end-of therapy (EOT) post-randomization. A successful global clinical response will be defined as an FAS-evaluable subject who is judged by the CAC to be alive and have a complete or partial response at the time points of interest. The CAC will also adjudicate IFI-attributable mortality through Day 42 and Day 84 in subjects as data allow.

The primary analysis will test for non-inferiority of all-cause mortality for POS compared to VOR through Day 42. The primary analysis will be conducted in the ITT population.

Secondary analyses will include a comparison of global clinical response at Week 6 in the FAS data set. The FAS population consists of all randomized subjects who have confirmed proven or probable IA (based on modified 2008 EORTC/MSG definitions) post-randomization and who receive at least one dose of study treatment and have at least one post-randomization observation for the analysis endpoint subsequent to at least one dose of study treatment (and have baseline data for those analyses requiring baseline data). Additional secondary analyses include all-cause mortality through Day 42 and Day 84 in the FAS population, global clinical response at both Week 6 and Week 12 in the FAS population and all-cause mortality through Day 84 in the ITT population. Safety will also be evaluated for both treatment groups using an All-Patients-as-Treated (APaT) population, which includes all subjects who received at least one dose of study treatment.

The primary endpoint, corresponding to the primary trial objective, is all-cause mortality through Day 42 in subjects in the ITT population. The primary analysis is to compare the POS arm to the VOR arm. The difference in mortality rate between arms (POS minus VOR) and the associated 95% confidence interval (CI) on the difference will be calculated using Miettinen and Nurminen's method [13] stratified by risk for mortality/poor outcome (high risk, not high risk). If the upper limit of that CI is less than 10% (the non-inferiority margin), then non-inferiority of POS will be declared. If non-inferiority is declared, it can be further concluded that POS is superior to VOR if the lower limit of the CI exceeds zero. Due to the principle of closed testing, no adjustment for multiplicity is required since non-inferiority can always be concluded whenever the data also supports superiority. Summary statistics and a tabulated treatment comparison will be provided.

Number of Trial Centers: Up to155 global centers will be selected for inclusion.

Duration of Participation: Each subject will participate in the trial for approximately 16 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 7 days, each subject will be receiving assigned treatment for a maximum of 12 weeks. In general, most subjects should receive the full 12 weeks of study therapy. After the Week 12 visit, each subject will have a final study visit 4 weeks after the Week 12 visit.

Duration of Trial: Approximately 4 years to complete study enrollment and 4 months (16 weeks) to complete study treatment and follow-up.

Key Inclusion/Exclusion Criteria:

Key Inclusion Criteria:

1. Each subject must be willing and able to provide written informed consent for the trial. The legal representative (e.g., parent or guardian) for a subject under the age of legal consent or who otherwise is unable to provide independent consent may provide written informed consent for the subject. Each subject of the age of assent must be willing and able to provide assent in addition to consent from the legal representative to participate in the trial.
2. Each subject must be ≥13 years of age weighing >40 kg [88 lb] and ≤150 kg [330 lb] at the time of randomization. Each subject between 13 and 14 years of age must weigh ≥ 50 kg [110 lb]. Subjects may be of either sex and of any race/ethnicity. For those sites that do not have the ability to enroll adolescents, subjects must be greater than ≥18 years of age.
3. Each subject must meet the criteria for proven, probable, or possible IA as per 2008 EORTC/MSG disease definitions at the time of randomization. Proven IA will include those subjects with the demonstration of fungal elements (by cytology, microscopy, or culture) in diseased tissue (sterile sampling). Probable IA includes subjects with at least 1 host factor, clinical criteria, as well as mycological criteria including both direct and indirect (i.e., detection of serum, or BAL fluid *Aspergillus* galactomannan antigen by sandwich EIA) methods. Two consecutive serum galactomannan EIA values ≥0.5 or a single value of ≥1.0 may be used as the sole microbiological criterion for probable IA. A single galactomannan EIA value of ≥1.0 in a BAL sample may be used to meet the microbiological criteria for probable IA. For subjects receiving piperacillin/tazobactam within 72 hours of serum galactomannan sampling, serum galactomannan criteria for probable IA will not meet the criteria for probable IA. Possible IA includes subjects with at least 1 host factor and clinical criteria but without mycological criteria. A modification to the 2008 EORTC/MSG criteria regarding risk factors has been made to allow for the inclusion of subjects with any duration of neutropenia as an acceptable inclusion host factor. See **Appendix 3** for tables of diagnostic criteria.
4. Each subject with possible IA at time of randomization must be willing or be in process of an ongoing diagnostic work up which is anticipated to result in a mycological diagnosis of proven or probable IA post-randomization.
5. Each subject 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. Subjects without central catheter access must be clinically stable and able to receive oral study therapy.
6. Each subject must have acute IA defined as duration of clinical syndrome of <30 days.
7. Each subject must be willing to adhere to dosing, study visit schedule, and mandatory procedures as outlined in the protocol. The subject must be willing to continue on study therapy for up to 12 weeks and remain in the study through the 1-month follow-up.
8. The subject must have the ability to transition to oral study therapy during the course of the study.
9. Female subjects of child-bearing potential must be using a medically accepted method of birth control before beginning study-drug treatment and agree to continue its use for 30 days after stopping the medication, or have been surgically sterilized (e.g., hysterectomy or tubal ligation). For those subjects using oral or injectable hormonal contraception, a barrier method of birth control (e.g., condom in combination with spermicide) is necessary. Female subjects of childbearing potential should be counseled in the appropriate use of birth control while in this study. Vasectomy of the partner and tubal ligation should each be considered effective methods of birth control.

   Female subjects who are not currently sexually active must agree and consent to use one of the above-mentioned methods should they become sexually active while participating in the study.

10. To participate in the pharmacogenetic analysis, the subject must be willing to give written

informed consent for the pharmacogenetic testing and able to adhere to dose and visit schedules. **Note:** A subject unwilling to sign the informed consent for pharmacogenetic testing may be included in the trial; however, pharmacogenetic samples must not be obtained.

11. Subject is not taking prohibited antifungal prophylaxis or treatment as defined by the protocol. Examples of allowable Antifungal Therapy Allowed Prior to Randomization are shown in Figure 1.

Key Exclusion Criteria:

1. The subject has chronic (>1-month duration) IA, relapsed/recurrent IA, or refractory invasive aspergillosis which has not responded to prior antifungal therapy.
2. The subject has chronic pulmonary aspergillosis, pulmonary sarcoidosis, aspergilloma, or allergic bronchopulmonary aspergillosis (ABPA).
3. The subject has a known mixed invasive mold fungal infection including Zygomycetes, and/or a known invasive *Aspergillus* fungal infection in which either study drug may not be considered active.
4. The subject has received any systemic (oral, intravenous, or inhaled) antifungal therapy for this infection episode for 4 or more consecutive days (≥96 hours) immediately prior to randomization.
5. The subject has developed the current episode of IA infection (possible, probable, or proven infection) during the receipt of more than 13 days of an azole or polyene antifungal agent given for prophylaxis that is considered to be a mold-active, antifungal agent (including itraconazole, posaconazole, voriconazole, isavuconazole, inhaled or systemic amphotericin or lipid-associated amphotericin), Any duration of echinocandin antifungal use is allowed (prior to randomization).
6. The subject has received POS or VOR as empirical treatment for this infection for 4 days (96 hours) or more within the 15 days immediately prior to randomization.
7. The subject has received any treatment specifically listed in **Table 2** which is more recent than the indicated washout period prior to randomization.
8. A subject must not have any condition that, in the opinion of the investigator, may interfere with optimal participation in the study, i.e., any condition requiring the use of prohibited drugs or unstable medical conditions other than the hematological disorder such as cardiac or neurologic disorder or impairment expected to be unstable or progressive during the course of this study (e.g., seizures or demyelinating syndromes, acute myocardial infarction within 3 months of study entry, myocardial ischemia, or unstable congestive heart failure, unstable arrhythmias, atrial fibrillation with ventricular rate <60/min, or history of torsades de pointes, symptomatic ventricular or sustained arrhythmias, unstable electrolyte abnormalities [e.g., ≥Grade 2 hypokalemia or hypomagnesemia]).
9. The subject has known hypersensitivity or other serious adverse reaction to any azole antifungal therapy, or to any other ingredient of the study medication used.
10. The female subject is pregnant, intends to become pregnant, or is nursing at the time of randomization.
11. The subject has any known history of Torsade de Pointes, unstable cardiac arrhythmia or proarrhythmic conditions, or a history of recent myocardial infarction within 90 days of study entry.
12. The subject has QTc (either Fridericia or Bazett's correction) interval ≥ 500 msec on electrocardiogram performed at screening or baseline.
13. The subject has significant liver dysfunction (defined as total bilirubin > 1.5 times upper limit of normal AND AST or ALT > 3 times upper limit of normal with normal alkaline phosphatase [ALP] on screening labs) at the time of randomization.
14. The subject has hepatic cirrhosis or a Child-Pugh score of C (severe hepatic impairment) at the time of randomization. See **Appendix 4** for Child-Pugh Classification.
15. The subject has severe renal insufficiency (estimated creatinine clearance <20 mL/min) or on

hemodialysis at the time of randomization or is likely to require dialysis during the study.

16. The subject has a known hereditary problem of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.
17. The subject has acute symptomatic pancreatitis within 6 months of study entry or has a diagnosis of chronic pancreatitis at the time of randomization.
18. The subject has an active skin lesion consistent with squamous cell carcinoma at the time of randomization, or a current or prior history of malignant melanoma within 5 year of study entry.
19. The subject is on artificial ventilation or receiving acute Continuous positive airway pressure (CPAP)/ Bilevel Positive Airway Pressure (BPAP) at the time of randomization.
20. A subject has known or suspected Gilbert's disease at the time of randomization.
21. The subject requires treatment with other medications that cannot be stopped and for which there is a known contraindication to co-administration of one or more of the study drugs.
22. The subject is not expected to survive for at least 1-week post-randomization.
23. The subject must not have prior enrollment in this study. The subject must not have prior enrollment in other POS studies within 90 days of study entry.
24. The subject or a family member is among the personnel of the investigational or sponsor staff directly involved with this trial.

INVESTIGATIONAL PRODUCT, DOSE, MODE OF ADMINISTRATION

Investigational Product:

- POS IV Loading dose (Day 1): 300 mg IV Q 12 hours (BID) for 2 doses.
- POS IV Maintenance dose (Beginning with the third dose): 300 mg IV Q 24 hours (once daily)
- POS Oral (through Week 12): POS tablet 300 mg QD to begin following transition from POS IV.

Transition to oral therapy may occur when the subject is considered clinically stable and able to take oral medication. If clinically indicated, some subjects may begin therapy with oral medication. If this occurs, a loading dose of POS 300 mg BID will be taken for the first day only. Subjects who are randomized to receive reference product (VOR Oral) will receive a double-dummy tablet with appearance consistent with POS tablet when transition to oral therapy.

IV infusions will be masked to blind the differences in appearance of study drug. Matching placebo infusions of 5% dextrose in water will be used for the additional daily doses in subjects randomized to POS to make the number of infusions per day (2) similar in the 2 treatment arms.

Reference Product:

- VOR IV Loading dose (Day 1): 6 mg/kg of body weight administered IV Q 12 hour (BID).
- VOR IV Maintenance dose (Beginning on Day 2): 4 mg/kg of body weight administered IV Q 12 hours (BID).
- VOR Oral (through Week 12): VOR oral capsule 200 mg BID to begin following transition from VOR IV.

Transition to oral therapy may occur when the subject is considered clinically stable and able to take oral medication. If clinically indicated, some subjects may begin therapy with oral medication. If this occurs, a loading dose of VOR 300 mg BID will be taken for the first day only. Subjects who are randomized to receive investigational product (POS Oral) will receive a double-dummy capsule with appearance consistent with VOR capsule when transition to oral therapy.

IV infusions will be masked to blind the differences in appearance of study drug.

STATISTICAL METHODS:

Type of Blinding: Double-Blind, Double-Dummy (for Oral Administration)

Only the investigational pharmacists or qualified medical personnel responsible for preparing the study drug will have knowledge of the treatment identity and will prepare study medications according to the protocol guidelines; all other study personnel will be blinded to study treatment. The unblinded pharmacists will not be involved in any post-treatment assessments for the subjects enrolled in this trial. Preparation of IV study therapy will be done by study personnel who are not otherwise involved in the clinical assessment (efficacy and safety assessments) of the subject. In order to maintain the blind, preparation of the intravenous study drugs must be performed by someone other than the persons who will evaluate the subject for clinical response and presence of adverse experiences.

IV infusions will be masked to blind the appearance of the IV study drugs. Matching placebo infusions of 5% dextrose will be used for the additional daily doses to make the number of infusions per day (2) similar in both treatment arms.

Oral POS tablets and oral VOR capsules will be administered using a double-dummy, double-blind method to blind study personnel and subjects as to the assigned treatment arm. Oral VOR will be given as over-encapsulated tablets with each capsule containing 100 mg of VOR or a placebo to VOR. The POS oral tablet will also be blinded by use of a dummy tablet with each tablet containing 100 mg of POS or a placebo to POS.

As VOR labeling recommends, dosage adjustment based upon hepatic insufficiency will be made. Appropriate dosing modifications will be included in the trial design in a blinded fashion. There is no planned dose reduction or dose adjustment of POS IV or POS oral tablet or POS dummy tablet.

This study will be conducted using in-house blinding procedures.

The primary hypothesis will be evaluated through Day 42 and the additional efficacy and safety data will be evaluated at Week 12, and 4 weeks following the Week 12 visit. All subjects will be followed for the entire study duration. For the final analyses, all data will be screened, discrepancies resolved, and protocol violators identified before the data are unblinded. All data-handling guidelines and actions will also occur prior to data unblinding according to sponsor's SOP for double-blind studies with in-house blinding.

Subject Replacement Strategy: Subjects will not be replaced in this study.

Randomization: Subjects will be randomly assigned (in a 1:1 ratio) to receive either POS or VOR according to a computer-generated randomization schedule using the interactive voice response system (IVRS).

Stratification: Subjects will be stratified prior to treatment assignment by risk status for mortality/poor outcome.

High Risk: Any one of the following are present at Baseline or in the patient's medical history:

- Allogeneic hematopoietic stem cell transplant (HSCT).
- Relapsed leukemia, undergoing salvage chemotherapy.
- Liver transplant recipients [12].

Not High Risk: Any other eligible subject (none of the high-risk criteria are present at Baseline or in the subject's medical history)

Data Sets to be Analyzed: The primary analysis will be performed on the ITT population. The ITT population consists of all randomized subjects who have received at least one dose of study drug. Secondary analyses will be based on the FAS population which includes subjects with confirmed proven or probable IA (based on 2008 modified EORTC/MSG definitions) and who: 1) receive at least one dose of study treatment; 2) have at least one post-randomization observation for the analysis endpoint subsequent to at least one dose of study treatment; 3) have baseline data for those analyses that require baseline data. Safety analyses will be based on the all-patients-as-treated (APaT) population, which includes all subjects who received at least one dose of study treatment. The FAS population consists of all randomized subjects who have at least one post-randomization observation for the analysis endpoint subsequent to at least one dose of study treatment (and have baseline data for those analyses requiring baseline data).

Sample Size: Approximately 600 subjects will be enrolled in this study, receive study drug and be randomly assigned in a 1:1 ratio to receive either POS or VOR. This sample (approximately 300 randomized subjects in each azole arm) will have ~ 82.7% power (with 1-sided alpha=0.025) to show non-inferiority of POS compared to VOR using a 10% margin assuming an all-cause mortality through Day 42 of 23% for both treatment groups. This assumed rate is based on a meta-analysis of historical VOR mortality data [27]. If the criteria for non-inferiority are met, then a superiority analysis of POS over VOR will be assessed.

Efficacy Analysis:

The primary analysis will be performed on the ITT population, which consists of all randomized subjects who received at least one dose of study treatment.

The primary endpoint in this study is all-cause mortality through Day 42 and which will be compared between the POS arm and the VOR arm for the ITT population. The primary analysis will be assessed using a non-inferiority margin of 10%. Ninety-five percent Confidence Intervals (CI), adjusted for stratification factors for the difference in success rates (POS minus VOR) will be computed. If upper limit of that CI is less than 10%, then non-inferiority of POS will be declared. If non-inferiority is declared, then superiority of POS over VOR will be assessed and will be declared if the lower limit of the CI is greater than 0.

Secondary endpoints include the global clinical response at Week 6 and Week 12 in the FAS population, all-cause mortality through Day 42 and Day 84 in the FAS population and all-cause mortality through Day 84 in the ITT population. All will be evaluated using a similar methodology as that for the primary analysis.

Other endpoints (i.e., time to death [all causes] in the FAS population; and mortality due to IA at Weeks 6 and 12 in the FAS population) will also be analyzed. Adjudicated global clinical response Weeks 6 and 12 in subjects with possible, probable, or proven IA subjects (ITT population) will also be assessed as a secondary endpoint.

Survival will be assessed using a Kaplan Meier estimates and will be compared between the two arms using the Log-Rank test.

Other analyses: Sparse pharmacokinetic (steady state trough) sampling will be performed on all subjects throughout the treatment period. Data regarding food intake relative to posaconazole tablet administration will be collected and the effect of food on the steady state pharmacokinetics of posaconazole tablet will be evaluated. Plasma concentrations over time in individual subjects including adolescents will be evaluated including an evaluation of plasma concentrations at the time of adverse events. In subjects receiving IV study therapy, at the time of maximum concentration, data regarding ECG parameters will be evaluated. Exploratory analysis may be conducted on pharmacogenomic endpoints and their association with key efficacy and safety parameters at a later date, as data allow.

Safety Analysis: The incidence of serious adverse events (SAEs), incidence of treatment-emergent and treatment-related AEs (overall, treatment-related, and selected AEs of interest) as well as other safety endpoints will be summarized by treatment groups.

The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. The following four categories are Tier 1 events:

- Hepatic safety: Elevated AST or ALT lab value that is ≥3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing;
- CNS and visual safety: Treatment-emergent adverse events (TEAEs) related to CNS or visual disturbances. See **Section 8.5.2** for a list of terms;
- Dermatologic reactions: TEAEs including rash and photosensitivity rash;
- Adrenal steroidogenesis: TEAEs indicating adrenal insufficiency or temporally associated TEAEs of hypotension.

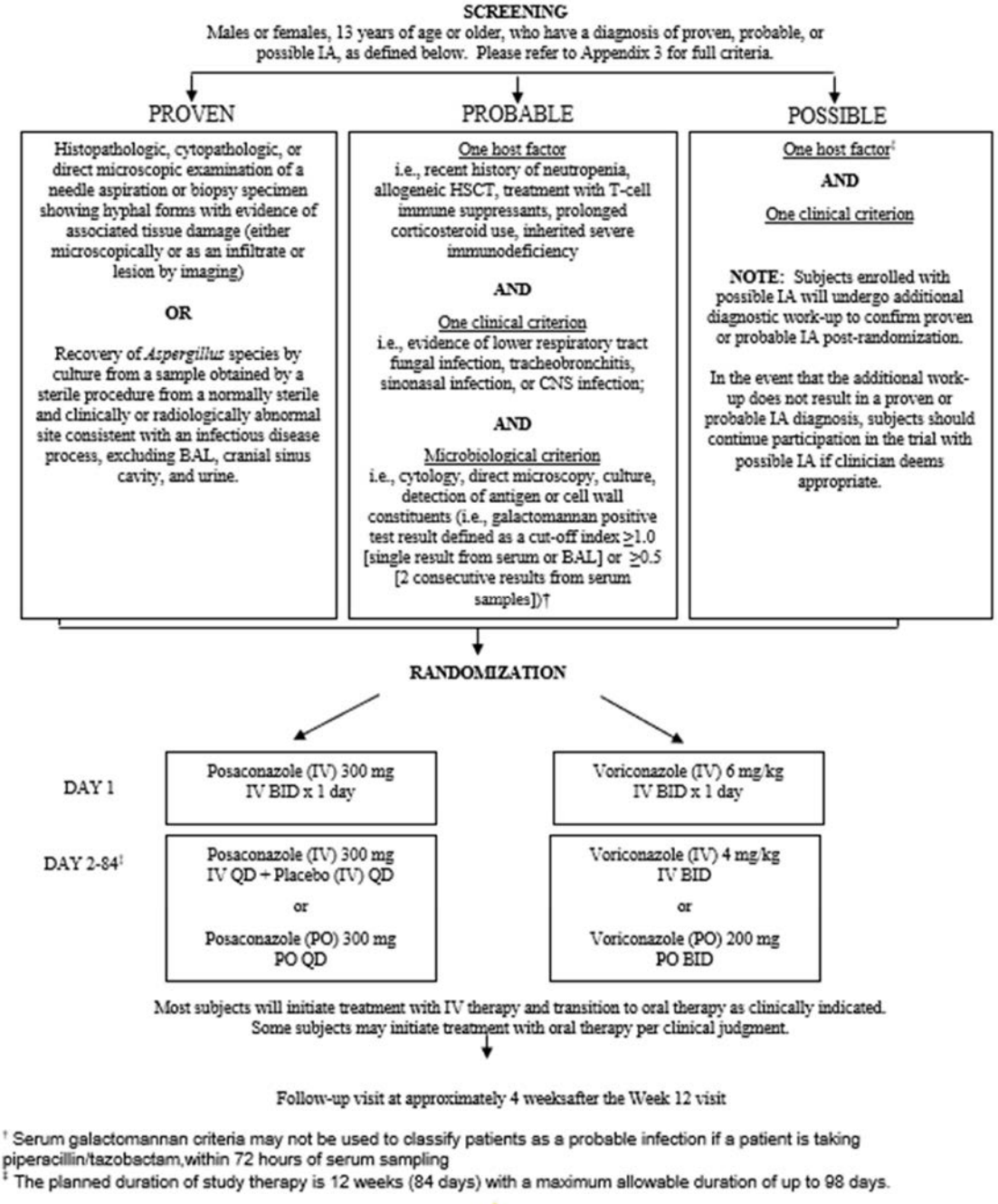
The following are Tier 2 events based on specific AE categories: (1) proportion of subjects with at least one adverse experience; (2) proportion of subjects with at least one drug related adverse experience; (3) proportion of subjects with at least one serious adverse experience; (4) proportion of subjects with at least one serious and drug related adverse experience; (5) proportion of subjects who discontinued study therapy due to an adverse experience. 95% confidence intervals (Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method.

The APaT population will be used to assess safety in this study. All patients who received at least one dose of study treatment will be included in the APaT population.

Pharmacogenetics: Exploratory analysis may be conducted on pharmacogenomic endpoints and their association with key efficacy and safety parameters at a later date, as data allow

eDMC: Safety will be monitored by the external Data Monitoring Committee (eDMC) on an ongoing basis and the eDMC will make recommendations to the Sponsor as appropriate.

2.1 Trial Design Diagram



† Serum galactomannan criteria may not be used to classify patients as a probable infection if a patient is taking piperacillin/tazobactam,within 72 hours of serum sampling
‡ The planned duration of study therapy is 12 weeks (84 days) with a maximum allowable duration of up to 98 days.

2.2 Trial Flow Chart

Study Procedures	Screening	Baseline	Treatment Phase						Follow-Up	Unscheduled
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**U[W]**
Day Relative to First Dose of Study Drug	**Days -7 to -1**	**Day 1**	**Day 3 (± 1 day)**	**Week 1 [Day 4 to 8]**	**Week 2 [Day 9 to 15]**	**Week 4 [Day 16 to 29]**	**Week 6 [Day 30 to 54]**	**Week 12 / EOT[a] [Day 84 (±4 weeks)]**	**30 Days Posttherapy (±2 weeks)**	**Unscheduled**
Informed Consent/assent	X									
Review Inclusion/Exclusion Criteria	X	X								
Issue Subject Identification Card	X									
Collect Subject Identification Card									X	
Medical/Disease History	X									
Pharmacogenetics Sampling (optional)[b]		X								
Stratification and Randomization by IVRS		X								
Problem Focused Physical Examination	X	X		X	X	X	X	X	X	X
Weight	X									
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X
Recording of Previous Treatments[d]	X	X								
Assessment of Clinical Signs and Symptoms of Invasive Aspergillosis	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)[z]	X	X[e]	X	X				X[f]		X
Hematology[g]	X	X	X	X	X	X	X	X	X	X
Serum Chemistry[h]	X	X	X	X	X	X	X	X	X	X
Serum hCG Pregnancy Test[i]	X									X

Study Procedures	**Screening**	**Baseline**	**Treatment Phase**						**Follow-Up**	**Unscheduled**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**U[w]**
Day Relative to First Dose of Study Drug	**Days -7 to -1**	**Day 1**	**Day 3 (± 1 day)**	**Week 1 [Day 4 to 8]**	**Week 2 [Day 9 to 15]**	**Week 4 [Day 16 to 29]**	**Week 6 [Day 30 to 54]**	**Week 12 / EOT[a] [Day 84 (±4 weeks)]**	**30 Days Posttherapy (±2 weeks)**	**Unscheduled**
Serum for *Aspergillus* Galactomannan EIA[j, x]	X	X	X	X	X	X	X	X	X	X
Serum for Beta-D-Glucan Assay[j]	X	X	X	X	X	X	X	X	X	X
Mycology Testing[k]	X	X		X	X	X	X	X		X
Blood for CYP 2C19 genotyping[l]		X								
Diagnostic Imaging[m, x]	X	X[n]			X[n]	X[n]	X[o]	X	X[p]	X
Study Drug Dosing[q]		X	X	X	X	X	X	X		X
Concomitant Treatments[r]		X	X	X	X	X	X	X	X	X
Assess Global Clinical Response							X[t]	X		
Plasma Pharmacokinetic Assessment[s]		X		X	X	X	X	X		X
Collect Unused Medications			X	X	X	X	X	X		X
Study Medication Diary/ Dosing Compliance Assessment [y]			X	X	X	X	X	X		X
Drug Accountability Inventory			X	X	X	X	X	X		X
Safety (Adverse Events) Evaluation	X	X	X	X	X	X	X	X	X	X
I / IFI Assessment[u]							X	X	X	
Mortality Assessment [u]			X	X	X	X	X	X	X	X

Study Procedures	Screening	Baseline	Treatment Phase						Follow-Up	Unscheduled
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**U[W]**
Day Relative to First Dose of Study Drug	**Days -7 to -1**	**Day 1**	**Day 3 (± 1 day)**	**Week 1 [Day 4 to 8]**	**Week 2 [Day 9 to 15]**	**Week 4 [Day 16 to 29]**	**Week 6 [Day 30 to 54]**	**Week 12 / EOT[a] [Day 84 (±4 weeks)]**	**30 Days Posttherapy (±2 weeks)**	**Unscheduled**

[a] Subjects who receive less than 12 weeks of therapy, must complete the End of Therapy (EOT) procedures. The planned duration of study therapy is 12 weeks (84 days) with a maximum allowable duration of up to 98 days.

[b] Informed consent for pharmacogenetic samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. DNA samples for future use should be collected after informed consent for Pharmacogenetics sampling has been obtained.

[c] Vital signs should be recorded in the eCRF daily for hospitalized subjects and on scheduled days, if outpatient. While subjects are on IV treatment, vital signs should be collected daily. Temperature recorded should be highest temperature (maximum temperature) for each day. For screening period, daily maximum temperature for 5 days prior to Day 1 should be recorded.

[d] A record of all prior medication (prescription or over the counter) taken by the subject within 7 days before starting the study is to be obtained and recorded in the subject's eCRF. A record of chemotherapeutic agents used for any chemotherapy regimen within 30 days of Enrollment is to be obtained. A record of all prior immunosuppressive therapies and antifungal therapy should be recorded for 30 days prior to Baseline through Day 1.

[e] The Day 1 ECG should be performed prior to initiation of study treatment.

[f] Assessments to be performed for early termination due to treatment failure or premature discontinuation due to adverse events (AEs) where the exam would be pertinent (i.e., ECG for cardiac AE, etc.).

[g] The hematology panel will include: red blood cell count (RBC), white blood count (WBC), WBC differential, absolute neutrophil count (ANC), hemoglobin, hematocrit, and platelet count.

[h] The following serum chemistry tests should be performed: calcium, magnesium, albumin, glucose, potassium, sodium, chloride, creatinine, total protein, lactate dehydrogenase (LDH), uric acid, blood urea nitrogen (BUN) or urea, total bilirubin, alkaline phosphatase (ALK-P), AST (or SGOT), and ALT (or SGPT).

[i] A serum beta-hCG test should be performed at screening for all women of childbearing potential.

[j] Serum for *Aspergillus* Galactomannan enzyme immunoassay (EIA) and Beta-D-Glucan should be collected at all requested timepoints. The quantitative value and time of collection of the galactomannan sample should be documented for all galactomannan tests performed on patients. The results of all galactomannan samples taken during the period from screening to the 1 month follow up visit should be provided. Broncho-alveolar lavage fluid should be collected for the *Aspergillus* galactomannan assay, as necessary; however, the use of Plasma-Lyte for the bronchoscopy is not allowed. Galactomannan EIA serological test results may not be used to confirm a probable diagnosis of invasive aspergillosis if subjects are taking piperacillin/tazobactam within 72 hours of serum sampling.

[k] Mycology testing includes standard fungal cultures from all sites of suspected *Aspergillus* infection, as clinically appropriate. Unless clinically inappropriate or not warranted due to the patient's health, condition or disease progression/ regression, mycology testing should occur at the following visits: screening/ baseline, Week 6 and Week 12. Additional mycology testing will be done as clinically indicated and should correlate with potential disease regression/progression. Repeated sampling of infected sites (e.g., repeated lung biopsies) to evaluate for response to therapy may not be feasible or clinically warranted. Identification to species level and minimum inhibitory concentration (MIC) testing will be done by a central reference laboratory on subcultures provided by each investigative site. All fungal isolates clinically relevant to infection should be stored locally for shipment to a central laboratory.

[l] Blood for DNA will be obtained as a mandatory sample to determine CYP2C19 genotype status.

Study Procedures	Screening	Baseline	Treatment Phase						Follow-Up	Unscheduled
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	U[W]
Day Relative to First Dose of Study Drug	Days -7 to -1	Day 1	Day 3 (± 1 day)	Week 1 [Day 4 to 8]	Week 2 [Day 9 to 15]	Week 4 [Day 16 to 29]	Week 6 [Day 30 to 54]	Week 12 / EOT[a] [Day 84 (±4 weeks)]	30 Days Posttherapy (±2 weeks)	Unscheduled

[m] At screening/ baseline, Week 6 and Week 12, Diagnostic imaging required of all attributable infected sites of disease. High-resolution CT scan required for all subjects with pulmonary sites of infection. A chest X-ray is deemed insufficient for assessment of pulmonary IA.

[n] Imaging will only be performed at this visit if the clinical infectious condition changes relative to the previous assessment and repeat imaging is judged warranted by the clinician.

[o] Imaging for the Week 6 visit can be performed at Week 6 ± 2 weeks.

[p] Imaging for this visit will only be performed if there is relapse or worsening of the clinical infectious condition relative to the end-of-treatment assessment.

[q] Study drug dosing (POS or VOR) will occur on every day from Day 1 through Day 84 (maximum allowable duration of up to 98 days). While hospitalized, the timing of dosing will be recorded in the dosing record at the time of dosing. While outpatient, subjects will maintain daily dosing record with recording of actual time of dosing at the time of administration. While receiving IV treatment, vital signs should be collected daily. While receiving POS tablet or POS tablet placebo, the timing and characteristics of food taken should be recorded in the study medication diary and eCRF for each tablet dose.

[r] All concomitant treatments, include medications and therapeutic procedures, should be recorded in the eCRF.

[s] Plasma samples will be collected in all subjects including adolescents prior to the first dose of study treatment at Baseline, and at pre-dose on Day 7, Week 2, Week 4, Week 6, and Week 12 (EOT). For adult subjects on IV therapy, at the Week 1 visit an additional plasma sample will be collected at the time of completion of the 90-minute infusion (i.e. at the time of anticipated C_{max}). This PK sample should be collected via peripheral venipuncture and not be drawn from the central catheter. For adolescents on IV therapy, plasma samples will be collected at the time of completion of their 90-minute infusion at Day 7, Week 2, Week 4, Week 6 and Week 12 (EOT). These PK samples should be collected via peripheral venipuncture and not be drawn from the central catheter. Subjects who are receiving oral study therapy at the week 1 study visit do not need to collect the additional PK sample. If a subject discontinues early, a PK sample (predose, if possible) should be collected at the time of study therapy discontinuation with the time of PK sample noted.

[t] Visit 7 window (Week 6, Day 30-54) is slightly different from the window for the Global Clinical Response assessment at Week 6 (± 2 weeks)[u] All subjects randomized and treated are to be followed for mortality assessment throughout the study period until Day114, regardless of whether the subject discontinues study therapy prior to Visit 8 Day 84.

[W] Labs and Procedures at unscheduled visits should only be performed as clinically appropriate.

[x] All imaging results and galactomannan testing performed within 7 days of randomization should be recorded. For imaging and galactomannan testing, if the procedure is performed prior to screening a patient for the study and meets protocol requirements. The results can be used for screening procedures as long as procedures were done within 7 Days of randomizing the patient.

[y] Food information will be collected in study medication diaries for patients receiving POS tablet or POS tablet placebo, the timing and characteristics of food taken should be recorded in the eCRF for each tablet dose.

[z] For subjects on IV therapy an ECG will be performed at the Week 1 study visit following the completion of the 90-minute infusion. At this time, a plasma sample will also be collected (see footnote “s”) Subjects who are receiving oral study therapy at the week 1 study visit may have the ECG performed without regard to the timing of study therapy.

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4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
ABPA	Allergic bronchopulmonary aspergillosis
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
AMA	American Medical Association
AmB	Amphotericin B deoxycholate
APaT	All-Patients-as-Treated
ALT	Alanine serum transaminase (or SGPT)
ALP	Alkaline phosphatase (or ALK-P)
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
AST	Aspartate serum transaminase (or SGOT)
AUC	Area under the curve
BAL	Broncho-alveolar lavage
BID	Twice daily dosing
BUN	Blood urea nitrogen
CAC	Clinical adjudication committee
Cavg	Average concentration
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CFR	Code of Federal Regulations
Cmax	Maximum concentration
CNS	Central nervous system
CRF	Case report form
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common terminology criteria for adverse events
CTD	Clinical trial directive
CYP2C19	Cytochrome P450 2C19
CYP2C9	Cytochrome P450 2C9
CYP3A4	Cytrochrome P450 3A4
DAO	Data as observed
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDMC	External data monitoring committee

Term	Definition
EDC	Electronic data capture
EIA	Enzyme immunoassay
EMEA	European Medicines Agency
EOC	Executive oversight committee
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of therapy
ERC	Ethics review committee
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
hCG	Human chorionic gonadotropic
HESDE	Historical evidence of sensitivity to drug effects
HIV	Human immunodeficiency virus
HMG-CoA	Beta-hydroxy-beta-methylglutaryl-CoA
HSCT	Hematopoietic stem cell transplant
IA	Invasive Aspergillosis
ISA	Isavuconazole
ICF	Informed Consent Form
ICH	Internal Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IFI	Invasive Fungal Infection
IMP	Investigational Medicinal Product
IND	Investigational new drug
IRB	Institutional review board
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
MDS	Myelodysplastic syndrome
MIC	Minimum inhibitory concentration
mITT	Modified Intention to Treat
MRI	Magnetic resonance imaging
MSG	Mycoses study group
NCI	National Cancer Institute
NI	Non-inferior

Term	Definition
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NSAID	Non-steriodal anti-inflammatory drug
PD	Pharmacodynamic
PDLC	Pre-defined limit of change
PGt	Pharmacogenetic (or PG)
PK	Pharmacokinetic
PO	Oral administration
POS	Posaconazole
PND	Post-natal day
PP	Per-protocol
PQC	Product quality complaint
Q12h	Every 12 hours
Q24h	Every 24 hours
QD	Once daily
QT interval	Interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram that represents the time during which contraction of the ventricles occurs
QTc interval	QT interval corrected for heart rate
RBC	Red blood cell count
RNA	Ribonucleic acid
RSI	Reference safety information
SAC	Scientific advisory committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
USA	United States of America
VOR	Voriconazole
WBC	White blood count

5.0 INTRODUCTION

5.1 Therapeutic Rationale

Current guidelines for the treatment of IA recommend the use of VOR as primary therapy [10], [23]. Early initiation of antifungal therapy is recommended while the definitive diagnostic evaluation is in process. The duration of azole treatment is not yet well defined; current recommendations call for a minimum duration of 6 to 12 weeks in immunocompromised subjects. These recommendations are based upon the findings of controlled clinical studies that found initial treatment with VOR to be superior to amphotericin B deoxycholate (AmB) in the treatment of acute IA. In an open-label controlled study after 12 weeks of therapy, the global clinical response to therapy was 53% in subjects who were randomized to receive VOR with a survival rate of 71% compared to a response rate of 32% for AmB and a survival rate of 58% [2]. Invasive aspergillosis is a serious, life-threatening disease that occurs among patients with prolonged and/or severe impairment of the immune system. Without the initiation of antifungal therapy, the acute mortality rate has been shown to exceed 85 % (Appendix 2). With early diagnosis and the prompt initiation of therapy, the mortality rate of patients treated with a mold-active antifungal agent has improved [26]. A meta-analysis of all-cause mortality through Day 42 based on historical data of VOR treatment of IA found a mortality rate of 23 % [27]. In 2015, a recently completed prospective clinical study of ISA vs VOR given to patients with invasive aspergillosis reported through Day 42 all-cause mortality rate of 18.6% and 20.2, ISA and VOR treatment arms, respectively. In the same clinical study, with the use of the 2008 EORTC/MSG guidelines for the evaluation of clinical response among subjects with proven or probable IA, a successful clinical response at the end of therapy was noted to be 35% and 38.9%, ISA and VOR treatment arms, respectively [27].

More effective or safer antifungal therapy is sought for patients with IA [26, 28]. POS is a highly active triazole with the potential to have at least similar efficacy to VOR based on animal model data. POS demonstrates a more potent in vitro activity compared to VOR against the most common clinical isolates including *Aspergillus fumigatus and A. flavus* [3]. POS may also have some potential advantages in terms of tolerability, drug interactions, and safety. The most common treatment-related adverse events for VOR are visual disturbances, with approximately 21% of subjects experiencing abnormal vision, color changes, and/or photophobia. Similar visual disturbances are observed in ≤ 2% of subjects who have received POS.

VOR is metabolized primarily by the human hepatic cytochrome P450 enzyme CYP2C19. This enzyme exhibits genetic polymorphism, which can cause large differences in the pharmacokinetics of VOR. Individuals are classified as either extensive metabolizers or poor metabolizers of this enzyme, and the distribution of these genotypes varies greatly across different populations. Poor metabolizers have shown, on average, a 4-folder higher VOR exposure compared to the extensive metabolizers. This variability can have significant clinical impact, since VOR exposure can vary greatly between individuals and data suggests that visual

disturbances may be associated with higher VOR plasma concentrations [4]. POS is not affected by genetic polymorphisms since it primarily circulates in plasma as parent compound, and of the circulating metabolites, the majority are formed via UDP glucuronidation.

POS was shown to be effective in an open label, externally controlled salvage therapy trial of 107 patients with proven/probable aspergillosis. The global clinical response rate (complete and partial response) at the end of therapy was 42% in POS treated subjects, compared to 26% in external controls receiving standard therapy [5]. In addition, POS has activity against *Aspergillus spp.* other than *A. fumigatus*, and importantly, against Zygomycetes, which can mimic the clinical presentation of aspergillosis in high risk patients. In this study of refractory IA, there was an exposure response association; subjects in the highest quartile with the highest POS exposure (mean Cavg of 1250 ng/mL) had a higher response (approximately 75%) compared to lower concentration quartiles.

Merck has developed new IV and oral formulations of POS that are able to achieve a higher exposure target with reduced variability compared to POS oral suspension [6]. POS IV Solution is an aqueous injectable solution containing 18 mg/mL of POS to be diluted in 5 % dextrose in water prior to IV administration. The primary excipient in POS IV Solution and VOR IV is sulfobutylether-β-cyclodextrin (SBEβCD). The administration of this excipient to subjects with impaired renal function has been associated with potential limitations; however, a recent study with VOR has suggested that there is no difference between IV or oral administration and the impact on renal function [7]. POS tablet is designed to maximize systemic absorption and overcome the food-effect limitations of the oral suspension formulation. This study will utilize both the IV and tablet formulations for POS and VOR for the treatment of subjects with IA.

5.2 Subject Population Rationale

The primary study population is the intent-to-treat (ITT) population, which includes all randomized subjects who received at least one dose of study drug. However, of further interest in this study is the subset of subjects with a diagnosis of proven or probable invasive aspergillosis (IA) based on modified 2008 EORTC/MSG definitions [10]. Subjects with possible IA may also be enrolled into the study with further evaluation of proven or probable IA, which must be confirmed post-randomization to be included in the FAS analysis on the secondary endpoints. (Note, inclusion in the FAS further requires subjects have at least one post-randomization observation for the analysis endpoint subsequent to at least one dose of study treatment [and have baseline data for those analyses requiring baseline data]).

Subjects with proven invasive fungal infection (IFI) will have confirmed infection based upon detection of the fungus by histological analysis or culture of a specimen taken from sterile material from a site of infection. Subjects with probable IFI will require the presence of appropriate host factors, clinical criterion, and a mycological

criterion including both direct tests and indirect tests including serum galactomannan antigen detection. Host factors include: recent history of neutropenia temporally related to a fungal disease (Any duration of neutropenia is also acceptable for possible criteria in this study), receipt of an allogeneic HSCT, treatment with T-cell immune suppressants, prolonged corticosteroid use, and inherited severe immunodeficiency. See **Appendix 3** for the criteria for diagnosing invasive aspergillosis.

Subjects selected for this study will be 13 years of age or greater. Subjects between 13 and 14 years of age must weigh ≥ 50 kg [110lb].

5.2.1 Preclinical data Relative to Inclusion of Adolescent patient population with IV solution

POS IV Solution was evaluated in two studies in juvenile dogs, one in pre-weaning dogs post-natal 2-8 weeks of age during POS IV Solution administration and one study in post-weaning dogs aged 10-22 weeks during POS IV Solution administration.

Well-characterized POS toxicities (the same as those seen in adult animals) were observed in both studies. In addition, in the pre-weaning study following 6 weeks of POS IV administration (animals exposed to POS IV from post-natal day 14 through post-natal day 56) enlargement of the lateral ventricles in the brain was observed compared to concurrent placebo and saline control groups. Plasma exposure to POS in these juvenile dogs was approximately 5x human therapeutic AUC with POS IV (300 mg IV). No difference in the incidence of brain ventricular enlargement between control and treated animals was observed following a 5-month treatment-free period, consistent with complete resolution. There were no neurologic or behavioral abnormalities in the dogs with this finding. This finding was not seen with administration of POS IV Solution to post-weaning dogs (aged 10-22 weeks) or with oral POS administration to juvenile dogs throughout development (from PND 4 days through 9 months of age), or in juvenile rats. The finding of brain ventricular dilation observed in pre-weaning juvenile dogs after 6 weeks of POS IV Solution administration is considered to be equivalent to the period of development in humans from an age of 3 months to approximately two years of age.

Findings of ventricular dilation in the brain were not observed in young adult dogs administered POS IV Solution for three months or in young adult monkeys administered POS IV Solution for 1 month, in which similar or higher POS exposures were attained compared to the juvenile study.

This data supports allowing the inclusion of adolescent patients, 13 years of age and up. As a result of this data, the study population has been expanded to include the enrollment of adolescents outside of the European Union (i.e., in those regions with an approved indication for use of oral POS in the adolescent age population (13 years of age and older).

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

5.3 Dose and Administration Rationale

At the time of study enrollment, subjects will be randomized in a 1:1 ratio to receive one of two possible treatment arms: POS or VOR. All IV therapy must be administered via a central line (e.g., central venous catheter, peripherally-inserted central catheter, etc.). Further details around IV dosing can be found in Section 7.4.1.3.2.

Both IV and oral therapy are given to treat IA. In general, patients receive IV therapy at the beginning of treatment and transition to oral therapy when able. If patients are clinically stable and able to take oral medication, they may begin treatment on oral therapy. In this study, both the IV and oral formulations will be used. Most subjects will begin on IV therapy and transition to oral; however, some subject may start the study receiving oral therapy. For IV therapy, study drug will be blinded and administered via central line. Peripheral dosing will not be possible for this study, since each IV study drug has different infusion times. Dosing duration is 90 minutes. The dosing of study drug via peripheral venous administration may not occur due to the potential occurrence of thrombophlebitis when IV study drug is given via peripheral route. For oral therapy, study drug will be blinded using double-dummy tablets or capsules to mask study drug identity.

5.3.1 Posaconazole Dose Rationale

Subjects enrolled into this arm of the study will be treated with POS IV and/or tablet formulations. A dose of POS 300 mg QD has been selected for this study based upon prior clinical development of POS. Merck has developed new IV and oral formulations of POS that are able to achieve a higher exposure target with reduced variability compared to POS oral suspension [6]. Phase 1B/3 studies have been conducted in patients treated with POS IV solution and POS tablet given as antifungal prophylaxis [31]. In patients, the mean steady state Cavg exposure for POS IV solution 300 mg QD was 1430 ng/ml; the mean steady state Cavg exposure for POS tablet 300 mg QD was 1460 ng/ml [29]. With these new formulations, the desired exposure target (Cavg at least 1250 ng/mL) will be more rapidly and more consistently achieved. This target concentration is associated with higher response rates in subjects with IA [5]. Subjects will receive a loading dose of 300 mg POS BID on Day 1, followed by 300 mg QD thereafter. Most subjects will start therapy via the IV route and transition to the oral route when able to tolerate oral medications.

5.3.2 Voriconazole Dose Rationale

Subjects enrolled in this arm of the study will be treated with VOR IV and/or capsule formulations. The dose selected for the study is consistent with the current VOR prescribing information and recommendations for patients with invasive

aspergillosis. The most recent guidelines of the Infectious Diseases Society of America (2008) and the American Thoracic Society (2011) for the treatment of invasive aspergillosis recommend IV VOR 6 mg/kg every 12 hour for one day followed by 4 mg/kg every 12 hours until improvement, followed by oral VOR 200 mg every 12 until resolution or stabilization of all clinical and radiographic manifestations [10], [23]. This dosage of VOR was also used in the most recent clinical study of invasive aspergillosis [27]. These guidelines are consistent with the current VOR labeling as well as 2012 recommendations by the American Society of Health System Pharmacists [18]. Controlled clinical trials have not shown a benefit of higher dosing of VOR; higher VOR dosing may lead to higher drug exposure which has been associated with an increased risk of hepatic or visual adverse events [8]. According to the current guidelines, VOR is the current recommended therapy for subjects with IA [10], [23]. When on IV therapy, subjects will receive a loading dose of 6 mg/kg BID on Day 1, followed by a maintenance dose of 4 mg/kg BID. If the subject is on oral therapy, a loading dose of 300 mg BID will be given on Day 1, and 200 mg BID thereafter. Most subjects will start therapy via the IV route and transition to the oral route when able to tolerate oral medications. The dose to be used for VOR IV and oral is the standard dose recommended for administration. With this dose at steady state most subjects will achieve drug concentrations within the range considered to be therapeutic (1-5.5 ug/mL). In a study by Pascual et al (2008) of patients treated with VOR for invasive mycoses including aspergillosis, the lack of a response to therapy was more frequent in patients with VOR concentrations < 1 ug/mL, and VOR concentrations > 5.5 ug/mL were associated with more frequent neurotoxicity [8]. VOR product labeling indicates that the oral maintenance dose of 200 mg achieves a VOR exposure similar to 3 mg/kg IV and a 300 mg oral maintenance dose achieves an exposure similar to 4 mg/kg IV. If clinically indicated, the subject may switch back to IV therapy if the subject is taking oral therapy and their clinical condition is not improving. Please refer to VOR EU product circular for full details [32].

6.0 TRIAL OBJECTIVES

6.1 Primary Trial Objective

To compare the all-cause mortality for posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) through Day 42 in all randomized subjects who received at least one dose of study treatment (in the ITT [Intention to Treat] population). The hypothesis to be tested is that the all-cause mortality through Day 42 in the POS treatment group is non-inferior to that in the VOR treatment group.

6.2 Secondary Trial Objectives

- To evaluate the all-cause mortality for POS vs. VOR through Day 42 in the FAS population.

- To evaluate the global clinical response for POS vs. VOR at Week 12 in the FAS population.
- To evaluate the all-cause mortality for POS vs. VOR through Day 84 in both the FAS and ITT populations.
- To evaluate the global clinical response for POS vs. VOR at Week 6 in the FAS.
- To evaluate the time to death (all causes) for POS vs. VOR in the FAS population.
- To evaluate mortality due to IA through Day 42 and Day 84 for POS vs. VOR in the FAS population.
- To evaluate the safety and tolerability of POS and VOR by analyzing Tier 1 Safety events and all adverse events.
- To evaluate the safety of POS compared to VOR therapy in the All-Patients-as-Treated (APaT) population.
- To evaluate, in the subset of subjects that have pharmacokinetic data and food intake records, the pharmacokinetic profile of POS and VOR, including an evaluation of the effect of food intake on the POS tablet steady state pharmacokinetic profile, and to evaluate the exposure-response (efficacy and safety endpoints) relationships of POS and VOR in a subset of subjects with available data.

6.3 Exploratory Objectives

- To explore the effects of CYP2C19 polymorphisms and predicted metabolic enzyme activity on POS and VOR plasma concentration.
- To explore pharmacogenetic endpoints and their association with key efficacy and safety parameters.
- To explore the effect of treatment on serological biomarkers (e.g., serum galactomannan EIA, beta-D-glucan).

7.0 INVESTIGATIONAL AND ANALYSIS PLAN

7.1 Overall Trial Design

This is a Phase 3, randomized, double-blind study of POS versus VOR in subjects with IA as defined by modified 2008 EORTC/MSG consensus criteria. Subjects with features consistent with proven, probable, or possible IA will be enrolled. Subjects who are enrolled with a diagnosis of possible IA will undergo additional diagnostic work-up to confirm proven or probable IA post-randomization to be included in the secondary FAS population. All randomized subjects who receive at least one dose of study drug will be included in the primary ITT population.

At the time of study enrollment, subjects will be randomized to receive one of two possible treatment arms: POS or VOR for a maximum total duration of therapy of 12 weeks. In general, most subjects should receive the full 12 weeks of study therapy. Subjects will be randomized to POS or VOR in a 1:1 ratio. Overall, approximately 600 subjects will be enrolled in the study to obtain 300 ITT-evaluable subjects per arm. Subjects who are randomized and receive at least one dose of study drug will comprise the primary analysis population (ITT dataset).

Most subjects will begin antifungal azole (VOR or POS) therapy via the IV route; however, some may begin study therapy via the oral route. Subjects who may begin study therapy via the oral route may include subjects with renal insufficiency (creatinine clearance < 50 ml/min), or subjects without central venous catheter access. Azole therapy will be switched from IV route to the oral route when the subject is considered clinically stable and able to take oral medication. See **Table 1** for an overview of the two treatment arms. The assigned azole treatment (POS or VOR) will be provided in a double-blind manner. A follow-up evaluation will be done 1 month after treatment completion. Ultimately, subjects who complete 12 weeks of study treatment will participate in the study for a total of approximately 16 weeks post-randomization.

Table 1 Overview of Active Study Drug Dosing by Treatment Arms

Treatment Arms	IV Therapy[a]	Oral Therapy
Arm 1 – Posaconazole (POS)	POS IV: Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD	POS oral: Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD
Arm 2 – Voriconazole (VOR)	VOR IV: Day 1[b]: 6 mg/kg per body weight administered BID Day 2-84[c]: 4 mg/kg per body weight administered BID	VOR oral: Day 1[b]: 300 mg BID Day 2-84[c]: 200 mg BID
[a] Subjects will begin IV study drug and then step down/transition to oral study drug. If clinically indicated, some subjects may begin study drug with oral therapy instead of IV therapy. [b] Day 1 refers to the first day of subject taking either IV or Oral therapy. Subjects will only take one formulation, either IV or oral at a time [c] The planned duration of study therapy is 12 weeks (84 days) with a maximum allowable duration of up to 98 days. IV=intravenous; POS=posaconazole; VOR=voriconazole		

Diagnostic, attributable mortality, and efficacy data from all subjects will be reviewed by an independent CAC who will be blinded to the assigned treatment arm. The CAC will determine acceptability of the diagnostic criteria of a proven or probable IFI according to modified MSG/EORTC consensus criteria [9]. Subjects who are randomized receive at least one dose of study drug and whose diagnosis of proven or probable IA is confirmed by the CAC will comprise the FAS dataset. (The FAS further requires subjects to have received at least one dose of study drug and have at least one post-randomization observation for the analysis endpoint subsequent to at least one dose of study treatment [and have baseline data for those analyses requiring baseline data]). The CAC will adjudicate the global clinical response to

treatment (as per 2008 EORTC/MSG guidelines) at 6 weeks and at 12 weeks post-randomization. A successful global clinical response will be defined as an FAS-evaluable subject who is judged by the CAC to be alive and have a complete or partial response at the time point of interest. The CAC will also adjudicate IFI-attributable mortality through Day 42 and Day 84 in subjects as data allow.

The primary analysis will be performed on the ITT population. The ITT population consists of all randomized subjects who received at least one dose of study treatment.

The primary endpoint in this study is all-cause mortality through Day 42 between the POS arm and the VOR arm for the ITT population. The primary analysis will be assessed using a non-inferiority margin of 10%. Ninety-five percent Confidence Intervals (CI), adjusted for stratification factors for the difference in success rates (POS minus VOR) will be computed. If upper limit of that CI is less than 10%, then non-inferiority of POS will be declared. If non-inferiority is declared, then superiority of POS over VOR will be assessed and will be declared if the lower limit of the CI is greater than 0.

The secondary endpoints include the global clinical response at Week 6 and Week 12 in the FAS population and all-cause mortality through Day 42 and Day 84, in the FAS and ITT populations. All will be evaluated using a similar methodology as that for the primary analysis. Survival will be assessed using a Kaplan Meier estimates and will be compared between the two arms using the Log-Rank test.

7.2 Beginning and End of the Trial

Each subject is considered to be enrolled in the trial when the subject (or the subject's legal representative) has provided written informed consent.

Each subject is considered to have ended participation in the trial when he/she has completed the last protocol-specified contact (e.g., visits or telephone contacts) or prematurely discontinues from the study.

A subject is considered to have completed the trial after he/she has completed the end of therapy visit and follow-up assessments.

A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in Section 7.3.3.

A subject is considered to have been lost to follow-up if he/she is unable to be contacted by the investigator. The end of participation for a subject lost to follow-up is the last known contact (e.g., visit or telephone contact).

The overall trial begins when the first subject is enrolled (i.e., signs the informed consent form). The overall trial ends when the last remaining subject has ended participation in the trial, by completing the trial, being discontinued from the trial, or being lost to follow-up.

Each subject will be monitored for the occurrence of SAEs immediately after the subject has signed informed consent. Each subject will be followed for serious adverse events for up to and including 30 days after the last dose. Follow-up procedures related to pregnancy or SAEs may continue beyond the end of the clinical trial. Of note, all subjects are to be followed for mortality for the entire study period (i.e., until the final study visit at 16 weeks) regardless of the duration of study treatment.

Once a subject has ended participation in the trial, the investigational products from the trial will no longer be available to the subject and any future care will be provided according to the subject's personal physician.

A subject is considered to have completed study treatment if the subject has recovered from IA during a maximum of 12 weeks of study treatment. All subjects who are randomized to the study and receive at least one dose of study drug must complete the Week 6 and the Week 12 visits and will be followed for 4 weeks following the Week 12 visit. Each subject will participate in the trial for approximately 16 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 7 days, each subject will be receiving assigned treatment (Section 7.4.1.1) for a maximum of 12 weeks. In general, most subjects should receive the full 12 weeks of study therapy. After the Week 12 visit each subject will have a final study visit at approximately 4 weeks (30 days) following the Week 12 visit for a total duration of study of approximately 16 weeks.

7.3 Trial Population

This study will investigate two extended spectrum azoles (POS and VOR) in subjects with proven or probable IA based modified 2008 EORTC/MSG definitions [10]. Subjects with possible IA may also be enrolled into the study with further evaluation of proven or probable IA, which must be confirmed post-randomization to be included in the FAS study population.

Subjects with proven invasive fungal infection (IFI) will have confirmed infection based upon detection of the fungus by histological analysis or culture of a specimen taken from sterile material from a site of infection.

Subjects with probable IFI will require the presence of appropriate host factors, clinical criterion, and a mycological criterion. Mycological criteria include:

- Direct test (cytology, direct microscopy, or culture)
    - Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by the presence of fungal elements indicating a mold, or recovery by culture of a mold (e.g., *Aspergillus* species).

- Indirect tests of aspergillosis (detection of antigen or cell-wall constituents) include: galactomannan antigen detected in serum or bronchoalveolar lavage fluid.

If using the galactomannan test for diagnosis, a positive test result is defined as two consecutive serum values of ≥0.5 or a single serum value ≥1.0. Similarly, a single value of ≥1.0 in a BAL sample would qualify the subject for meeting the criteria as probable IA. For subjects receiving piperacillin/tazobactam within 72 hours of serum galactomannan sampling, serum galactomannan criteria for probable IA will not meet the criteria for probable IA. Patients with hematologic malignancy or recipients of HSCT who have a positive serum galactomannan assay without clinical or radiologic findings should not be enrolled, or if enrolled, should be excluded from the analysis of efficacy. The quantitative value and time of measurement of the galactomannan index should be documented.

Subjects with possible IA will meet the criteria for a host factor and a clinical criterion, but without confirmatory mycological criterion. Subjects who are enrolled with a diagnosis of possible IA will undergo additional diagnostic work-up to confirm proven or probable IA post-randomization. Subjects with possible IA diagnosis will continue in the study, however these subjects will not be considered part of the FAS population. All enrolled subjects who receive at least one dose of study drug will be part of the ITT population. By enrolling subjects as early as possible, it is hoped that better outcomes overall will be achieved, based on data indicating that early intervention improves survival [11, 26]. A subject under the age of legal consent or who otherwise is unable to provide independent consent may participate provided that a legal representative (such as a parent or legal guardian) provides written informed consent on his/her behalf. Any minor must provide assent prior to entering into the study.

7.3.1 Subject Inclusion Criteria

A subject must meet all the criteria listed below to participate in the trial.

1. Each subject must be willing and able to provide written informed consent for the trial. The legal representative (e.g., parent or guardian) for a subject under the age of legal consent or who otherwise is unable to provide independent consent may provide written informed consent for the subject. Each subject of the age of assent must be willing and able to provide assent in addition to consent from the legal representative to participate in the trial.

2. Each subject must be ≥13 years of age weighing >40 kg [88 lb] and ≤150 kg [330 lb] at the time of randomization. Each subject between 13 and 14 years of age must weigh ≥50 kg [110 lb]. Subjects may be of either sex and of any race/ethnicity. For those sites who do not have the ability to enroll adolescents, subjects must be greater than ≥18 years of age.

3. Each subject must meet the criteria for proven, probable, or possible IA as per 2008 EORTC/MSG disease definitions at the time of randomization. Proven IA will include those subjects with the demonstration of fungal elements (by cytology, microscopy, or culture) in diseased tissue (sterile sampling). Probable IA includes subjects with at least 1 host factor, clinical criteria, as well as mycological criteria including both direct and indirect (i.e., detection of serum, or BAL fluid *Aspergillus* galactomannan antigen by sandwich EIA) methods. If using the galactomannan test for diagnosis, a positive test results is defined as two consecutive serum values of ≥0.5 or a single serum value ≥1.0. Similarly, a single value of ≥1.0 in a BAL sample would qualify the subject for meeting the criteria as probable IA. For subjects receiving piperacillin/tazobactam within 72 hours of serum galactomannan sampling, serum galactomannan criteria for probable IA will not meet the criteria for probable IA. Possible IA includes subjects with at least 1 host factor and clinical criteria but without mycological criteria. A modification to the 2008 EORTC/MSG criteria regarding risk factors allows for the inclusion of subjects with any duration of neutropenia as an acceptable inclusion host factor. See **Appendix 3** for tables of diagnostic criteria.

4. Each subject with possible IA at time of randomization must be willing or be in process of an ongoing diagnostic work up which is anticipated to result in a mycological diagnosis of proven or probable IA post-randomization.

5. Each subject 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. Subjects without central catheter access must be clinically stable and able to receive oral study therapy.

6. Each subject must have acute IA defined as duration of clinical syndrome of <30 days.

7. Each subject must be willing to adhere to dosing, study visit schedule, and mandatory procedures as outlined in the protocol. The subject must be willing to continue on study therapy for up to 12 weeks and remain in the study through the 1-month follow-up visit.

8. The subject must have the ability to transition to oral study therapy during the course of the study.

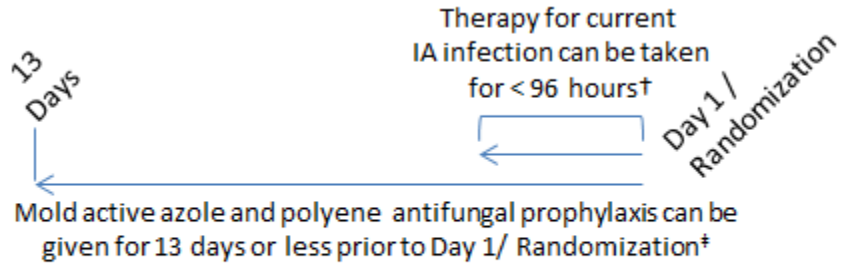
9. Female subjects of child-bearing potential must be using a medically accepted method of birth control before beginning study-drug treatment and agree to continue its use for 30 days after stopping the medication, or have been surgically sterilized (e.g., hysterectomy or tubal ligation). For those subjects using oral or injectable hormonal contraception, a barrier method of birth control (e.g., condom in combination with spermicide) is necessary. Female subjects of childbearing potential should be counseled in the appropriate use of birth control while in this study. Vasectomy of the partner and tubal ligation should each be considered effective methods of birth control.

   Female subjects who are not currently sexually active must agree and consent to use one of the above-mentioned methods should they become sexually active while participating in the study.

10. To participate in the pharmacogenetic analysis, the subject must be willing to give written informed consent for the pharmacogenetic testing and able to adhere to dose and visit schedules. Note: A subject unwilling to sign the informed consent for pharmacogenetic testing may be included in the trial; however, pharmacogenetic samples must not be obtained.

11. Subject is not taking prohibited antifungal prophylaxis or treatment as defined by the protocol. Examples of allowable Antifungal Therapy Allowed Prior to Randomization are shown in Figure 1.

Figure 1Mold Active Antifungal Therapy Allowed Prior to Randomization



† All systemic antifungal therapy (mold-active and non-mold active) must be stopped at Day 1 Randomization
‡ Any duration of echinocandin antifungal therapy is allowed prior to randomization

7.3.2 Subject Exclusion Criteria

A subject meeting any of the exclusion criteria listed below must be excluded from participating in the trial:

1. The subject has chronic (>1-month duration) IA, relapsed/recurrent IA, or refractory IA which has not responded to prior antifungal therapy.

2. The subject has pulmonary sarcoidosis, aspergilloma, or allergic bronchopulmonary aspergillosis (ABPA).

3. The subject has a known mixed invasive mold fungal infection including Zygomycetes, and/or a known invasive *Aspergillus* fungal infection in which either study drug may not be considered active.

4. The subject has received any systemic (oral, intravenous, or inhaled) antifungal therapy for this infection episode for 4 or more consecutive days (≥96 hours) immediately prior to randomization.

5. The subject has developed the current episode of IA infection (possible, probable, or proven infection) during the receipt of more than 13 days of an azole or polyene antifungal agent given for prophylaxis that is considered to be a mold-active, antifungal agent(including itraconazole, posaconazole, voriconazole, isavuconazole, inhaled or systemic amphotericin or lipid-associated amphotericin), Any duration of echinocandin antifungal use is allowed (prior to randomization).

6. The subject has received POS or VOR as empirical treatment for this infection for 4 days (96 hours) or more within the 15 days immediately prior to randomization.

7. The subject has received any treatment specifically listed in **Table 2** which is more recent than the indicated washout period prior to randomization.

Table 2 Prohibited Medications Prior to Start of Study Treatment and During Study Treatment

Prohibited Medications Prior to Start of Study Treatment and During Study Treatment	**Washout Period[a]**
Systemic antifungal therapy (oral, intravenous or inhaled) for > 3 consecutive days (≥96 hours) for treatment of this infection.	Not eligible to participate in the study
Systemic antifungal therapy (oral, intravenous or inhaled) for ≤ 3 consecutive days (<96 hours) for treatment of this infection.	Discontinue at Randomization
Investigational drugs (new chemical or biological entities): Investigational use of approved products or chemotherapy regimens may be permitted with the approval of the sponsor's project physician prior to use.	30 days[c]
Prophylaxis of IFI with azole or polyene antifungal drugs. This includes itraconazole, posaconazole, voriconazole, isavuconazole, inhaled or systemic amphotericin or lipid-associated amphotericin)	Discontinue at randomization
Nasal sprays of amphotericin B and aerosolized amphotericin B	Discontinue at randomization

Prohibited Medications Prior to Start of Study Treatment and During Study Treatment	**Washout Period[a]**
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)
Ergot alkaloids (ergotamine, dihydroergotamine or other licensed or investigational members of this class).	2 days
Medications that are known to result in a false positive galactomannan EIA result: amoxicillin/clavulanate, and Plasma-Lyte.[e]	Prohibited during screening phase
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
HMG-CoA reductase inhibitors metabolized via CYP3A4 (e.g., simvastatin, lovastatin, and atorvastatin).	24 hours
Cyclophosphamide[b, d]	24 hours
Fosamprenavir, Ritonavir and efavirenz	24 hours
Vinca Alkaloids [d]	24 hours
Sirolimus	7 days

[a] These waiting times should be observed prior to start of study treatment and during study treatment in subjects receiving a prohibited drug as prior therapy or should be observed after study drug is stopped before the prohibited medication is prescribed. No concurrent use is permitted. Deviations from these washout periods must be approved by the sponsor prior to use of study drug or prohibited agent.

[b] Low dose cyclophosphamide use is allowed during the treatment period with a temporary interruption of study therapy on the day of cyclophosphamide dosing.

[c] Investigational use of MK-8228 will require a 14-day washout period (rather than 30 days)

[d] Concomitant use of Cyclophosphamide and vinca alkaloids is prohibited on study therapy. Subjects can remain on study if use of cyclophosphamide or vinca alkaloids therapies is needed but a washout of study drug for 24 hours must occur.

[e] Medications that are known to result in a false positive galactomannan EIA result can be used on study, but when used do not allow for galactomannan to contribute to a confirmatory probable IA diagnosis. Please refer to figure 2.1 for additional details.

HMG-CoA=beta-hydroxy-beta-methylglutaryl-CoA; IFI = invasive fungal infection

8. A subject must not have any condition that, in the opinion of the investigator, may interfere with optimal participation in the study, i.e., any condition requiring the use of prohibited drugs or unstable medical conditions other than the hematological disorder such as cardiac or neurologic disorder or impairment expected to be unstable or progressive during the course of this study (e.g., seizures or demyelinating syndromes, acute myocardial infarction within 3 months of study entry, myocardial ischemia, or unstable congestive heart failure, unstable arrhythmias, atrial fibrillation with ventricular rate <60/min, or history of torsades de pointes, symptomatic ventricular or sustained arrhythmias, unstable electrolyte abnormalities [e.g., ≥Grade 2 hypokalemia or hypomagnesemia]).

9. The subject has known hypersensitivity or other serious adverse reaction to any azole antifungal therapy, or to any other ingredient of the study medication used.

10. The female subject is pregnant, intends to become pregnant, or is nursing at the time of randomization.

11. The subject has any known history of Torsade de Pointes, unstable cardiac arrhythmia or proarrhythmic conditions, or a history of recent myocardial infarction within 90 days of study entry.

12. The subject has QTc (either Fridericia or Bazett's correction) interval $\geq$ 500 msec on electrocardiogram performed at screening or baseline.

13. The subject has significant liver dysfunction (defined as total bilirubin > 1.5 times upper limit of normal AND AST or ALT > 3 times upper limit of normal with normal alkaline phosphatase [ALP] on screening labs) at the time of randomization.

14. The subject has hepatic cirrhosis or a Child-Pugh score of C (severe hepatic impairment) at the time of randomization. See Appendix 4 for Child-Pugh Classification.

15. The subject has severe renal insufficiency (estimated creatinine clearance <20 mL/min) or on hemodialysis at the time of randomization or is likely to require dialysis during the study.

16. The subject has a known hereditary problem of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

17. The subject has acute symptomatic pancreatitis within 6 months of study entry or has a diagnosis of chronic pancreatitis at the time of randomization.

18. The subject has an active skin lesion consistent with squamous cell carcinoma at the time of randomization, or a current or prior history of malignant melanoma within 5 year of study entry.

19. The subject is on artificial ventilation or receiving acute Continuous positive airway pressure (CPAP)/ Bilevel Positive Airway Pressure (BPAP) at the time of randomization.

20. A subject has known or suspected Gilbert's disease at the time of randomization.

21. The subject requires treatment with other medications that cannot be stopped and for which there is a known contraindication to co-administration of one or more of the study drugs.

22. The subject is not expected to survive for at least 1-week post-randomization.

23. The subject must not have prior enrollment in this study. The subject must not have prior enrollment in other POS studies within 90 days of study entry.

24. The subject or a family member is among the personnel of the investigational or sponsor staff directly involved with this trial.

7.3.3 Subject Discontinuation Criteria

A subject may discontinue from the clinical trial at any time for any reason.

It is the right and the duty of the investigator or sub-investigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual subject. In addition, the investigator or sub-investigator is to stop treatment of any subject with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results.

In this trial, a subject may discontinue from treatment, but continue to participate in the regularly scheduled activities as long as the subject does not withdraw consent. Discontinuation from treatment is “permanent”: once a subject is discontinued treatment, even though he/she continues to be monitored in the trial, he/she shall not be allowed to begin treatment again.

At a minimum collect the following information when a subject discontinues:

1. The reason the subject discontinued;
2. The date of the last dose of test products from the trial;
3. The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate;
4. (Serious) Adverse events;
5. Compliance with the test product administration as specified in this protocol;
6. Final Assessments:

   Every effort should be made to ensure that all procedures and evaluations scheduled for the final trial visit are performed (Section 2.2, Trial Flow Chart);
7. Retrieve all investigative products and test articles from the subject.

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

1. The subject or legal representative (such as a parent or legal guardian) withdraws consent;
2. Adverse event criteria as specified in Section 7.7.2.3.1.
3. Request of the subject (subjects have the right to discontinue treatment at any time for any reason);

4. Pregnancy;

5. Subjects with a prolonged QTc interval on a manual measurement of their post baseline ECG: greater than 500 msec. Study drug should be interrupted while evaluation and treatment of other etiologies is ongoing, and restarted within 5 days if QTc is within normal limits (less than or equal to 500 msec);

6. Subjects that develop clinically indicated visual problems (Grade 3 and/or Grade 4);

7. Subjects that develop an exfoliative cutaneous reaction, develops a skin lesion consistent with squamous cell carcinoma or melanoma.

8. Subjects who, during the course of the study, it is determined that they have a mold fungal infection caused by an organism that may be insufficiently covered by the current study therapy, or some other infection that requires combination antifungal therapy. Subjects who develop candidemia on study therapy may receive an echinocandin agent in addition to study therapy for a maximum duration of 14 days. A subject who needs a longer duration than 14 days of echinocandin therapy should discontinue study therapy.

7.3.4 Replacement of Subjects

A subject who discontinues from the trial will not be replaced.

7.4 Treatments

7.4.1 Trial Treatments

7.4.1.1 Treatments Administered

Treatment should be started as close as possible to the date in which randomized treatment is assigned, preferably on the same day.

Upon acceptance into the study, once all of the inclusion and exclusion criteria are met, at Baseline/Day 1 subjects will be stratified into two strata; high risk or not high risk (see Section 7.4.1.2 for details). Within each stratum, subjects will be randomly assigned to one of two possible treatment arms: POS or VOR for a total duration of therapy of 12 weeks. The planned duration of study therapy is 12 weeks (84 days) with a maximum allowable duration of up to 98 days. Subjects will be randomized to POS or VOR in a 1:1 ratio. Table 3 provides an overview of the treatment arms.

Table 3 Overview of Active Study Drug Dosing by Treatment Arms

Treatment Arms	IV Therapy[a]	Oral Therapy
Arm 1- Posaconazole (POS)	POS IV: Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD	POS oral: Day 1[b]: 300 mg BID Day 2-84[c]: 300 mg QD
Arm 2 – Voriconazole (VOR)	VOR IV: Day 1[b]: 6 mg/kg per body weight administered BID Day 2-84[c]: 4 mg/kg per body weight administered BID	VOR oral: Day 1[b]: 300 mg BID Day 2-84[c]: 200 mg BID

[a] Most subjects begin IV study drug and then step down/transition to oral study drug. If clinically indicated, some subjects may begin study drug with oral therapy instead of IV therapy.

[b] Day 1 refers to the first day of subject taking either IV or Oral therapy. Subjects will only take one formulation, either IV or oral at a time

[c] The planned duration of study therapy is 12 weeks (84 days) with a maximum allowable duration of up to 98 days.

IV=intravenous; POS=posaconazole; VOR=voriconazole

The dosing regimens will be as follows:

Arm 1 POS:

POS IV loading dose, 300 mg IV BID on Day 1; followed by 300 mg POS IV QD beginning on Day 2; followed by POS tablet 300 mg QD to begin following transition from POS IV. Transition to oral therapy may occur when the subject is considered clinically stable and able to take oral medication. Most subjects will initiate IV therapy, and then transition to oral; however, some subject may initiate via the oral route if clinical indicated. Subjects taking oral therapy on Day 1 will receive POS tablet 300 mg BID as a loading dose; followed by POS tablet 300 mg QD.

Subjects randomized to Arm 1 POS will receive a placebo infusion of 5% dextrose in water once a day to make the total number of infusions per day (2) similar for both treatment arms. Subjects will also receive double-dummy capsules with appearance consistent with VOR capsules when transition to oral therapy.

Arm 2 VOR:

VOR IV loading dose, 6 mg/kg IV BID on Day 1; followed by 4 mg/kg VOR IV BID maintenance dose, beginning on Day 2; followed by oral VOR capsule 200 mg BID to begin following transition from VOR IV. Transition to oral therapy may occur when the subject is considered clinically stable and able to take oral medication. Most subjects will initiate IV therapy, and then transition to oral; however, some subject may initiate via the oral route if clinical indicated. Subjects taking oral therapy on Day 1 will receive VOR capsule 300 mg BID as a loading dose; followed by VOR capsule 200 mg BID.

Subjects randomized to Arm 2 VOR will also receive double-dummy tablets with appearance consistent with POS tablets when transition to oral therapy.

7.4.1.2 Method of Treatment Assignment, Randomization, and/or Stratification

Subjects will be stratified prior to treatment assignment by risk status for mortality and poor outcome. Randomized treatment assignment will be stratified as follows:

High Risk: Any one of the following are present at Baseline or in the patient's medical history:

- Allogeneic hematopoietic stem cell transplant (HSCT).
- Relapsed leukemia, undergoing salvage chemotherapy.
- Liver transplant recipients [12].

Not High Risk: Any other eligible subject (none of the high-risk criteria are present at Baseline or in the subject's medical history)

Within each stratum, subjects will be randomly assigned (in a 1:1 ratio) to receive either POS or VOR according to a computer-generated randomization schedule using the interactive voice response system (IVRS).

7.4.1.3 Selection and Timing of Dose for Each Subject

7.4.1.3.1 Selecting the Dose for Each Subject

The rationale for the selection of doses to be used in this trial is presented in Section 5.3. Dosing for all of the subjects will be based on Table 3. The VOR IV dose will be calculated based on the screening weight of the subject. Details of the calculations can be found in the Pharmacy Manual.

Most subjects will begin antifungal azole (VOR or POS) therapy via the IV route. Azole therapy will be switched from IV route to the oral route when the subject is considered clinically stable and able to take oral medication. If during the course of the study, the subject can no longer tolerate oral medication, the subject may be switched back to IV therapy. Subjects with worsening clinical symptoms may also be switched back to IV therapy as clinically indicated. Based upon product labeling, similar study drug exposures for a 300 mg dose have been noted for POS IV and POS tablet, while 4 mg/kg IV VOR dosing achieves exposures similar to a 300 mg oral maintenance dose of VOR. Please refer to VOR EU product circular for full details [32].

If clinically indicated, some subjects may initiate study therapy via the oral route: Day 1 dosing of oral therapy is: POS 300 mg BID or VOR 300 mg BID.

For subjects with mild to moderate hepatic cirrhosis (Child-Pugh score of A or B), the standard loading dose will be used, but the maintenance dose will be reduced. See Appendix 4 for Child-Pugh Classification. Appropriate dosing modifications will be included in the trial design in a blinded fashion.

7.4.1.3.2 Determining the Timing of Dose Administration for Each Subject

7.4.1.3.2.1 Posaconazole

Table 4 provides what subjects randomized to the POS arm will receive when on IV therapy.

Table 4 Summary of POS IV Therapy

	Day 1 Dose	Day 2-84 Dose	Day 2-84 Dose for subjects with hepatic impairment
Drug	POS 300 mg twice a day	POS 300 mg first dose, placebo infusion second dose	POS 300 mg first dose, placebo infusion second dose
Volume	200 mL	150 mL	150 mL
Infusion rate	100 mL/hr	100 mL/hr	100 mL/hr
Infusion Duration	2 hr	1.5 hr	1.5 hr

Table 5 provides what subjects randomized to the POS arm will receive when on oral therapy.

Table 5 Summary of POS Tablet Therapy

	Daily Oral Dose 300mg QD[a]	Daily Oral Dose for subjects with hepatic impairment 300mg QD
First Dose	2 orange VOR capsule placebos 3 yellow POS tablets	1 orange VOR capsule placebos 3 yellow POS tablets
Second Dose	2 orange VOR capsule placebos	1 orange VOR capsule placebos

[a] If the subject starts on Day 1 with POS Tablet, they will receive 300 mg BID. The first dose should be: 3 orange VOR capsule placebos, and 3 yellow POS tablets. The second dose should be: 3 orange VOR capsule placebos, and 3 yellow POS tablets.

7.4.1.3.2.1.1 POS IV Solution

Subjects will have their IV infusions begun at the same time each day and are not to be administered until after the collection of the specified blood samples (Section 7.6).

POS IV will be given every 12 hours on the first day, with infusions being not less than 10 hours or no more than 14 hours apart. The subsequent POS IV infusions will be administered once daily 24 hours (± 2 hours) apart, in order to control one

source of variability in drug levels. Subjects who are randomized to POS will also receive a placebo infusion of 5% dextrose in water to make the number of infusions per day (2) similar for both treatment arms. Subjects will receive an IV infusion (POS or placebo) every 12 hours.

If the dosing of study medication is delayed, the dose should be administered as soon as possible. If it is more than 6 hours since the missed dose, the missed dose should be skipped, and the next dose should be administered at the regularly scheduled time. Any missed doses should be properly documented in the subject's eCRF and source documentation. The infusions will be administered via a programmable pump. On Day 1 the infusions will run for approximately 2 hours. The infusions on the subsequent days will run for approximately 1.5 hours. If necessary, the IV infusions may be prepared up to 24 hours prior to administration and stored at 2°C to 8°C refrigerated. The IV infusions should return to room temperature prior to administration.

IV infusions should be administered via a peripherally inserted central catheter, or a dedicated lumen of a central venous catheter. No infusions of study drug should be given via a peripherally inserted peripheral catheter as the duration of infusion mandated in the study for IV study therapy differs for peripheral catheter administration as compared to central catheter administration. Dosing duration is 90 minutes. The dosing of study drug via peripheral venous administration may not occur due to the potential occurrence of thrombophlebitis when IV study drug is given via peripheral route. POS IV infusions will be prepared in 5% dextrose in water.

Subjects will receive the IV infusions at a hospital or clinic. No IV doses should be missed.

See the Unblinded Pharmacy Binder and Administrative Binder for detailed POS IV Solution preparation and administration procedures.

7.4.1.3.2.1.2 Posaconazole Tablet

POS tablet will be started on the day after completion of the IV therapy (within 12 hours of the placebo infusion matching VOR IV) and continue up to Week 12 post randomization. POS tablet will be administered as a 300 mg dose QD (three 100 mg tablets, once a day). Every attempt should be made to ensure that the subject takes study medication at approximately the same time every day. If the dosing of study medication is delayed, the dose should be taken as soon as possible. Any missed doses should be properly documented in the subject's eCRF and source documentation.

If clinically indicated, some subjects may initiate study therapy via the oral route. For these subjects POS tablet will be administered on Day 1 as a 300 mg dose BID (three 100 mg tablets, twice a day at approximately 12-hour intervals). After Day 1, the dose will be 300 mg QD (three 100 mg tablets, once a day).

If a subject vomits within 15 minutes of POS tablet administration, the dosing should be repeated as soon as possible, following appropriate antiemetic treatment. The adverse event, supportive treatments, and ability to subsequently dose study medication should be appropriately recorded in the subject's eCRF. If repeated vomiting occurs, the subject should switch to POS IV therapy.

Details of the patient's food intake surrounding each dose of POS tablet or dummy placebo tablet should be recorded relative to each dose of POS tablet. Specifically, food intake data to be recorded should include whether the subject had no food, a light meal, a moderate meal or a full meal within 2 hours before or within 1 hour after taking study drug.

The exact time of POS study drug taken prior to collection of the population PK sample, as well as the exact time the Population PK sample blood draw occurs will be recorded in the appropriate eCRF.

7.4.1.3.2.2 Voriconazole

Table 6 provides what subjects randomized to the VOR arm will receive when on IV therapy.

Table 6 Summary of VOR IV Therapy

	Day 1 Dose	Day 2-84 Dose	Day 2-84 Dose for subjects with hepatic impairment[a]
Drug	VOR 6 mg/kg twice a day	VOR 4 mg/kg twice a day	VOR 2 mg/kg twice a day
Volume	200 mL	150 mL	150 mL
Infusion rate	100 mL/hr	100 mL/hr	100 mL/hr
Infusion Duration	2 hr	1.5 hr	1.5 hr

[a] The maintenance dose of VOR should be reduced for subjects with mild to moderate hepatic impairment (Child-Pugh Class A and B).

Table 7 provides what subjects randomized to the VOR arm will receive when on oral therapy.

Table 7 Summary of VOR Capsule Therapy

	Daily Oral Dose 200mg BID[a]	Daily Oral Dose for subjects with hepatic impairment[b] 100mg BID
First Dose	2 orange VOR capsules 3 yellow POS tablet placebos	1 orange VOR capsules 3 yellow POS tablet placebos
Second Dose	2 orange VOR capsules	1 orange VOR capsules

[a] If the subject starts on Day 1 with VOR Solid Oral, they will receive 300 mg BID. The first dose should be: 3 orange VOR capsules, and 3 yellow POS tablet placebos. The second dose should be: 3 orange VOR capsules, and 3 yellow POS tablet placebos.

[b] The maintenance dose of VOR should be reduced for subjects with mild to moderate hepatic impairment (Child-Pugh Class A and B).

7.4.1.3.2.2.1 Voriconazole IV

Subjects will have their IV infusions begun at the same time each day and are not to be administered until after the collection of the specified blood samples (Section 7.6).

VOR IV infusions must be given every 12 hours with no dose given less than 10 hours or no more than 14 hours apart. If the dosing of study medication is delayed, the dose should be administered as soon as possible. If it is more than 6 hours since the missed dose, the missed dose should be skipped, and the next dose should be administered at the regularly scheduled time. Any missed doses should be properly documented in the subject's eCRF and source documentation. The infusions will be administered via a programmable pump. On Day 1 the infusions will run for approximately 2 hours. The infusions on the subsequent days will run for approximately 1.5 hours. If necessary, the IV infusions may be prepared up to 24 hours prior to administration and stored at 2°C to 8°C refrigerated. The IV infusions should return to room temperature prior to administration.

IV infusions should be administered via a peripherally inserted central catheter, or a dedicated lumen of a central venous catheter. VOR IV infusions will be prepared in 5% dextrose in water.

Subjects will receive the IV infusions at a hospital or clinic. No IV doses should be missed.

See the Unblinded Pharmacy Binder and Administrative Binder for detailed VOR IV preparation and administration procedures.

7.4.1.3.2.2.2 Voriconazole Capsule

VOR oral capsule will be started on the day after completion of the IV therapy (within 12 hours of the last dose of IV VOR) and continued up to Week 12 post randomization. VOR will be administered as a 200-mg dose BID (two 100-mg capsules, twice a day at approximately 12-hour intervals). VOR oral capsules SHOULD NOT BE TAKEN WITH A MEAL and should be taken at least one hour before or one hour following a meal. If the dosing of study medication is delayed, the dose should be taken as soon as possible at least one hour before or one hour following a meal. Any missed doses should be properly documented in the subject's eCRF and source documentation.

If clinically indicated, some subjects may initiate study therapy via the oral route. For these subjects VOR oral capsule will be administered on Day 1 as a 300-mg dose BID (three 100 mg capsules, twice a day at approximately 12-hour intervals). After Day 1, the dose will be 200 mg BID (two 100-mg capsules, twice a day at approximately 12-hour intervals).

If a subject vomits within 15 minutes of VOR capsule administration, the dosing should be repeated as soon as possible, following appropriate antiemetic treatment. The adverse event, supportive treatments, and ability to subsequently dose study medication should be appropriately recorded in the subject's eCRF. If repeated vomiting occurs, the subject should switch to VOR IV therapy.

7.4.1.4 Blinding Trial Treatments

Double-Blind, Double-Dummy (for Oral Administration)

Only the investigational pharmacists or qualified medical personnel responsible for preparing the study drug will have knowledge of the treatment identity and will prepare study medications according to the protocol guidelines; all other study personnel will be blinded to study treatment. The unblinded pharmacists will not be involved in any post-treatment assessments for the subjects enrolled in this trial. Subjects will receive the blinded IV study therapy from the unblinded pharmacist. In order to maintain the blind, preparation of the intravenous study drugs must be performed by someone other than the persons who will evaluate the subject for clinical response and presence of adverse experiences.

IV infusions will be masked to blind the appearance of the IV study drugs. Matching placebo infusions of 5% dextrose will be used for the additional daily doses to make the number of infusions per day (2) similar in both treatment arms. Subjects in both treatment arms will receive the same number of infusions per day with equivalent infusion rates and volumes. This is not dependent on the treatment arm.

POS tablets and VOR capsules will be administered using a double-dummy, double-blind method to blind study personnel and subjects as to the assigned treatment arm. Oral VOR will be given as over-encapsulated tablets with each capsule

containing 100 mg of VOR or a placebo to VOR. The POS oral tablet will also be blinded by use of a dummy tablet with each tablet containing 100 mg of POS or a placebo to POS. Subjects in both treatment arms will receive the same number of tablets and capsules per day when on oral therapy. This is not dependent on the treatment arm.

As VOR labeling recommends, dosage adjustment based upon hepatic insufficiency will be made. The maintenance dose of VOR will be reduced in subjects with mild to moderate hepatic impairment (Child-Pugh Class A and B). Subjects on VOR IV will receive 2 mg/kg maintenance dose BID. Subjects on VOR capsules will receive 100 mg BID. Appropriate dosing modifications will be included in the trial design in a blinded fashion. There is no planned dose reduction or dose adjustment of POS IV or POS tablet or POS dummy tablet.

This study will be conducted using in-house blinding procedures. See Section 7.7.2.6.4 for a description of the method of unblinding a subject during the trial, should such action be warranted.

7.4.1.5 Investigational Medicinal Products

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

7.4.1.5.1 Identity of Investigational Medicinal Products

The following study medications will be used in the trial:

Posaconazole 100 mg IV, 18mg/mL, 5.6mL fill

Posaconazole 200 mg IV, 18mg/mL, 11.2mL fill

Posaconazole 300 mg IV; 18mg/mL, 16.7mL fill (When available, may replace 100/200 mg vials)

Voriconazole 200 mg IV

Posaconazole 100 mg tablets

Posaconazole Placebo tablets

Voriconazole 100 mg capsules

Voriconazole Placebo capsules

7.4.1.5.2 Source

All products listed in Section 7.4.1.5.1 will be provided by the sponsor.

7.4.1.5.3 Labeling

Labeling for POS IV and VOR IV vials and cartons should include but not limited to the following information and will comply with the regulatory requirements for the clinical site: Space for Randomization #, component ID and the following statement "For Intravenous Use Only".

In addition, the POS IV cartons will include the following: Contents: One 100 mg and one 200-mg POS vial.

Labeling for POS active/placebo tablet bottles should include but not limited to the following information and will comply with the regulatory requirements for the clinical site: Space for Randomization #, component ID and the following statement: Oral Use.

Labeling for VOR active/placebo capsule bottles should include but not limited to the following information and will comply with the regulatory requirements for the clinical site: Space for Randomization #, component ID, the following statements: Oral Use and should be taken at least one hour before or after a meal.

The labeling of the POS active/ placebo tablets bottle and VOR active/placebo capsules bottle will maintain the double-blind double-dummy design of the trial. The labeling of the POS IV and VOR IV will be open label.

7.4.1.5.4 Packaging

POS IV will be supplied as a carton with one 100 mg and one 200 mg POS IV vials. A rollout of POS IV 300 mg vials will also occur during the study.

VOR IV will be supplied as a carton with one 200 mg VOR vial.

POS active and placebo will be supplied as bottles of 30 tablets each.

VOR active and placebo will be supplied as bottles of 40 capsules each.

The packaging of the POS active/placebo tablets bottle and VOR active/placebo capsules bottle will maintain the double-blind double-dummy design of the trial. The packaging of the POS IV and VOR IV will be open label.

7.4.1.5.5 Storage

Trial treatment supplies must be stored in a secure, limited-access location under the storage conditions specified on the supply label and pharmacy manual. Site storage conditions should be monitored by the site personnel for adherence to label and pharmacy manual specifications and reviewed during site visits.

7.4.1.5.6 Dispensing

The investigator or qualified designee(s) will dispense trial treatments at the designated site(s) to subjects who have provided written informed consent and have met the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

See the Trial Flow Chart in Section 2.2 for a schedule of when clinical supplies are to be dispensed to the subjects.

7.4.1.5.7 Replacement of Investigational Product

Refer to the Unblinded Pharmacy Binder and Administrative Binder for details regarding replacement of clinical supplies.

7.4.1.5.8 Investigational Medicinal Product Accountability

Accurate and current accounting of the dispensing and return of investigational products will be maintained on an ongoing basis by a member of the trial site staff:

- Investigational medicinal products dispensed to each site will be recorded in the trial-specific Site Investigational Medicinal Product (IMP) Accountability Log (or equivalent document approved by the sponsor);

Investigational medicinal products dispensed to each subject will be recorded.

In this study, as part of the routine recording of the amount of study treatment taken by each patient, at each site, the volume of infusion administered, and the number of tablets/capsules dispensed and returned will be counted, reviewed, and recorded at regular intervals at the local level. Pharmacy records of dispensing and return of study medication will be recorded using local documentation records and will be monitored and reviewed by un-blinded study monitors throughout the study period. Pharmacy records will be retained at the local pharmacy and available for Sponsor review. Site records will be used to ensure and document study medication compliance. Study medication dosing will be recorded in the electronic case report for each study medication component (IV or oral, placebo or active drug) based upon local documentation records.

After use by the subject, the following test articles may be collected and destroyed according to the hospital's hazardous/medical waste policies, as applicable:

- IV bags and solution set
- Used POS and VOR IV vials

In the event the investigational products destruction is arranged by the site, copies of the destruction records should be returned to the sponsor.

The sponsor's trial monitor will instruct the site on the return of all investigational products supplies. A final inventory of the total amount of investigational products received at each trial site against the amount used and returned must be recorded in the Site IMP Accountability Log. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

7.4.2 Non-Trial Treatments

7.4.2.1 Prior and Concomitant Medications

7.4.2.1.1 Medications, Supplements, and Other Substances Prohibited Prior to Randomization and During the Trial

A record of all prior medication (prescription or over the counter) taken by the subject within 7 days before starting the study and all concomitant therapy taken by the subject during the study is to be obtained and recorded in the subject's eCRF. Parenteral nutrition products will also be documented as concomitant therapy. A record of chemotherapeutic agents used for any chemotherapy regimen within 30 days of Enrollment is to be obtained. A record of all prior immunosuppressive therapies and antifungal therapy should be recorded for 30 days prior to Baseline through Day 1. The identity of the therapy, route, and regimen, the dates started and stopped (or notation of "continuing" if that is the case), and the reason for use are to be included in the record.

Nasal sprays of amphotericin B (AMB) and aerosolized AMB are prohibited during the Treatment Phase. If subjects are on such treatment before study entry, such drugs must be discontinued at the time of Enrollment. Investigational drugs (i.e., other drugs not yet approved for marketing by the FDA or local health authorities) are also prohibited during the Treatment Phase.

Topical nonabsorbable antifungals may be used for the treatment of oropharyngeal candidiasis, vaginal candidiasis, or cutaneous fungal infection. These include: oral AMB, miconazole (oral or topical), nystatin (oral or topical), oral or topical clotrimazole. All other topical, nonabsorbable antifungal therapies must be approved by the sponsor prior to use. No other topical or oral antifungal agents may be used as prophylactic treatments (e.g., clotrimazole as prophylaxis in patients with mucositis).

The medications, supplements, and other substances prohibited prior to and after randomization are listed in Table 2 in Section 7.3.2 with the subject exclusion criteria.

The washout period for study medication after discontinuation is approximately 7 days. Subjects should be monitored for untoward reactions if any of the prohibited medications are administered during the washout period (7 days post treatment) and AEs related to potential drug interactions should be recorded in the subject's eCRF.

Refer to Section 7.4.2.1.2 for information regarding coadministration of POS with CYP3A4 substrates. Tables are also included regarding coadministration of VOR with other drugs.

7.4.2.1.2 Concomitant Medications, Supplements, and Other Substances Allowed During the Trial

POS is a potent inhibitor of CYP3A4. Coadminstration of POS with CYP3A4 substrates may result in large increases in exposure of CYP3A4 substrates. Caution is advised during coadministration of POS with CYP3A4 substrates and the dose of the CYP3A4 substrate may need to be reduced. Plasma concentrations of the CYP3A4 substrate and/or AEs should be closely monitored and the dose adjusted as needed.

VOR is metabolized by CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these enzymes may increase or decrease VOR exposure, respectively.

Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an adverse event of the subject.

The following medications, supplements, and other substances are allowed during the trial; however, caution is advised during coadministration (See Table 8).

Table 8 Medications, Supplements, and Other Substances Allowed During the Trial

Drug/Drug Class	Recommendations for Drug Dosage Adjustment/Comments
Cyclosporine Tacrolimus	When initiating therapy with study drug follow with monitoring of blood levels of these drugs. When study drug is discontinued, concentrations must be frequently monitored, and the dose increased as necessary.
Methadone	Monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.
Fentanyl Alfentanil Oxycodone	Reduction in the dose of fentanyl and other long-acting opiates metabolized by CYP3A4 should be considered when coadministered with study drug. Extended and monitoring for opiate associated adverse events may be necessary.
NSAIDs including. ibuprofen and diclofenac	Monitoring for adverse events and toxicity related to NSAIDs. Dose reduction of NSAIDs may be needed.
Oral Contraceptives containing ethinyl estradiol and norethindrone	Monitoring for adverse events related to oral contraceptives is recommended during coadministration. If oral contraceptives are used, an additional form of contraception should be used.
Warfarin	Monitor PT or other suitable anticoagulation tests. Adjustment of warfarin dosage may be needed.
Omeprazole	Monitoring for adverse events is recommended during coadministation.
Other HIV Protease Inhibitors	Monitoring for adverse events and toxicity related to other HIV protease inhibitors

Drug/Drug Class	Recommendations for Drug Dosage Adjustment/Comments
Other NNRTIs[a]	Monitoring for adverse events and toxicity related to NNRTI
Benzodiazepines	Monitoring for adverse events and toxicity (i.e., prolonged sedation) related to benzodiazepines metabolized by CYP3A4 (e.g., midazolam, triazolam, alprazolam). Adjustment of benzodiazepine dosage may be needed.
Dihydropyridine Calcium Channel Blockers	Monitoring for adverse events and toxicity related to calcium channel blockers. Adjustment of calcium channel blocker dosage may be needed.
Sulfonylurea Oral Hypoglycemics	Monitoring of blood glucose and for signs and symptoms of hypoglycemia. Adjustment of oral hypoglycemic drug dosage may be needed.

[a] Non-Nucleoside Reverse Transcriptase Inhibitors

7.4.2.2 Other Treatments

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: amiodarone, chlorpromazine, clarithromycin, domperidone, droperidol, levomethadyl, mesoridazine, methadone, erythromycin, sparfloxacin, and thioridazine.

In addition to the medications in Table 8, the drugs listed below 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:

- Oral hypoglycemic agents
- Digoxin
- Coumadin-type anticoagulants
- Calcium channel blockers
- Theophylline
- Antiretroviral therapy (e.g., atazanavir, or tenofovir).

POS interferes with the hepatic clearance of triazolam and midazolam, and thus, may enhance the sedative effects of these agents. Therefore, these agents are not allowed unless monitoring is provided for excessive sedation.

Please refer to POS and VOR product circulars for the most up to date details regarding the drugs and any updates in contraindications.

7.4.3 Procedures for Monitoring Subject Compliance With Administration of Trial Treatments

At all protocol-specified visits, the investigator or qualified designee is to record whether treatment had been taken per protocol in the preceding interval. If not, the date(s) and reason for each dosing noncompliance must be recorded in the subject's eCRF.

7.5 Trial Schedule

The visit-by-visit schedule of trial activities is provided in the Trial Flow Chart in Section 2.2.

The timing of each visit is relative to Day 1, which is defined as administration of the first dose of trial medication (Section 7.4.1.1).

All visits should be performed within the windows specified in Section 2.2, the Trial Flow Chart. Every attempt should be made to have each subject attend each visit as scheduled. However, if a subject is unable to attend a visit within the specified windows, the visit should be scheduled as closely as possible to these windows. A subject should not miss a protocol-specified visit due to scheduling difficulties.

7.6 Trial Procedures

The Trial Flow Chart in Section 2.2 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described below.

In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations for all subjects at each trial site.

Screening and randomization visits may occur on the same day to help accommodate the initiation of treatment in ill patients.

1. **Explain Trial and Obtain Written Informed Consent**

   - Study Informed Consent

     The investigator or qualified designee will explain the trial to the subject, answer all of his/her questions, and obtain written informed consent before performing any trial-related procedure. A copy of the informed consent will be given to the subject (see Section 9.1.2 for further description of the Informed Consent).

   - Assent

     For a subject under the age of consent, a legal representative must provide written informed consent on his/her behalf, and assent will be obtained from the minor.

- Pharmacogenetic Informed Consent (Optional)

The investigator or qualified designee will explain the Pharmacogenetic (PGt) testing to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to PGt testing. A copy of the informed consent will be given to the subject.

2. **Review Inclusion/Exclusion Criteria**

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

3. **Issue or Collect Subject Identification Card**

The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent. The investigator or qualified designee will retrieve the card from the subject at the last in-person contact (see Section 9.1.3 for further description of the Subject Identification Card).

4. **Obtain Medical / Disease History**

A complete medical history will be obtained by the investigator or qualified designee and recorded in the eCRF. The medical history should include details regarding underlying conditions that may qualify the subject for possible, probable, or proven IA according to modified 2008 EORTC/MSG criteria. The medical history should include details regarding any ongoing or prior cancer diagnoses, immunosuppressive conditions (including HIV), and transplant procedures (BMT and solid organ). The history should also include details regarding recent or ongoing bacterial infectious episodes, and any prior histories of invasive fungal infection as well as details regarding the current episode of IA. The history should also include any details of prior or ongoing visual disturbances (including, but not limited to: abnormal vision, blurred vision, photopsia, visual hallucination, decreased acuity, hallucination). Any history of hepatitis should also be recorded.

5. **Pharmacogenetic (PGt) Samples (Optional)**

Informed consent specific for PGt sampling, must be obtained prior to collection. To obtain sufficient DNA for pharmacogenetic studies, a single 8.5-mL blood sample will be drawn indicated in Section 2.2, Study Flow Chart, into the appropriate tubes provided by the sponsor (see Laboratory Manual for information on PG sample management, and see Appendix 5 for a summary of procedures for PGt.).

6. **Stratification and Randomization by IVRS**

IVRS will be utilized to assign a Screening Number, Subject Number, randomization, and log of treatment status (either completed treatment or discontinued treatment). Drug will be allocated and dispensed at Day 1. Subjects will be randomized to either POS or VOR. Since randomization is performed at Baseline (Day 1), it must be determined that the subject has met all eligibility criteria prior to randomization. IVRS will be utilized for drug allocation and dispensing at scheduled study visits.

7. **Problem Focused Physical Examination**

A problem focused physical examination will be performed and all abnormal findings are to be recorded in the eCRF.

8. **Body Weight**

Body weight will be recorded at screening. Actual body weight is to be recorded at screening for all subjects in the eCRF

9. **Vital Signs**

Vital signs, including temperature, pulse, and blood pressure, will be taken. Vital signs will be recorded daily for hospitalized subjects and on scheduled days if outpatient. While subjects are on IV treatment, vital signs should be collected daily. Temperature recorded should be highest temperature (maximum temperature) for each day. For the screening period, vital signs including daily maximum temperature, pulse, and blood pressure should be recorded beginning on the first day of screening immediately following signing of informed consent and daily thereafter.

10. **Review Prior Medications**

Review of appropriate prior medications, including the necessary washout times, with the subject. Prior medications to be recorded include all antifungal drugs taken within 30 days before starting the trial. A record of all chemotherapy agents and immunosuppressive agents used within 30 days before starting the trial is to be obtained. All prior medication taken by the subject within 7 days before starting the trial is to be obtained.

11. Clinical Signs and Symptoms of IA

Details regarding all clinical signs and symptoms that may be related to fungal or bacterial infections should be evaluated and recorded. Any clinical sign and symptom that may be possibly, probably, or related to a fungal infection should be identified. All subjects will be evaluated for the presence of IA based on modified 2008 EORTC/MSG definitions at all visits (**Appendix 2**).

12. Electrocardiogram (ECG)

An ECG must be performed at Screening (Visit 1) for purposes of protocol eligibility.

The Day 1 ECG should be performed prior to initiation of study treatment.

Prior to study enrollment or study drug administration, all ECGs should be reviewed to determine study eligibility.

For subjects on IV therapy an ECG will be performed at the Week 1 study visit (Day 4-8) following the completion of the 90-minute infusion.

Subjects who are receiving oral study therapy at the week 1 study visit may have the ECG performed without regard to the timing of study therapy.

A standard 12-lead ECG, reporting ventricular rate, PR, QRS, QT, and QTc intervals, will be performed using equipment provided by the sponsor for this purpose. Any clinically significant abnormality must be followed until stabilization or return to Baseline.

During the Treatment Phase, if a QTc interval is found to be abnormal (greater than 500 msec) an assessment is to be done 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 magnesium, calcium, and potassium levels).

ECGs performed will be transferred to a blinded third-party for an evaluation of the QT, QTc (Fridericia 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.

Procedures for printing, archiving, and review of ECGs will be specified by the central laboratory vendor.

Note: When the collection of vital signs, ECGs, and PK samples coincide, the blood samples for PK determination (so that the PK samples are collected on time) should be collected first, then 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.

13. Safety Laboratory Test (Hematology and Chemistry)

Safety laboratory tests (**Table 9** and **Table 10**) will be tested centrally. At baseline, clinical laboratory tests can be done locally if central laboratory results are not available to determine eligibility.

On Day 1, clinical laboratory tests should be drawn prior to initiation of study treatment. If clinically indicated, safety laboratory tests may be repeated more often to evaluate clinical symptoms of AEs and must be followed until stabilization or return to Baseline. Clinical laboratory tests may be performed at the local certified laboratory and if abnormal and clinically significant will be repeated at the investigator's discretion. The results of the any local laboratory tests should be recorded in the subject's eCRF and source documentation. Blood specimens may be drawn either peripherally or via a central venous catheter. A Study Laboratory Manual will be provided for sample acquisition, shipping and labeling instructions.

Table 9 Laboratory Tests- Hematologic Studies

Red blood cell count (RBC)
Hematocrit
Hemoglobin
Platelet count
Total white blood cell count (WBC)
Differential (total neutrophils [granulocytes] or segmented neutrophils plus bands, lymphocytes, monocytes, eosinophils and basophils).
Absolute Neutrophil Count (ANC)

Table 10 Laboratory Tests- Serum Chemistries

Total protein	Total Bilirubin
Albumin	Alkaline Phosphatase (ALK-P)
Calcium	Lactate Dehydrogenase (LDH)
Glucose	Uric Acid
Serum Glutamic Oxaloacetic Transaminase (SGOT)/Aspartate Serum Transaminase (AST)	Serum Creatinine
Serum Glutamine Pyruvic Transaminase (SGPT)/Alanine Serum Transaminase (ALT)	Blood Urea Nitrogen (BUN or Urea)
	Electrolytes (sodium, potassium, magnesium, and chloride)

If an unscheduled ECG is performed, a full set of electrolytes, including a determination of serum potassium (K), calcium (Ca), and magnesium (Mg), should be drawn on the same days as the ECGs are performed. The results must be documented in the eCRF, as well as in the subject's source documentation, and any electrolyte abnormalities corrected.

If any central laboratory result is outside the reference range and is Grade 2 or higher, the test should be repeated locally at appropriate time intervals until it returns to Baseline or becomes a clinically insignificant finding, and appropriate standard of care should be instituted.

14. **hCG Pregnancy Test**

A serum human chorionic gonadotropic (hCG) determination will be required for all female subjects of childbearing potential and must be performed at Baseline or within 72 hours before the start of the study drug. Negative serum results must be available to the investigator before the subject can begin taking the study drug.

15. ***Aspergillus* Galactomannan EIA**

Serum will be collected for *Aspergillus* Galactomannan enzyme immunoassay (EIA) at Screening, Baseline, all scheduled Treatment Visits, and the 30-day Posttherapy Visit. At Baseline, serum drawn for *Aspergillus* Galactomannan EIA should be split into two aliquots and tested. Broncho-alveolar lavage (BAL) fluid can also be collected for testing as necessary. Results from any previous *Aspergillus* Galactomannan tests will also be recorded in the subject's eCRF. The quantitative value and time of collection of the galactomannan sample should be documented for all galactomannan tests performed on patients. The results of all galactomannan samples taken during the period from screening to the 1 month follow up visit should be provided. Galactomannan EIA serological test results may not be used to confirm a probable diagnosis of Invasive Aspergillosis if subjects have taken piperacillin/tazobactam within 72 hours of serum sampling.

- Serum: a positive result is defined as two consecutive results with a cut-off index ≥0.5., or a single value of ≥1.0.

- Broncho-alveolar lavage fluid: a positive result is defined as a cut-off index ≥1.0 based on testing of a single BAL fluid sample.

16. **Beta-D-Glucan**

Serum will be collected for Beta-D-Glucan assay at Screening, Baseline, all scheduled Treatment Visits, and the 30-day Posttherapy Visit.

17. **Mycology Testing**

Mycology testing includes standard fungal cultures from all sites of suspected *Aspergillus* infection, as clinically appropriate. Unless clinically inappropriate or not warranted due to the patient's health, condition or disease progression/ regression, mycology testing should occur at the following visits: screening/ baseline, Week 6 and Week 12. Additional mycology testing will be done as clinically indicated and should correlate with potential disease regression/ progression. All fungal culture results (positive or negative) are to be recorded. All fungal isolates clinically relevant to infection should be stored locally for possible shipment to central laboratory. Identification to species level and minimum inhibitory concentration (MIC) testing will be done by a central laboratory on subcultures provided by site.

18. **Bacterial Testing**

Results of all bacteriologic culture results (positive and negative) regarding bacterial conditions evaluated during the screening, treatment, or follow-up period are to be recorded in the subject's eCRF. Bacteriologic cultures will be performed locally.

19. **CYP2C19 Genotyping**

Blood for DNA will be obtained at baseline to determine CYP2C19 genotype in patients enrolled in the study. 2C19 genotype results will be studied to determine any genetic associations with safety and response to VOR and POS. To obtain sufficient DNA for this mandatory main study DNA analysis, a single 6-mL blood sample will be drawn indicated in Section 2.2, Study Flow Chart, into the appropriate tubes

20. **Diagnostic Imaging**

Diagnostic imaging is required for all attributable infected sites of disease at Screening/Baseline, Week 6, and Week 12/EOT. The type of imaging used (e.g., CT or MRI) will depend on the site of infection. For all pulmonary sites of infection, digital high-resolution CT scanning is required. Each site of infection identified during screening should be followed throughout the study by repeating the same type of scan and the same imaging modality. All imaging that is performed will be transferred to a central imaging laboratory and will be made available to a blinded third-party for evaluation of infection. The central imaging laboratory will be responsible for quantification of images. Please refer to the Imaging Operations Manual for requirements and instructions. Assessments made by the central imaging vendor will not be used for clinical management. See Appendix 6 for a summary of the imaging charter that will be used by the central imaging laboratory.

21. **Drug Dosing**

The date and time of administration of each dose of study drug should be recorded in the subject's eCRF. While hospitalized, the timing of dosing will be recorded in the dosing record at the time of dosing. If study drug is administered as an outpatient, then the subject will maintain a dosing card and bring it to each scheduled visit. Refer to Section 7.4.1.1 for POS and VOR treatment administration. While subjects are receiving IV treatment, infusion site examination will be performed prior to dosing and at the end of infusion. Vital signs should be recorded daily for subjects on IV treatment. Food intake information associated with POS tablet or dummy placebo tablet will be recorded.

22. **Concomitant Treatments**

A record of medications and therapeutic procedures during the trial is to be obtained and recorded in the subject's eCRF.

23. **Assess Global Clinical Response**

The investigator will assess global clinical response at 6 weeks and 12 weeks of therapy. In the event of early therapy discontinuation, global clinical response will be assessed at that time.

In addition, an independent CAC will assess global clinical response based upon EORTC/MSG criteria and will be blinded as to the assigned treatment arm. All data collected related to the evaluation of global clinical response will be collected including clinical signs and symptoms, imaging, serologic testing, and fungal culture and histology. The assessment of global clinical response performed by the CAC will not be used for clinical management.

24. **Plasma Pharmacokinetic Assessment**

Blood trough samples for determination of POS and VOR concentrations in plasma will be collected on Baseline, Day 7, Week, 2, Week 4, Week 6, and Week 12. Blood samples will be collected pre-dose as near to the morning dose as possible and the actual time of blood sample collection should be documented in the subject's eCRF. If a subject discontinues early, a trough level sample should be taken as feasible. The recommended timing of this blood sample would be at least 8 hours and no more than 24 hours after the last dose of study drug. However, if this timing is not feasible, a blood sample should be taken and the date and time of the last prior POS dose as well as the date and time of the blood sample should be noted.

For adolescent subjects on IV therapy, plasma samples will be collected at the time of completion of their 90-minute infusion at Day 7, Week 2, Week 4, Week 6 and Week 12 (EOT). These PK samples should be collected via peripheral venipuncture and not be drawn from the central catheter. For adult subjects on IV therapy at the Week 1 study visit an additional C_{max} PK sample should be collected at the time of the completion of the 90-minute infusion. This PK sample should be collected via peripheral venipuncture and not be drawn from the central catheter.

25. **Collect Unused Medications**

Unused medications will be collected at each site visit.

26. **Dosing Compliance Assessment**

Dosing compliance will be assessed using the dosing card completed by each subject.

27. **Drug Accountability Inventory**

Drug accountability will be performed at the times indicated in the Flow Chart. The investigator or qualified designee will be responsible for accounting for all drug supplies dispensed to and returned by the subjects and will complete all drug accountability documentation.

28. **Record (Serious) Adverse Events**

See Section 7.7.2.4 for instructions on the assessment and reporting of (Serious) Adverse Events and Section 7.7.2.5 for instructions on the reporting of (Serious) Adverse Events to the sponsor. All adverse events related to the Tier 1 safety events should be captured at all scheduled visits. The Tier 1 events include: hepatic safety, CNS and visual safety, dermatologic reactions, and adrenal steroidogenesis. See Section 7.7.2.1 for a list of the safety events.

29. **Final Survival / IFI Assessment**

For each subject, a survival assessment, if the subject is alive or dead, will be performed. If the subject dies, the date of death will be recorded in the eCRF. It should be recorded if the subject has a recurrent or relapse of IA infection or on long-term antifungal prophylaxis following completion of study treatment.

7.7 Assessments

7.7.1 Efficacy Assessments

7.7.1.1 Primary Endpoint

The Primary Endpoint is related to the Primary Trial Objective. The Primary Endpoint for the trial is the all-cause mortality through Day 42 post-randomization in the ITT population.

7.7.1.2 Secondary Endpoints

The secondary endpoints are: all-cause mortality through Day 42 and through Day 84 post-randomization in the FAS population, global clinical response for POS vs. VOR at Week 6 and Week 12 post-randomization in the FAS population, all-cause mortality through Day84 post-randomization in the ITT population time to death (all causes) in the FAS population and Mortality due to IA through Day 42 and Day 84 in the FAS population.

See Table 11 for the definitions for global clinical response from the 2008 MSG/EORTC guidelines [9].

Table 11 Global Clinical Response Definitions from the 2008 MSG/EORTC Guidelines

Outcome, Response	Criteria
Success	
Complete response	Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease, resolution of radiological lesion(s), and documented clearance of infected sites that are accessible to repeated sampling.
Partial response	Survival within the prespecified period of observation, improvement in attributable symptoms and signs of disease, improvement of radiological lesion(s)[a], and evidence of clearance of infected sites that are accessible to repeated sampling. In the case of radiological stabilization[b], resolution of all attributable symptoms and signs of fungal disease; or where biopsy of an infected site shows no evidence of hyphae; or where culture is negative.
Failure	
Stable response	Survival within the prespecified period of observation and minor or no improvement in fungal disease; or persistent isolation of *Aspergillus spp* or histological present in infected sites.
Progression of fungal disease	Worsening of clinical symptoms and signs of disease plus new sites of disease or radiological worsening; or persistent isolation of *Aspergillus spp* from infected sites.
Death	Death during the prespecified period of evaluation, regardless of attribution.

[a] improvement of radiological lesions is defined as at least 25% reduction in diameter of radiological lesion.
[b] radiological stabilization is defined as 0%-25% reduction in the diameter of the lesion.

Imaging data should be performed at the timepoints designated and if not able to be performed, the analysis closest to the designated timepoint will be used. For the global clinical response endpoint (6 weeks) the assessment would be ± 2 weeks. At the 12-week time point, it could be ± 4 weeks.

7.7.2 Safety Monitoring and Assessments

7.7.2.1 Safety Endpoints

- The incidence of serious adverse events (SAEs), incidence of treatment-emergent and treatment-related AEs (overall, treatment-related, and selected AEs of interest) as well as other safety endpoints will be summarized by treatment groups.

- The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. The following four categories are Tier 1 events:

  - Hepatic safety: Elevated AST or ALT lab value that is ≥3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing;

  - CNS and visual safety: Treatment-emergent adverse events (TEAEs) related to visual and CNS disturbances. See Section 8.5.2 for a list of terms;

  - Dermatologic reactions: TEAEs including rash and photosensitivity rash;

  - Adrenal steroidogenesis: TEAEs indicating adrenal insufficiency or temporally associated TEAEs of hypotension.

- The following are Tier 2 events based on specific AE categories: (1) proportion of subjects with at least one adverse experience; (2) proportion of subjects with at least one drug related adverse experience; (3) proportion of subjects with at least one serious adverse experience; (4) proportion of subjects with at least one serious and drug related adverse experience; (5) proportion of subjects who discontinued study therapy due to an adverse experience. 95% confidence intervals (Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method.

The APaT population will be used to assess safety in this study. All patients who received at least one dose of study treatment will be included in the APaT population.

7.7.2.2 Definition of Terms

7.7.2.2.1 Adverse Event

Per the International Conference on Harmonization (ICH), an adverse event (AE) 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 AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

7.7.2.2.2 Serious Adverse Event

Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

1. Results in death;
2. Is life-threatening;
3. Requires hospitalization or prolongation of existing inpatients' hospitalization;
4. Results in persistent or significant disability or incapacity; and/or
5. Is a congenital anomaly or birth defect;
6. Is a cancer;
7. Is associated with an overdose;
8. Is an 'Other Important Medical Event'.

Life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. These are considered "Other Important Medical Events".

7.7.2.2.3 Events of Clinical Interest

An "Event of Clinical Interest" is a non-serious adverse event or occurrence that is designated to be of special interest and must be reported to the sponsor as though it were a serious adverse event – as described in Section 7.7.2.5.1.

The following events are considered events of clinical interest for this trial:

1. An overdose of Sponsor's product, as defined in Section 7.7.2.2.4, Overdose, that is not associated with clinical symptoms or abnormal laboratory results is to be reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

2. An elevated AST or ALT lab value that is ≥3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 x ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing is to be reported as a non-serious ECI.

7.7.2.2.4 Overdose

An overdose is a significant variation above the recommended/scheduled dosage for a product. In this current trial an overdose of POS IV Solution, POS tablet, VOR IV, and VOR capsule is any dose higher than 2-times the scheduled dose specified in Section 7.4.1.1 of this protocol.

7.7.2.2.5 Clinical Supply Complaint

A clinical supply complaint is defined as any communication concerning manufacturing, packaging, labeling or distribution (including adverse storage at depots) of a clinical supply that describes a potential defect related to its identity, strength, quality or purity after it is released and left the control of a Merck-approved packaging facility for distribution. A clinical supply GCP inquiry is defined as any communication of an event taking place at a trial site after the product was satisfactorily received at the trial site, which puts product disposition in question. Examples include adverse storage of product at the trial site and dosing past expiration. Alleged Counterfeit, Diversion and Tampering (CDT), adverse events and trial site errors/issues which do not put product disposition in question should not be reported.

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. This responsibility includes reporting of all clinical supply complaints and/or clinical supply GCP inquiries to the Sponsor.

Clinical supplies complaints and GCP inquiries, as defined above, must be reported to the Sponsor within 1 business day of first becoming aware of the issue. Sponsor Contact information and related reporting details can be found in the Investigator Trial File Binder

7.7.2.2.6 Planned Hospitalization

A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

7.7.2.3 Monitoring

7.7.2.3.1 Monitoring Adverse Events

Each subject will be monitored for the occurrence of AEs immediately after the subject has signed informed consent. Each subject will be followed for serious adverse events for up to and including 30 days after the last treatment visit described in Section 7.2. Of note, all subjects are to be followed for mortality for the entire study period (i.e., until the final study visit at 16 weeks) regardless of the duration of study treatment.

Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator.

AEs, actions taken as a result of AEs, and follow-up results must be recorded in the electronic Case Report Forms (eCRF; Section 9.2), as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the trial and SAEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). The frequency and duration of the event(s) should be recorded

Adverse event reporting will be conducted as follows:

- **Laboratory Abnormalities**

  Laboratory abnormalities which have clinical manifestations, or which require an intervention should be recorded on the AE screen; use a clinical term if applicable.

- **Minor or Routine Surgical Procedures**

  All minor surgical procedures (unless pre-planned as part of routine care, e.g., Hickman catheter placement) and the reason for the procedure are AEs. (For example, removal of a Hickman catheter for thrombosis after study drug has been given would be reported as an AE, i.e., incision and drainage of abscess requiring admission to the hospital would be indicated as an SAE with outcomes of hospitalization and additional therapy.)

Adrenal Insufficiency

Evaluation of electrolytes should be conducted. If adrenal insufficiency is present without associated electrolyte disturbances, the study drug may be continued. If the subject experiences adrenal insufficiency with associated electrolyte disturbances and related blood pressure grading, then the subject will be discontinued from treatment.

Grade 4 Adverse Events

The following guidelines will be used regarding continuation of treatment:

- If considered probably related to study drug, subject will be discontinued from treatment.

- If considered possibly related to study drug: the subject will be discontinued from treatment, except in the case of AEs for which a relationship to the primary disease and/or other concomitant drugs is equally likely. In these cases, a decision to discontinue study drug or interrupt study drug will be made by the investigator. If the AE again worsens to Grade 4 after study drug has been reintroduced, the subject must be discontinued from treatment.

- If considered unlikely to be related to study drug: study drug may be continued at the discretion of the investigator.

Grade 3 Adverse Events

Outcomes for Grade 3 AEs include the following:

- If a subject experiences a Grade 3 AE (other than CNS/visual) considered at least possibly or probably related to study drug, a decision to continue, interrupt or discontinue study drug will be made by the investigator, taking into account the event severity, clinical significance, treatment options, and likelihood of relationship to study drug versus underlying disease and/or other concomitant drugs.

- If a subject experiences a Grade 3 AE considered unlikely to be related to study drug, study drug may be continued.

Less Severe Adverse Events

Interruption or discontinuation of study drug may be appropriate in some cases for less severe AEs, which are medically significant. In such cases, the investigator should consult with the project physician or designee to decide the most appropriate course of action with regard to dosing.

7.7.2.3.2 Monitoring Laboratory Assessments

All laboratory assessments will be performed either centrally at a certified laboratory selected by the sponsor, or at the investigators local lab. The clinical laboratory values will be reported to the investigator by the laboratory and he/she will review them for significance and consideration as an AE. Clinical laboratory test may be performed at the local certified laboratory. All results of tests done in the local laboratory must be recorded in the eCRF, as well as in the subject's source documentation.

7.7.2.4 Assessment of Adverse Events

7.7.2.4.1 Assessment of Severity

Where the determination of adverse event severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically-qualified investigator.

The National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 or the most current version (NCI CTCAE) will be used for grading severity of AEs (see http://ctep.cancer.gov/reporting/ctc.html). For AEs not covered by this grading system, the following definitions will be used:

The severity of AEs will be graded according to the following definitions:

Mild:	awareness of sign, symptom, or event, but easily tolerated;
Moderate:	discomfort enough to cause interference with usual activity and may warrant intervention;
Severe:	incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention;

7.7.2.4.2 Assessment of Causality

A medically-qualified investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product using the guidelines listed below:

- Yes, there is reasonable possibility of drug relationship. There is evidence of exposure to test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause.

- No, there is not a reasonable possibility of drug relationship. Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.7.2.4.3 Reference Safety Information (RSI) for the Assessment of Expectedness of Adverse Events

Refer to the Investigator's Brochure (IB) for detailed background information on POS (MK-5592 [SCH 56592]).

Refer to the recent Summary of Product Characteristics (SmPC) for detailed background information on VOR IV and tablets.

7.7.2.4.4 Known Potential Toxicities of Investigational Products

The following observations are the most common known potential toxicities of the investigational product POS:

1. gastrointestinal events (diarrhea, nausea, vomiting),
2. fever
3. headache, and
4. cough.

The following observations are the most common known potential toxicities of the investigational product VOR:

1. visual disturbances (abnormal vision, color vision changes, and photophobia).
2. fever,
3. nausea, and
4. rash.

Refer to the Investigator's Brochure or approved labeling for additional information on AEs related to toxicities observed to date.

7.7.2.4.5 Known Adverse Events Relating to the Underlying Clinical Condition

Any adverse event which is worse than expected with the primary disease or its treatment (i.e., greater severity or more prolonged in duration) should be reported as an AE.

7.7.2.5 Reporting Safety Observations by the Investigator to the Sponsor

7.7.2.5.1 Expedited Reporting of Safety Observations by the Investigator to the Sponsor

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor's Global Safety representative or designee by entering all information relevant to the event in the appropriate eCRFs within **24 hours of learning of the event**. The Safety Data Reporting form 1727 – or a sponsored-approved equivalent form – should be used in the event that the EDC system is not functioning.

1. SAE (including SAEs associated with overdose, pregnancy, exposure during pregnancy or lactation
2. Death;
3. Planned hospitalizations (not previously reported in the medical history);
4. Events of clinical interest;
5. Cancer.

Any occurrence of pregnancy or exposures during pregnancy or lactation NOT associated with an SAE in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor or designee by entering all information relevant to the event in the appropriate eCRFs within **24 hours of learning of the event**. The Safety Data Reporting form 1727 – or a sponsored-approved equivalent form - should be used in the event that the EDC system is not functioning.

If the investigator is unsure about when to report an observation from the lists above, the event or outcome should be reported to the sponsor or designee by entering all information relevant to the event in the appropriate eCRFs within 24 hours of learning of the event. The Safety Data Reporting form 1727 – or a sponsor-approved equivalent form – should be used in the event that the EDC system is not functioning.

Any observation reported to the sponsor or designee that is also an AE, is to be recorded in the eCRF (Section 9.2), as well as in the subject's source documentation, along with any actions taken as a result of AE and follow-up results.

If an autopsy is performed, available results should be entered into the EDC screens.

The investigator must assess causality of the event as relative to the investigational product administered in the trial as described in Section 7.7.2.4.2. The EDC uses 2 categories of causality as described in Section 7.7.2.4.2. The Safety Data Reporting form 1727 uses 3 categories of causality. If the Safety Data Reporting form 1727 must be used to report an event because the EDC system is not available, the investigator is to record causality according to the guidance for the form using the 3 categories. The 3 categories from the form will be mapped to the 2 categories for evaluation by the sponsor according to the guidance in Table 12).

Table 12 Mapping Causality for SAE from EDC to Safety Data Reporting form 1727

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Record the following		Use the following criteria as guidance
On the eCRFs	**On the 1727 Form**	
No	Unlikely Related	No temporal association, or the cause of the event has been identified, or the drug, biological, or device cannot be implicated based on available information
Yes	Possibly Related	Temporal association, but other etiologies are likely to be the cause; however, involvement of the drug, biological, or device cannot be excluded based on available information
	Probably Related	Temporal association, other etiologies are possible, but unlikely based on available information

7.7.2.5.2 Expedited Reporting by the Sponsor to a Regulatory Health Authority

Global Safety will monitor data for safety. The Sponsor will manage the expedited reporting of relevant safety information to concerned health authorities, competent authorities, and IRBs/IECs in accordance with local laws and regulations.

7.7.2.5.3 Protocol-Specific Exceptions to (Serious) Adverse Event Reporting to Global Safety and Other Points to Consider

The following will **not** be considered SAEs:

- In all subjects, surgical procedures that are required for treatment of the underlying disease. Surgical procedures should not be reported as SAEs unless they are required due to medical conditions other than aspergillosis (in such case the medical condition itself, rather than the surgical procedure, will be reported as an SAE).

7.7.2.6 Discontinuation, Treatment Interruption, and Unblinding of Blinded Treatment Due to Safety Observations

7.7.2.6.1 Discontinuation

See Section 7.3.3 for the criteria by which a subject must be discontinued. Should a subject be discontinued from the trial, complete the visit activities as specified for discontinuation in the Trial Flow Chart in Section 2.2.

7.7.2.6.2 Temporary Interruption of Treatment for a Subject

Subjects who become temporarily unable to tolerate oral drug will be temporarily discontinued from the oral study medication and the IV medication should be substituted as provided in Section 7.4.1.3.2. Additionally, if the subject cannot have IV therapy administered, the subject can take oral study therapy.

When the subject is again able to tolerate oral medication, the oral study drug should be administered.

Low dose cyclophosphamide use is allowed during the treatment period with a temporary interruption of study therapy on the day of cyclophosphamide dosing.

Temporary interruption may be required due to adverse events as described in Section 7.7.2.3.1. A temporary interruption of no more than 3 sequential days without study medication will be allowed with resumption of treatment.

7.7.2.6.3 Modification of Dose and/or Administration of Investigational Product for a Subject

For subjects with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) may be enrolled in the study; however, the dose of VOR IV and capsules will need to be adjusted. The dose on Day 1 will be as described, but the dose thereafter will be reduced. Appropriate dosing modifications will be included in the trial design in a blinded fashion. There is no planned dose reduction or dose adjustment of POS IV or POS oral tablet or POS dummy tablet.

7.7.2.6.4 Unblinding Treatment for a Subject During the Trial

To assess an occurrence of a safety observation, Global Safety may unblind the treatment of any subject for whom a safety observation was reported investigator to the sponsor as described in Section 7.7.2.5.1.

Unblinding by the request of the investigator should occur only in the event of adverse event for which it is necessary to know the trial treatment to determine an appropriate course of therapy for the subject.

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of

serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call-center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded

7.7.3 Pharmacogenetics

7.7.3.1 Pharmacogenetics Endpoints

Exploratory pharmacogenetics (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. Pharmacogenetic studies will be conducted with Biostatistics design and analysis and compared to PK/PD results or clinical outcomes.

CYP2C19 exhibits genetic polymorphism, which can cause large differences in the pharmacokinetics of VOR. Individuals are classified as either extensive metabolizers or poor metabolizers of this enzyme, and the distribution of these genotypes varies greatly across different populations. Exploratory analysis genetic testing of the CYP2C19 polymorphisms and PK/PD, safety and efficacy relationships may be conducted as the data allow.

7.7.3.2 PD/PGt, PK/PGt and Safety/PGt Analysis

Pharmacogenetic interrelationships may be explored.

7.7.4 Other Endpoints

Sparse pharmacokinetic (steady state trough) sampling will be performed on all subjects throughout the treatment period. Food intake data at the time of POS tablet administration will be collected to evaluate the effect of food intake on POS steady state pharmacokinetic profile. For adolescents on IV therapy, plasma samples will be collected at the time of completion of their 90-minute infusion at Day 7, Week 2,

Week 4, Week 6 and Week 12 (EOT). These PK samples should be collected via peripheral venipuncture and not be drawn from the central catheter. PK/PD correlation tests assessing achievable serum drug levels of POS and VOR vs. minimum inhibitory concentrations for *Aspergillus* isolates and global clinical response will be conducted on all randomized subjects with available data. Exposure/response assessments will be conducted including an exploration of the relationship between PK/PD indices with efficacy and safety timepoints as available data allow.

7.8 Criteria for Early Termination of the Trial

The clinical trial may be stopped if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. The external Data Monitoring Committee will evaluate the results and safety assessments and can make recommendation for stopping the trial early.

In addition, further recruitment in the trial or at (a) particular site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

8.0 STATISTICAL AND ANALYTICAL PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or 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 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

8.2 Hypotheses/Estimation

8.2.1 Primary

Objective: To compare the all-cause mortality for posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) through Day 42 in all randomized subjects who received at least one dose of study treatment (in the ITT [Intention to Treat] population). (see Section 8.4.1).

Hypothesis: The all-cause mortality rate through Day 42 in the POS IV/oral 300-mg QD treatment group is non-inferior to that in the VOR IV 4 mg/kg BID/oral 200- mg BID treatment group.

8.2.2 Secondary

Objective: To evaluate the all-cause mortality for POS vs. VOR through Day 42 in the FAS population.

Objective: To evaluate the all-cause mortality for POS vs. VOR through Day 84 in the ITT population.

Objective: To evaluate the all-cause mortality for POS vs. VOR through Day 84 in the FAS population

Objective: To evaluate the adjudicated global clinical response for POS vs. VOR at Week 12 in the FAS population.

Objective: To evaluate the adjudicated global clinical response for POS vs. VOR at Week 6 in the FAS population.

Other secondary objectives are:

- To evaluate time to death (all causes) in subjects with proven or probable IA receiving POS versus VOR.
- To evaluate the mortality due to IA through Day 42 and Day 84 in subjects receiving POS vs. VOR.
- To evaluate the safety and tolerability of POS and VOR by analyzing Tier 1 Safety and all adverse events.
- To evaluate the safety of POS compared to VOR therapy in the All-Patients-as-Treated (APaT) population.

- To evaluate, in the subset of subjects that have pharmacokinetic data and food intake records, the pharmacokinetic profile of POS and VOR, including an evaluation of the effect of food intake on the POS tablet steady state pharmacokinetic profile, and to evaluate the exposure-response (efficacy and safety endpoints) relationships of POS and VOR in a subset of subjects with available data.

8.2.3 Exploratory

- To explore the effects of CYP2C19 polymorphisms and predicted metabolic enzyme activity on POS and VOR plasma concentration.

- To explore pharmacogenetic endpoints and their association with key efficacy and safety parameters.

- To explore the effect of treatment on serological biomarkers (e.g., galactomannan EIA, beta-D-glucan).

  Please note the analyses to test the above three exploratory objectives may be conducted at a later date, as data allow.

8.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.3.1 Efficacy/Pharmacokinetics Endpoints

A description of efficacy measures is provided in Section 7.7.1.

8.3.2 Safety Endpoints

An initial description of safety measures is provided in Section 7.7.2.

The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters (requires that at least 4 patients in any treatment group exhibit the event) will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

The following four categories are Tier 1 events†:

- Hepatic safety: Elevated AST or ALT lab value that is ≥3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing;

- CNS and visual safety: Treatment-emergent adverse events (TEAEs) related to visual and CNS disturbances. See Section 8.5.2 for a list of terms

- Dermatologic reactions: TEAEs including rash and photosensitivity rash;

- Adrenal steroidogenesis: TEAEs indicating adrenal insufficiency or temporally associated TEAEs of hypotension.

† The team has listed specific terms, see section 8.5.2, that they believe fall under these broader categories, however these categories may include additional related terms when full data reporting for the study is complete.

The following are Tier 2 events based on specific AE categories: (1) at least one adverse experience; (2) drug related adverse experience; (3) serious adverse experience; (4) serious and drug related adverse experience; (5) discontinued study therapy due to an adverse experience.

8.4 Analysis Populations

This study will investigate two extended spectrum azoles (POS and VOR) in subjects with proven or probable IA based on modified 2008 EORTC/MSG definitions. Subjects with possible IA may also be enrolled into the study with further evaluation of proven or probable IA.

8.4.1 Efficacy Analysis Populations

The Intention to Treat (ITT) population will serve as the primary population for the analysis of all-cause mortality through Day 42 in this study. The ITT population consists of all randomized subjects who received at least one dose of study treatment.

The Full Analysis Set (FAS) population will serve as the secondary population for the analysis of efficacy data in this study. The FAS population consists of all randomized subjects who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 EORTC/MSG definitions), and receive at least one dose of study drug.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using the ITT and FAS populations. Details on the approach to handling missing data are provided in Section 8.5 Statistical Methods.

8.4.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.5 Statistical Methods.

8.5 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.6, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. For both the efficacy and safety analyses, unless otherwise specified, all statistical tests will be conducted at α=0.05 level (two-sided).

8.5.1 Statistical Methods for Efficacy Analyses

All-Cause Mortality

The primary endpoint, corresponding to the primary trial objective, is all-cause mortality through Day 42 in subjects in the ITT population.

The primary analysis is to compare the POS arm to the VOR arm. The difference in mortality rate between arms (POS minus VOR) and the associated 95% confidence interval (CI) on the difference will be calculated using Miettinen and Nurminen's method [13] stratified by risk for mortality/poor outcome (high risk, not high risk). If the upper limit of that CI is less than 10% (the non-inferiority margin), then non-inferiority of POS will be declared. If non-inferiority is declared, it can be further concluded that POS is superior to VOR if the lower limit of the CI exceeds zero. Due to the principle of closed testing, no adjustment for multiplicity is required since non-inferiority can always be concluded whenever the data also supports superiority. Summary statistics and a tabulated treatment comparison will be provided.

Other secondary endpoints include all-cause mortality through Day 42 and Day 84 for the FAS population and will be evaluated using similar methodology as will be used for the primary endpoint in the ITT population.

Mortality will be evaluated through Day 42 and through Day 84 with no time window applied either before or after the target day.

Survival will also be assessed using Kaplan-Meier methodology and compared between the two arms using the Log-Rank test stratified by risk for mortality/poor outcome (high risk, not high risk).

Proportion Of Subjects Achieving Global Clinical Response

A secondary endpoint is global clinical response (partial or complete response defined by the 2008 MSG/EORTC criteria) at 6 weeks post-randomization in the FAS population.

The analysis is to compare the POS arm to the VOR arm. The difference in proportions between arms (POS minus VOR) and the associated 95% confidence interval (CI) on the difference will be calculated using Miettinen and Nurminen's method [13] stratified by risk for mortality/poor outcome (high risk, not high risk). For the analysis, missing or unable to determine responses will be considered as failures.

An assessment between the two treatment arms will be performed on ITT subjects that are excluded from the FAS, looking at potentially key baseline prognostic factors, such as the stratification variable of risk status for mortality/poor outcome.

As one of the secondary endpoints, the global clinical response at Week 12 in the FAS population will be analyzed in a similar manner.

Global clinical response at Week 6 and Week 12 will be evaluated to include the completion of the response components within the visit windows, ±2 weeks for Week 6 and ±4 weeks for Week 12.

See Appendix 7 for detailed analysis methods and modeling procedures.

Table 13 summarizes the key efficacy analyses.

Table 13 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
All-cause mortality through Day 42	P	95% CI[b] to test for non-inferiority and if established, test for superiority	ITT	M=F[c]
Secondary Endpoints				
Proportion of subjects achieving global clinical response at Week 6 and 12	P	95% CI[b]	FAS	M=F[c]
All-cause mortality through Day 42 and Day 84	P	95% CI[b]	FAS	M=F[c]
All-cause mortality through Day 84	P	95% CI[b]	ITT	M=F[c]
Time to all-cause mortality	S	Kaplan-Meier product-limit estimates; stratified Log-rank test	FAS	Right Censoring
Mortality due to IA through Day 42 and Day 84	S	95% CI[b]	FAS	DAO

[a] P=Primary approach; S=Secondary approach.

[b] Miettinen and Nurminen's method [13] with stratification by risk status for mortality/poor outcome (high/not high).

[c] Missing or 'unable to determine' responses will be considered as failures.

[d] M=F: Missing = failure; DAO=Data as observed.

The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple [efficacy] endpoints, multiple timepoints, and/or interim analyses is described in Section 8.6, Multiplicity and Section 8.9, Interim Analyses.

8.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, vital signs, and ECG measurements.

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group

comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints prior to database lock will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, summary statistics for the difference between treatment groups will also be provided, along with nominal p-values for between-group differences. Mean change from baseline over time will be plotted with the corresponding standard errors.

The following four categories are Tier 1 events:

- Hepatic safety: Elevated AST or ALT lab value that is $\geq$3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is $\geq$2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing;

- CNS and visual safety: Treatment-emergent adverse events (TEAEs) of visual abnormalities (including terms related to visual hallucination, diplopia, nystagmus, photophobia, photopsia, dyschromatopsia, scotoma, hemianopia, optic neuritis, uveitis, optic disc disorder, visual impairment, vision blurred, visual acuity reduced, blindness, optic atrophy, papilledema, and optic neuropathy); confusion, hallucination, altered mental status, cognitive disturbance, dizziness, altered level of consciousness, depressed level of consciousness, asterixis, tremor, seizures, or encephalopathy.

- Dermatologic reactions: TEAEs of rash (including: MedDRA Terms of dermatitis exfoliative, dermatitis bullous, dermatitis allergic, dermatitis allergic, drug eruption, photosensitivity rash, phototoxic skin eruption, rash, rash erythematous, rash macular, rash maculo-papular, rash popular, rash pruritic, rash vesicular, toxic skin eruption, and urticarial);

- Adrenal steroidogenesis: TEAEs indicating adrenal insufficiency or temporally associated TEAEs of hypotension.

CNS and visual AEs are of particular interest in subjects taking VOR. Each of these AEs tends to occur with higher VOR plasma concentration so that they will be analyzed as Tier 1 events. Additionally, severity of these events will be summarized and the time to first occurrence of these events will be analyzed using time-to-event methodology. Association between plasma concentration in both groups may be also explored.

Tier 2 analysis of treatment difference and 95% CI will be provided for the following events based on specific AE categories: (1) at least one adverse experience; (2) drug related adverse experience; (3) serious adverse experience; (4) serious and drug related adverse experience; (5) discontinued study therapy due to an adverse experience. Other AE categories such as SOCs (System Organ Class) or PDLC (Pre-Defined Limit of Change) in which there are more than 4 events in both groups, Tier 2 analysis of treatment difference and 95% CI will also be provided.

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	•Hepatic Safety •CNS and visual safety •Dermatologic reactions •Adrenal steroidogenesis	X	X	X
Tier 2	Proportion of subjects: (1) with at least one AE (2) with a drug related AE (3) with a serious AE (4) with serious and drug related AE (5) discontinued study therapy due to an adverse experience Specific AEs, SOCs, or PDLCs (incidence ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 of subjects in all of the treatment groups) Change from baseline in laboratory measurements			X

[a] Adverse Experience references refer to both Clinical and Laboratory AEs.

Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; a listing of subjects and their values falling outside the PDLC will also be provided; X = results will be provided; AE = Adverse Experience

8.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, race, etc.), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.6 Multiplicity

Efficacy

No multiplicity adjustment is necessary as there is only one primary efficacy hypothesis based on a single efficacy endpoint at a single timepoint. Statistical significance in this setting is equivalent to nominal significance and will be based on a one-sided alpha level of 0.025.

If non-inferiority is declared, it can be further concluded that POS is superior to VOR if the lower limit of the CI exceeds zero. Due to the principle of closed testing, no adjustment for multiplicity is required since non-inferiority can always be concluded whenever the data also supports superiority.

Safety

No multiplicity adjustment will be used for the safety analysis.

8.7 Sample Size and Power Calculations

8.7.1 Justification of Non-inferiority Margin for Response Rate

Since both VOR, the current standard of care for IA, and POS are both triazole anti-fungal agents, a non-inferiority design was selected, hypothesizing that POS has at least a similar effect on overall all-cause mortality through Day 42 compared to VOR. In terms of safety, POS may have a better overall profile compared to VOR, notably in terms of hepatic safety, central nervous system and visual side effects. Thus, the intent was to establish POS as an alternative to VOR that was equally efficacious but with improved tolerability.

In terms of assessing non-inferiority, the upper bound of the 95% CI on the difference (POS-VOR) in the all-cause mortality rates will be compared to 10%, the pre-specified non-inferiority margin, as described in Section 8.5.1. A summary of the

statistical power under various assumptions of true clinical mortality rates assuming this margin is presented in Section 8.7.2.

It is noted that the selected margin needs to be relevant in terms of what percentage of the effect VOR above placebo is retained with POS. If the margin for determining the non-inferiority of POS relative to VOR is too large, the possibility exists that POS could be found to be non-inferior to VOR and simultaneously be no better than placebo. Therefore, the size of the non-inferiority margin must be small enough to ensure this does not happen. For example, a NI margin in which more than 50% of the benefit of VOR could be lost would be considered unacceptable. Thus, the rationale for the NI margin of 10% is presented below and based on the preservation of the majority of the effect size (>50%) of VOR compared to placebo under a number of scenarios. Since there are no direct studies of VOR versus placebo in the treatment of IA, the approach consists of linking data from a variety of studies of VOR and the assumed mortality in placebo/untreated patients being treated for acute IA.

8.7.1.1 Summary of Historical Response Data for VOR in IA

The first step in determining a non-inferiority margin is determining that the control treatment had a consistent effect in past studies, i.e., "Historical evidence of sensitivity to drug effects" (HESDE).

A literature search was performed using combinations of search terms such as the following: invasive aspergillosis (IA), VOR, controlled clinical trial. There were no placebo-controlled studies for the treatment of IA, only studies that were active-controlled. Overall, three articles were identified that best described the relevant IA patient population and which contained information about all-cause mortality of VOR versus active control and had sufficient data to assess clinical outcomes on individual patients after a period of observation following completion of antifungal drug treatment [2, 16, 27].

Based on the above data and additional information found in registration documents for VOR [17, 18], we identified 3 clinical trials and used a meta-analyses of the available data to estimate the VOR all-cause mortality rate, which will be used later to determine what percentage of the benefit in efficacy that VOR has over Placebo that would be retained by a 10% NI margin in this study comparing POS to VOR.

The first of the studies included in the meta-analysis below consists of two phase 3 studies 150-307 and 150-602, which enrolled 392 subjects in 1997 through 2000, using identical protocols worldwide (Study 307: Europe, Israel, and Australia; Study 602: US, Canada, Mexico, Brazil, and India), and evaluated VOR versus Amphotericin B (AmB) for the primary treatment of acute IA. Although these are separate studies using identical protocols, the original data analysis plan indicated that these study results were to be combined and as such, the published all-cause mortality rate is combined across both studies [2]. In these combined studies, the all-cause mortality of VOR was 18.8% (27/144, 95% CI 12.7, 26.1) compared to

34.6% (46/133) for patients receiving AmB in the primary treatment of acute IA. The majority of study patients had underlying hematologic malignancies, including bone marrow transplantation. The study also included patients with solid organ transplantation, solid tumors, and AIDS. The patients were mainly treated for definite or probable IA of the lungs. In these 2 studies, VOR was administered with 2 loading doses of 6 mg/kg IV q 12 h followed by 4 mg/kg q 12 h for at least 7 days followed by oral VOR 200 mg BID up to a total of 12 weeks.

In addition to these two combined studies, the meta-analysis was conducted including two additional studies: a study of VOR + Anidulafungin published by Marr et al (2015) [16, 26], and a recent study of ISA versus VOR published by Maertens [27].

The results presented by [26] were based on a prospective, randomized, double-blind clinical trial in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients and patients with hematological malignancies with proven or probable IA according to the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group consensus criteria. Subjects were randomized to receive either VOR monotherapy or VOR in combination with anidulafungin. All subjects received open-label VOR (6 mg/kg IV every 12 hours on Day 1) followed by 4 mg/kg IV every12 hours); combination therapy was administered for 2-4 weeks and the investigator could switch to VOR monotherapy after 2 weeks, to complete at least 6 weeks of AF therapy. In this study, the analysis population was defined as those subjects with proven or probably IA confirmed. Through Day 42 all-cause mortality for the VOR monotherapy patients was 27.5% (39/142, 95% CI 20.3, 35.6).

The results published by Maertens et al (2015) [27] were based on a Phase 3, double-blind, global multi-center non-inferiority trial, where patients with suspected invasive mold disease were randomized 1:1 to receive either ISA (equivalent to 200 mg ISA intravenously 3 times a day on Days 1 and 2 then either intravenously or orally once daily) or VOR (6 mg/kg intravenously twice daily on Day 1, 4 mg/kg intravenously twice daily on Day 2, then intravenously 4 mg/kg twice daily or orally 200 mg twice daily from Day 3 onwards). The all-cause mortality rate at Day 42 for ITT patients who received VOR was 20.2% (52/258, 95% CI 15.4, 25.6).

Based on these 3 studies, a random effects meta-analysis gave an overall estimate for all-cause mortality of 23.0% with a 95% asymptotic CI of (16.4, 29.6) [19]. The test for heterogeneity was found to be not significant (p=0.1443) based on the Cochran-Mantel-Haenszel (CMH) test.

Table 15 Meta-Analysis (3 studies)

Study	Patient Population	N	All-cause Mortality through Day 42(%) and (95% CI)
307/602	mITT	144	18.8% (27/144) (12.7, 26.1)
Marr et al (2015)	mITT	142	27.5% (39/142) (20.3, 35.6)
Maertens et al (2015)	ITT	258	20.2% (52/258) (15.4, 25.6)
Pooled (raw)		544	21.7% (118/544) (18.3, 25.4)
Pooled (meta-analysis)		544	23.0% (16.4, 29.6)

8.7.1.2 Percentage Effect Size Retained with Selected Margin

The percentage retained by POS in terms of mortality may be better understood as 1 minus the percentage of the effect size that one may be willing to lose given a selected NI margin, i.e. where effect size loss "allowed" is simply the selected NI margin as a percentage of the estimated effect of the active control VOR over placebo (Pbo) with respect to all-cause mortality.

Two different statistical approaches were used and differ as to which estimate of the effect of VOR over Pbo is used in the calculations. In both approaches, the 95% CI lower bound of the Pbo mortality is assumed. We first consider the "point estimate" approach, which takes the point estimate of the VOR mortality and subtracts the assumed Pbo mortality to determine the VOR effect size. The second, more conservative "fixed margin" approach, uses the 95% upper bound of the VOR mortality and subtracts the 95% lower bound of the Pbo mortality to determine the VOR effect size. The second approach is often referred to as the "95-95" method since the NI margin itself represents a 95% lower bound [20]. As a frame of reference, the minimal Pbo mortality that would have to be assumed to preserve at most 50% of the VOR effect is also calculated.

Since there were no Pbo-controlled studies for the treatment of IA, we assumed an all-cause mortality rate for Pbo of 75%. This is based on an internal meta-analysis of historical data from 1952 to 2006 cited in Maertens et al. [27]. That analysis reported the all-cause mortality rate in untreated patients of 84.8% with a 95% CI of (75.1, 94.5). Maertens et al. further indicate that this mortality rate is supported by a rate of 100% in untreated patients reported Denning (1996) [22].

In the first approach, the point estimate of the historical VOR effect is used (23.0% point estimate from the meta-analysis). Thus, the effect size for all-cause mortality of VOR over Pbo is estimated to be 52 percentage points (75% Pbo mortality minus 23% VOR mortality), and thus a NI margin of 10% represents approximately 20% of

this effect size (0.10/0.52). Therefore, ~80% of the effect size of VOR over Pbo is retained with a NI margin of 10%.

A more conservative approach instead uses the upper 95% CI limit for the historical VOR effect, here 29.6%. In this instance, then, the effect size for all-cause mortality of VOR over Pbo is estimated to be 45.4 percentage points (75% Pbo mortality minus 29.6% VOR mortality). A NI margin of 10% would then represent approximately 22% of the VOR effect size over Pbo (0.10/0.454) and ~78% of the effect size is retained.

Under both sets of assumptions, a large majority of the effect size of VOR over Pbo is preserved with a 10% non-inferiority margin. This is summarized in Table 16 below.

Finally, Table 16 also presents the minimal Pbo mortality rate that would have to be assumed in order for a 10% NI margin to preserve exactly 50% of the VOR over Pbo effect size. Using the most conservative estimate for VOR mortality of 29.6%, the minimal Pbo mortality would have to be 49.6%, which is substantially lower than any published mortality rate associated with Pbo found in the literature [25, 26, 19, 27].

Table 16 Percentage (%) of Effect Size Retained with 10% Margin

Method	VOR Mortality	Pbo Mortality	Effect Size (Pbo – VOR)	Percent of Effect Size Preserved with 10% NI Margin (1-0.10/Effect Size)
VOR Point Estimate	23.0%	75%	0.52	80.8%
VOR Upper CI Limit	29.6%	75%	0.454	78.0%
VOR Upper CI Limit, Minimal Pbo Mortality to Preserve 50% of VOR Effect	29.6%	49.6%	0.20	50%

The above calculations present a variety of scenarios and data assumptions supporting a 10% NI margin in this study. All relevant historical data on IA and VOR was reviewed in this assessment. If relevant new data on VOR becomes available in this patient population, the margin justification may be re-assessed.

One strength in establishing 'comparability' of the historical data is the active control treatment in study PN069 is nearly identical to the ones administered in Studies 307/602 studies, i.e., subjects in PN069 start with a VOR IV loading dose of 6 mg/kg IV BID on Day 1 followed by 4 mg/kg VOR IV BID maintenance dose, beginning on Day 2. Subject, if considered clinically stable, can then transition to oral VOR (200 mg BID), for a total of 12 weeks. Although some subjects in PN069, if clinically indicated, will be able to start oral VOR therapy on Day 1 (300 mg BID) followed by 200 mg BID, this difference is believed not to have an impact on the true effect of VOR on all-cause mortality.

The meta-analysis conducted gives credibility to the constancy of the treatment effect of VOR, i.e., a reasonably consistent estimate of the effect was observed. It is apparent that VOR itself is quite active and in the pivotal studies used for registration (Studies 307/602), VOR was not only shown to be non-inferior to AmB, but also superior, as the lower bound of 95% CI of the treatment difference excluded 0.

In summary, two different approaches were used to assess the % of the efficacy retained and included a conservative assessment (95%-95% method) which still resulted in a substantial % of efficacy retained (>50%) under realistic scenarios.

8.7.2 Sample Size and Power for Efficacy Analyses

Approximately 600 subjects in the ITT population (randomized and treated) will be enrolled in this study and randomly assigned to receive either POS monotherapy or VOR monotherapy in a 1:1 ratio. This study (with approximately 300 ITT population in each azole monotherapy arm) will have ~> 80% power (with 1-sided alpha=0.025) to show non-inferiority of POS monotherapy compared to VOR monotherapy using a 10% margin and assuming a mortality rate through Day 42 of 23% for VOR treated subjects (based on the estimated historical VOR all-cause mortality rate through Day 42 shown in Table 17 [25, 27].

Table 17 summarizes the study power for assumed VOR mortality rates ranging between 18% and 28%, for different number of subjects in each arm, with the POS mortality rate ranging from -2% to +2% from the VOR rate.

- For example, if the VOR mortality is assumed to be 18% and the POS mortality is assumed to be 19% with 600 subjects (300/arm) in ITT population, then this study design has 80.4% power to demonstrate non-inferiority with a 10% margin.

- Alternatively, if the VOR mortality is assumed to be 22% and the POS mortality is assumed to be 21% with 540 subjects (270/arm), then this study design has 87.2% power to demonstrate non-inferiority with a 10% margin.

Table 17 Power (%) Under Various Assumptions of All-cause Mortality Through 42 days (10% Non-inferiority Margin)

Underlying All-cause Mortality Through 42 days for VOR (%)	Underlying Difference in Mortality (%) (POS minus VOR)				
	-2.0	-1.0	0.0	1.0	2.0
600 subjects (300/arm)					
18%	97.2%	94.0%	88.5%	80.4%	69.9%
19%	96.7%	93.1%	87.3%	79.0%	68.4%
20%	96.1%	92.2%	86.1%	77.5%	66.9%
21%	95.5%	91.3%	84.9%	76.2%	65.5%
22%	94.8%	90.4%	83.8%	74.9%	64.2%
23%	94.2%	89.5%	82.7%	73.7%	63.0%
24%	93.6%	88.6%	81.6%	72.5%	61.8%
570 subjects (285/arm)					
18%	96.5%	92.8%	86.9%	78.4%	67.7%
19%	95.9%	91.9%	85.6%	76.9%	66.2%
20%	95.2%	90.8%	84.3%	75.4%	64.6%
21%	94.5%	89.9%	83.1%	74.1%	63.3%
22%	93.8%	88.9%	81.9%	72.7%	61.9%
23%	93.1%	88.0%	80.8%	71.5%	60.8%
24%	92.4%	87.0%	79.6%	70.3%	59.6%
540 subjects (270/arm)					
18%	95.6%	91.5%	85.0%	76.2%	65.3%
19%	94.9%	90.4%	83.7%	74.7%	63.8%
20%	94.1%	89.3%	82.3%	73.1%	62.3%
21%	93.4%	88.3%	81.0%	71.8%	61.0%
22%	92.6%	87.2%	79.8%	70.4%	59.6%
23%	91.8%	86.2%	78.6%	69.2%	58.5%
24%	91.0%	85.2%	77.4%	68.0%	57.3%

Note: The power is calculated based on a non-inferiority margin of 10% and α=0.025 (one-sided).

In terms of observed mortality rates that would meet the non-inferiority criteria, if an all-cause mortality rate of 23% is observed in the 300 VOR patients (23%=69/300), the largest observed all-cause mortality rate that could be observed among POS patients and still meet the non-inferiority criterion would be 26% (78/300). In this instance, the observed difference in mortality rates would be 3.0 percentage points (POS minus VOR) with a 95% CI of (-3.9, 9.9).

If an all-cause mortality rate of 23% is observed in 270 VOR patients (23%=62/270), the largest observed all-cause mortality rate that could be observed among POS patients and still meet the non-inferiority criterion would be 26% (69/270). In this instance, the observed difference in mortality rates would be again 3.0 percentage points (POS minus VOR) with a 95% CI of (-4.7, 9.8).

If the criteria for non-inferiority are met, then a superiority analysis of POS arm will be assessed.

8.7.3 Sample Size and Power for Safety Analyses

The safety hypotheses will be assessed by review of the accumulated safety data. Table 18 gives the difference in percentage points (POS minus VOR) that can be ruled out with different power levels and 95% confidence when there are 300 or 285 or 270 randomized subjects in each treatment group. The true frequency of subjects experiencing an AE on POS arm is assumed the same as that in the VOR arm. For a reasonably common adverse experience which occurs in 20% of subjects receiving either POS or VOR, the study with 300 randomized subjects in each arm has 90% power to declare, with 95% confidence that the true difference between group proportions is no more than 12.7 percentage points.

If a particular AE is not observed from the 300 randomized subjects receiving POS, it can be ruled with 2-sided 95% confidence interval that the upper limit of the true occurrence of this AE is no more than 1.8 percentage points.

Table 18 Difference in AE Proportions (POS minus VOR)† That Can Be Ruled Out With Different Number of Randomized Subjects in Each Group.

	Difference in Percentage Points that can be Ruled Out with Target Power when True AE Occurrence is				
Target Power	**10%**	**20%**	**30%**	**40%**	**50%**
600 subjects (300/arm)					
80%	8.8	11.0	12.1	12.5	12.5
85%	9.4	11.7	12.9	13.3	13.2
90%	10.3	**12.7**	13.9	14.3	14.2
95%	11.5	14.1	15.3	15.8	15.6
570 subjects (285/arm)					
80%	9.1	11.3	12.4	12.9	12.8
85%	9.7	12.0	13.2	13.7	13.6
90%	10.6	13.0	14.2	14.7	14.6
95%	11.9	14.4	15.7	16.2	16.0
540 subjects (270/arm)					
80%	9.4	11.6	12.8	13.2	13.1
85%	10.1	12.4	13.6	14.0	13.9
90%	10.9	13.4	14.6	15.1	14.9
95%	12.2	14.8	16.2	16.6	16.4

†The upper bound of the two-sided 95% confidence interval [21] for the difference in AE incidences (POS minus VOR) assuming the incidences are the same.

8.8 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of the following classification variables:

- Region (US, Ex-US)
- Sex (female, male)
- Age among adults (≥18 years to ≤median of adults, >median of adults)
- Ethnic Origin (Black, White, Other) and (Hispanic, Non-Hispanic)
- Risk status for mortality/poor outcome (high risk, not high risk).
- Patients population: (1) proven vs. probable IA; (2) site of IA infection (lung, sinus, multiple sites, etc.); (3) underlying disease; (4) neutropenic status at baseline (ANC <500 vs. >500)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.9 Interim Analyses

There is no formal interim analysis planned for this study.

A formal independent external Data Monitoring Committee (eDMC) will be assembled at the onset of the study and will examine data for safety. The eDMC will monitor safety and provide recommendations to the executive committee of the SPONSOR. The executive committee, composed of the SPONSOR Senior Management, will provide the overall scientific direction for the trial, and will receive and decide on any recommendations made by the eDMC regarding interrupting enrollment due to safety issues or early stopping of the study. Details regarding the eDMC will be described in External Data Monitoring Committee Charter.

8.10 Compliance (Medication Adherence)

In this study, as part of the routine recording of the amount of study treatment taken by each patient, at each site, the volume of infusion administered, and the number of tablets/capsules dispensed and returned will be counted, reviewed, and recorded at regular intervals at the local level. Pharmacy records of dispensing and return of study medication will be recorded using local documentation records and will be monitored and reviewed by un-blinded study monitors throughout the study period. Pharmacy records will be retained at the local pharmacy and available for Sponsor

review. Site records will be used to ensure and document study medication compliance. Study medication daily dosing will be recorded in the electronic case report for each study medication component (IV or oral, placebo or active drug) based upon local documentation records.

For IV study therapy, on each day, each patient should take a certain infusions/injections dosage encompassing both the assigned treatment and any matching placebo (sham infusions). A day within the study will be considered an "On-therapy" day if the patient receives at least one infusion.

For oral therapy, on each day, each patient should take a certain number of tablets and capsules encompassing both the assigned treatment and any dummy placebo tablets or capsules. A day within the study will be considered an "On-Therapy" day if the patient takes one capsules/tablet.

For a patient who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that patient. The compliance rate for each patient will be computed as follows:

$$Percent\ Compliance = \frac{Number\ of\ Days\ on\ Therapy}{Number\ of\ Days\ Should\ be\ on\ Therapy} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group.

8.11 Extent of Exposure

In addition, the Extent of Exposure to study treatment will be evaluated by summary statistics (N, mean, median, standard deviation) and frequencies for the "Number of Days on Therapy" by treatment group.

8.12 Data Monitoring Committee

The accruing data from patients in this trial will be monitored by an external Data Monitoring Committee (eDMC) on an ongoing basis. The composition, activities, and responsibilities of the eDMC are described in the eDMC Charter that will be provided to the eDMC are described in Section 8.9.

9.0 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

The trial must be conducted in accordance with Good Clinical Practice (GCP) as outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the trial must be conducted in accordance with: (i) the USA Code of Federal Regulations (CFR) if the trial is conducted under a USA IND,

regardless of the country involved; (ii) the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the trial is conducted in the EU; and (iii) any specific local regulations if the trial is conducted elsewhere.

9.1 Ethical Conduct of the Trial

9.1.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial as described in the protocol (or amendment), informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained and the sponsor has confirmed that it is acceptable for the investigator to do so.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the trial described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

In countries where the investigator submits the trial protocol and statement of informed consent to the IRB/IEC, the investigator or qualified designee will forward the approvals to the sponsor.

9.1.2 Subject Information and Consent

The details of the protocol must be provided in written format and discussed with each potential subject and written informed consent must be obtained for all subjects before any trial-related procedure is performed. In obtaining informed consent, the information must be provided in language and terms understandable to the subject. The subject, or the subject's legal representative, must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent form must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws. In addition, the sponsor specifically requests that the consent form identify it as the sponsor and state that use of the investigational product(s) is experimental and the side effects of the investigational product(s) are not completely known. The consent form must be approved by the appropriate IRB/IEC and sponsor before trial initiation at a trial site. Any subsequent changes to the approved informed consent form must

be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

9.1.3 Subject Identification Card

A Subject Identification Card is provided to each subject to carry on his or her person (e.g., in a wallet) at all times while the subject is participating in the trial. The Subject Identification Card must be provided to the subject no later than when IMP is dispensed. The card is to be shown to caregivers in the event of an emergency.

At a minimum, the card must contain the following information:

1. Protocol number;
2. The subject's protocol identification number;
3. A statement identifying the card-carrier as a participant in a clinical trial (e.g., "This person is participating in a clinical research trial.");
4. A statement indicating the person might be taking an investigational drug (e.g., "This person is taking an experimental drug which could have interactions with other medications, or placebo"); and
5. Contact information in the event of an emergency or hospitalization. The contact information on the card is to be the investigator or a designated site contact, rather a contact from within the sponsor.

The cards may also include other trial-specific information to assist with treatment decisions in the event of an emergency, such as types of concomitant therapies that may, or may not be, permitted as part of emergency treatment. As with any other information provided to subjects, the Subject Identification Card must be approved by the IRB/IEC. Monitors will request that Investigators provide Subject Identification Cards to each subject. Investigators will be asked to request that subjects carry the cards with them while they are participating in the trial.

The Investigator/site should collect the cards at the end of the trial and retain them with other clinical trial documents.

9.1.4 Registration of the Trial

The trial will be registered by the sponsor on a publicly accessible database. The results will be disclosed by the sponsor on a publicly accessible database.

9.1.5 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; 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 study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck & Co., Inc., is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

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

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. 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 study documentation and worksheets/case report forms.

International Conference of Harmonization 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 agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study 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 site's IRB/IEC.

9.1.6 Quality Control and Quality Assurance

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written 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 study.

9.2 Reporting Trial Data to the Sponsor

9.2.1 Data Collection Forms

The Sponsor will provide the site with data collection forms, be they Case Report Forms (CRF), either in paper format or electronic Case Report Forms (eCRF); diaries; Electronic Data Capture (EDC) screens; or other appropriate data collection forms as the trial requires. The investigator is to provide subject data according to the Sponsor's instructions, in the designated data collection form, compliant with GCP practices. The Sponsor will also provide the site with instructions for assisting other parties - such as a central laboratory - to collect data. As instructed by the Sponsor, a designated central laboratory may collect data in a database and provide the completed database to sponsor. All data collection forms and the databases from the trial are the exclusive property of sponsor.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the trial site. Any records or documents used as the source of information (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidances, laws, and regulations.

All data collection forms (e.g., CRFs, diaries; EDC screens), electronic database entries, etc., should be completed within 3 business days after the evaluation has occurred. All dates appearing on the sponsor's subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

9.2.2 Preparing Case Report Forms for All Subjects

A CRF must be completed for all subjects who have given informed consent. The Sponsor must not collect subject names, initials, or other personal information that is beyond the scope of the trial from any subject. Subjects are not to be identified by name or initials on the CRF or any trial documents. The only acceptable identification for a subject who may appear on a CRF or trial document is the unique

subject identification number. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary.

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. The investigator will attest in writing at the beginning of the trial that his/her electronic signature is the legally binding equivalent of a written signature and will acknowledge by entering his/her electronic signature that he/she has verified the accuracy of the recorded data.

9.2.3 Preparing Case Report Forms for Subjects Who Fail Screening

Data are to be collected from the time the informed consent form is signed until the subject is determined to have failed screening. A CRF with a minimum of the following information must be completed for subjects who fail screening:
(1) demographics, (2) subject status, (3) reason for screen failure, and (4) serious adverse events.

9.3 Publications and Other Rights

9.3.1 Rights to Publish by the Investigator

The investigator has the right to publish or publicly present the results of the trial in accordance with this Section 9.3 of the protocol. In the event that the protocol is a part of a multi-site trial, it is understood that it is the intent of the sponsor and the investigator to initially only publish or present the trial results together with the other sites, unless specific written permission is obtained in advance from the sponsor to publish separate results. The sponsor shall advise as to the implications of timing of any publication in the event clinical trials are still in progress at sites other than the investigator's site.

The investigator agrees not to publish or publicly present any interim results of the trial without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor 45 days prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and text of oral or other public presentations and text of any transmission through any electronic media, e.g., any computer access system such as the Internet, World Wide Web, etc.) that report any results of the trial. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts and the right to review and comment on the data analysis and presentation with regard to the following concerns:

1. Proprietary information that is protected by the provisions contained in Section 9.3.2;

2. The accuracy of the information contained in the publication; and

3. To ensure that the presentation is fairly balanced and in compliance with FDA regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of the sponsor's confidential information, investigator agrees to meet with the sponsor's representatives at the clinical trial site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

9.3.2 Use of Proprietary or Confidential Information in a Publication

No publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, the sponsor shall promptly identify such subject matter to investigator. If sponsor requests and at sponsor's expense, investigator shall use its best efforts to assist sponsor to file a patent application covering such subject matter with the USA Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.

9.3.3 Use of Trial Information in a Publication

Investigator is granted the right subject to the provisions of this protocol to use the results of all work provided by investigator under this protocol, including but not limited to, the results of tests and any raw data and statistical data generated for investigator's own teaching, research, and publication purposes only. Investigator/Institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by the sponsor in writing.

9.3.4 Authorship of Publications

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and must satisfy the 3 criteria that follow:

1. Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;

2. Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;

3. Authors must provide written approval of the final draft version of the publication prior to submission.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per the ICMJE guidelines for acknowledgment.

9.4 Trial Documents and Records Retention

During the trial and after termination of the trial – including after early termination of the trial – the investigator must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator's curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The sponsor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines, the EU Good Clinical Practices Directive, or applicable local laws, whichever is longer:

1. The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.

2. The European Union (EU) Commission Directive 2003/63/EC which requires that Essential Documents (including Case Report Forms) other than subjects' medical files, are retained for at least fifteen (15) years after completion or discontinuation of the trial, as defined in the protocol.

All trial documents shall be made available if required by relevant health authorities. The investigator should consult with the sponsor prior to discarding trial and/or subject files.

Sponsor will retain all sponsor-required documentation pertaining to the trial for the lifetime of the investigational product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that a paper copy can be obtained from it, if required.

10.0INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

10.1 Sponsor

The sponsor of this trial is indicated in Section 1, Title Page.

10.2 Investigators

10.2.1 Selecting Investigators

Only investigators qualified by training and experience to perform a clinical investigation with POS and VOR are selected. The sponsor will contact and select all investigators (i.e., the legally responsible party[ies] at each trial site), who, in turn, will select their staff.

10.2.2 Financial Disclosure Requirement

In connection with the clinical trial described in the protocol, the investigator certifies that, if asked, the investigator will read and answer the Certification/Disclosure Form or equivalent document truthfully and to the best of investigator's ability. Investigator also certifies that, if asked, the investigator will have any other applicable party(ies) (e.g., subinvestigators) read and answer the Certification/Disclosure Form as a condition of their participation in the trial.

If the financial interests reported on the Certification/Disclosure Form change during the course of the trial or within 1 year after the last subject has completed the trial as specified in the protocol, the investigator and the other applicable party(ies) are obligated to inform the sponsor of such financial change.

10.2.3 Clinical Study Report Coordinator Investigator

A Clinical Study Report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the trial. One of the investigators shall be selected by the sponsor to review the CSR and provide approval of the final CSR in writing. The investigator chosen to review and approve the CSR is to be called the CSR Coordinating Investigator. A second investigator shall be selected as the Alternate CSR Coordinating Investigator. The Alternate CSR Coordinating Investigator is to review and approve the CSR should the first CSR Coordinating Investigator be unable to do so. The sponsor is to select the CSR Coordinating Investigator and Alternate CSR Coordinating Investigator from the investigators using the following criteria:

1. Must be the Principal Investigator at a trial site actively enrolling subjects and participating in the trial;

2. Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing;

3. The sponsor will select the CSR Coordinating Investigator form the top three enrolling sites base on evaluable subjects.

10.3 Central Organizations

Central organizations to be used in the conduct, monitoring, and/or evaluation of this trial are provided on the Contact List.

10.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

10.3.2 Clinical Adjudication Committee

A Clinical Adjudication Committee (CAC) will evaluate each subject's data to determine the baseline classification of the fungal infection as possible, probable, or proven IA. The CAC will also evaluate the following events for the purposes of confirming them according to the criteria in Section 8 “Statistical Analysis Plan,” as well as evaluating the presence of confounding factors.

Six- and twelve-week global clinical response assessments will be performed by blinded clinicians based on the following information:

1. Clinical data, including signs and symptoms of infection;
2. Radiographic findings of infection;
3. Serologic testing;
4. Fungal culture and histology.

Once a sufficient number of subjects are classified as possible, probable, or proven IA the CAC can also be engaged to conduct a blinded sample size determination to see whether the number of FAS subjects (proven or probable IA) is on target with the current enrollment.

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the Adjudication Charter.

10.3.3 Data Monitoring Committee

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the Sponsor protocol; 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 eDMC. The eDMC will monitor the trial at an appropriate frequency, as described in the detailed eDMC charter.

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APPENDICES

Appendix 1 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 studies in compliance with the highest ethical and scientific standards. Protection of patient safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical studies 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 studies which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated studies (e.g., Medical School Grant Program), which are not under the control of Merck.

II. **Scientific Issues**

A. **Study Conduct**

1. **Study Design**

Except for pilot or estimation studies, 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, studies to assess or validate various endpoint measures, or studies to determine patient preferences, etc.

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

2. **Site Selection**

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

3. **Site Monitoring/Scientific Integrity**

Study sites are monitored to assess compliance with the study 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 studies it conducts. Some early phase or pilot studies 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 study, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the study results and conclusions. Merck funding of a study will be acknowledged in publications.

III. **Patient 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 patient safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck's Consent Form Review department (U.S. studies) or Clinical Research Director (non-U.S. studies) will approve the patient informed consent form.

B. **Safety**

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

All participation in Merck clinical trials is voluntary. Patients are enrolled only after providing informed consent for participation. Patients may withdraw from a Merck study 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 patient 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. **DNA Research**

DNA sequence analyses, including use of archival specimens collected as part of a clinical trial, will only be performed with the specific informed consent of the subject. With IRB approval, an exception to this restriction on use of archival specimens may be possible (for instance, if specimens are de-identified and are not referable to a specific subject).

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 studies. Merck does not pay incentives to enroll patients 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 patient referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible patients.

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 study. 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 studies 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 attachment to the study 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."

Appendix 2 Defining Opportunistic Invasive Fungal Infections (European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, National Institute of Allergy and Infectious Diseases Mycoses Study Group)

MAJOR ARTICLE

Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group

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Background. Invasive fungal diseases are important causes of morbidity and mortality. Clarity and uniformity in defining these infections are important factors in improving the quality of clinical studies. A standard set of definitions strengthens the consistency and reproducibility of such studies.

Methods. After the introduction of the original European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group definitions, advances in diagnostic technology and the recognition of areas in need of improvement led to a revision of this document. The revision process started with a meeting of participants in 2003, to decide on the process and to draft the proposal. This was followed by several rounds of consultation until a final draft was approved in 2005. This was made available for 6 months to allow public comment, and then the manuscript was prepared and approved.

Results. The revised definitions retain the original classifications of "proven," "probable," and "possible" invasive fungal disease, but the definition of "probable" has been expanded, whereas the scope of the category "possible" has been diminished. The category of proven invasive fungal disease can apply to any patient, regardless of whether the patient is immunocompromised, whereas the probable and possible categories are proposed for immunocompromised patients only.

Conclusions. These revised definitions of invasive fungal disease are intended to advance clinical and epidemiological research and may serve as a useful model for defining other infections in high-risk patients.

In 2002, a consensus group of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) published standard definitions for invasive fungal infections for clinical and epidemiological research [1]. These definitions were developed to facilitate the identification of reasonably homogeneous groups of patients for clinical and epidemiologic research, to help design clinical trials to evaluate new drugs and management strategies, and, last but not least, to foster communication between

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international researchers. The definitions assigned 3 levels of probability to the diagnosis of invasive fungal infection that develops in immunocompromised patients with cancer and in hematopoietic stem cell transplant recipients—namely, "proven," "probable," and "possible" invasive fungal infection. The definitions established a formal framework for defining invasive fungal infection with a variable certainty of diagnosis. Proven invasive fungal infection required only that a fungus be detected by histological analysis or culture of a specimen of tissue taken from a site of disease; in the case of *Cryptococcus neoformans*, detection of capsular antigen in CSF or a positive result of an India ink preparation of CSF was considered sufficient to establish a diagnosis of proven cryptococcosis. By contrast, probable and possible invasive fungal infections hinged on 3 elements—namely, a host factor that identified the patients at risk, clinical signs and symptoms consistent with the disease entity, and mycological evidence that encompassed culture and microscopic analysis but also indirect tests, such as antigen detection. These EORTC/MSG Consensus Group definitions have been used in major trials of antifungal drug efficacy, in strategy trials [2–6], for the formulation of clinical practice guidelines [7], for validation of diagnostic tests [8–13], and for performance of epidemiologic studies [14].

The previously published definitions were not without their shortcomings. For instance, the original category of possible invasive fungal infection allowed too many dubious cases to be included, particularly those involving neutropenia, nonspecific pulmonary infiltrates, and persistent fever refractory to broad-spectrum antibiotics but with no evidence of invasive fungal infection [15]. These cases may represent patients at higher risk of invasive fungal infection but are quite different from the cases, also defined as possible cases, for which more specific pulmonary abnormalities, such as a halo or air-crescent sign characteristic of invasive aspergillosis, were present. Indeed, the definitions were modified to allow enrollment of similar cases into clinical trials, because they are considered to represent likely invasive fungal disease even without supporting mycological evidence [2, 16]. This pragmatic approach solved the problem of recruitment of representative cases, but it clearly highlighted the need to refine further the definitions, to distinguish dubious cases from the more likely cases when mycological evidence was not forthcoming. The growing body of evidence regarding the value of high-resolution CT of chest and abdomen [17] and of indirect diagnostic tests—such as the detection of galactomannan in body fluids other than serum and plasma, of β-D-glucan in serum, and of fungal DNA in body fluids by PCR—provided additional incentive to review the definitions [18, 19]. The original definitions were also restricted to patients with cancer and to recipients of hematopoietic stem cell transplants; however, invasive fungal infections are known to affect other populations, including recipients of solid-organ transplants and patients with primary immunodeficiencies (e.g., chronic granulomatous disorder) [20, 21]. Finally, it was considered appropriate to explore the possibility of formulating specific criteria for diseases caused by less common fungal pathogens.

REVISION PROCESS

The EORTC/MSG Consensus Group met in Chicago, Illinois, on 14 September 2003 during the 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and included 13 members from the EORTC and 17 from the MSG. J. Powers also participated for the US Food and Drug Administration (FDA), and there were 5 observers from 4 pharmaceutical companies (J. Rex [Astra Zeneca], C. Sable [Merck], M. Bresnik [Gilead], and G. Triggs and A. Baruch [Pfizer]). B.d.P. and T.J.W. were confirmed as joint chairs, and J.P.D. was designated as secretary for the group. Three subcommittees were appointed to prepare proposals for mold infection, candidiasis, and endemic mycoses. The proposals were collated by the secretary, who integrated them into a general framework. They were then circulated by electronic mail to all group members. The ensuing comments again were centrally combined for a subsequent round of electronic consultation. The remaining issues that appeared difficult to solve by the electronic route were addressed in open meetings during the 15th European Congress of Clinical Microbiology and Infectious Disease in Copenhagen, Denmark, and the 45th Annual ICAAC in Washington, DC. A majority vote was decisive when a consensus among the members could not be achieved. The final draft was made available to the wider community for comment at the Doctor Fungus Web site [22] and The Aspergillus Web site [23]. Thereafter, the manuscript was prepared and was circulated among all group members for their final approval.

At the first meeting, all group members agreed to the need to refine and revise the definitions. It was also agreed unanimously that the definition set should remain easily reproducible and should offer the opportunity for a reasonable comparison of future data sets with data sets that had been collected in clinical trials that involved patients with proven and probable invasive fungal infections according to the original definitions. Finally, the group set out to reexamine the feasibility of using the definitions for treatment purposes, to devise a means of extending their applicability to other patient groups, to review the relevance of the findings obtained from studies based on the definitions for clinical practice, and to attempt to incorporate all the available laboratory tests and imaging techniques into the definitions.

REVISED DEFINITIONS

The term "invasive fungal disease" (IFD) was adopted to reflect more accurately the notion that we are dealing with a disease process caused by fungal infection. An adequate diagnostic evaluation of the infectious disease process, to exclude an alternative etiology, was deemed to be a necessary prerequisite to classify it as an IFD. The group reaffirmed that the definitions should be used only to assist in research and that the integrity of the original definitions with the classifications of proven, probable, and possible IFD would be preserved (tables 1–3). Infections caused by *Pneumocystis jiroveci* are not included. The criteria for proven and probable IFD (tables 1 and 2) were modified to reflect advances in indirect tests, whereas the category of possible IFD (table 3) was revised to include only cases that are highly likely to be caused by a fungal etiology, although mycological evidence is lacking. Hence, the definitions of probable and possible IFD were based on the same 3 elements as were the original definitions: host factors, clinical manifestations, and mycological evidence.

Host factors are not synonymous with risk factors but are characteristics by which individuals predisposed to acquire IFD can be recognized. Consequently, the presence of fever was removed as a host factor because it represents a clinical feature, not a host factor, and is nonspecific for IFD. The host factors were extended to receipt of a solid-organ transplant, hereditary immunodeficiencies, connective tissue disorders, and receipt of immunosuppressive agents—for example, corticosteroids or T cell immunosuppressants, such as calcineurin inhibitors, anti–TNF-α drugs, anti-lymphocyte antibodies, or purine analogues. The distinction between "minor" and "major" clinical criteria was abandoned in favor of more-characteristic and objectively verifiable evidence, such as the findings on medical imaging that indicated a disease process consistent with IFD by use of a standardized glossary of definitions. For example, in the case of chest CT imaging to categorize pulmonary lesions, the vast majority of immunocompromised patients with invasive pulmonary aspergillosis have focal rather than diffuse pulmonary infiltrates and present with at least 1 macronodule, with or without a halo sign [24]. These infections can also manifest as wedge-shaped infiltrates and segmental or lobar consolidation. Although none of the imaging findings is pathognomonic for IFD, the observation that, in the appropriate patient population, the outcome of antifungal therapy did not differ between febrile patients with nodular lesions and patients with mycological evidence of an IFD supports the use of this clinical criterion [17]. A similar consideration applies to patients with lesions on CT or ultrasound that are regarded as typical for chronic disseminated candidiasis. In the original definitions, patients with such lesions were defined as having probable hepatosplenic candidiasis without any need for mycological support. In the revised definitions, such cases are classified as possible IFD, thereby retaining the consistency of the definitions and preserving the distinction between probable IFD and possible IFD. For a patient with appropriate host factors and clinical evidence of pulmonary disease, bronchoalveolar lavage fluid that yields *Aspergillus*, Zygomycetes, *Fusarium*, or *Scedosporium* species or other pathogenic molds would constitute mycological support and would allow the case to be classified as probable pulmonary IFD.

As with the original definitions, indirect tests were considered for inclusion only if they were validated and standardized. Furthermore, because commercial tests for diagnostic use had to provide criteria for interpretation to gain approval, it was decided to rely entirely on the thresholds recommended by the manufacturer. On the basis of recent studies, the Platelia *Aspergillus* galactomannan EIA could be applied to CSF and bronchoalveolar lavage fluid, as well as plasma and serum. The β-D-glucan assay also was included as a marker for probable IFD, because this test detects other species of fungi besides *Aspergillus*, and a commercial test for it (Fungitell assay; Associates of Cape Cod) has been approved by the FDA. By contrast, molecular methods of detecting fungi in clinical specimens, such as PCR, were not included in the definitions because there is as yet no standard, and none of the techniques has been clinically validated.

THE CATEGORIES

Proven IFD. There was general agreement that the category of proven IFD should be retained, requiring proof of IFD by demonstration of fungal elements in diseased tissue for most conditions (table 1). Revisions were made to this category to reflect advances in indirect assays that are highly specific for the infection being detected. By its very nature, this category is likely to be valid irrespective of host factors or clinical features. Individual IFD entities—for example, proven aspergillosis—require culture and identification. Failing this, the disease is designated as proven mold IFD (table 1). The histological appearance of the endemic dimorphic fungi, *Histoplasma capsulatum*, as small intracellular budding yeasts; *Coccidioides* species as spherules; *Paracoccidioides brasiliensis* as large yeasts with multiple daughter yeasts in a "pilot-wheel configuration"; and *Blastomyces dermatitidis* as thick-walled, broad-based budding yeasts is sufficiently distinctive to permit a definitive diagnosis (table 3). *H. capsulatum* variety *capsulatum* resembles *Candida glabrata* or *Leishmania* species in tissue but can be distinguished from them by characteristic histological features of granulomatous inflammation in histoplasmosis in some patient groups and by staining with silver, which shows staining for the fungi but not for *Leishmania* species.

The category of proven IFD was modified to reflect advances

Table 1. Criteria for proven invasive fungal disease except for endemic mycoses.

Analysis and specimen	Molds[a]	Yeasts[a]
Microscopic analysis: sterile material	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells—for example, *Cryptococcus* species indicated by encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae[c]
Culture		
Sterile material	Recovery of a mold or "black yeast" by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine	Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 h ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process
Blood	Blood culture that yields a mold[d] (e.g., *Fusarium* species) in the context of a compatible infectious disease process	Blood culture that yields yeast (e.g., *Cryptococcus* or *Candida* species) or yeast-like fungi (e.g., *Trichosporon* species)
Serological analysis: CSF	Not applicable	Cryptococcal antigen in CSF indicates disseminated cryptococcosis

[a] If culture is available, append the identification at the genus or species level from the culture results.
[b] Tissue and cells submitted for histopathologic or cytopathologic studies should be stained by Grocott-Gomori methenamine silver stain or by periodic acid Schiff stain, to facilitate inspection of fungal structures. Whenever possible, wet mounts of specimens from foci related to invasive fungal disease should be stained with a fluorescent dye (e.g., calcofluor or blankophor).
[c] *Candida*, *Trichosporon*, and yeast-like *Geotrichum* species and *Blastoschizomyces capitatus* may also form pseudohyphae or true hyphae.
[d] Recovery of *Aspergillus* species from blood cultures invariably represents contamination.

Table 2. Criteria for probable invasive fungal disease except for endemic mycoses.

Host factors[a]
Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease
Receipt of an allogeneic stem cell transplant
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks
Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)
Clinical criteria[b]
Lower respiratory tract fungal disease[c]
The presence of 1 of the following 3 signs on CT:
Dense, well-circumscribed lesions(s) with or without a halo sign
Air-crescent sign
Cavity
Tracheobronchitis
Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
Sinonasal infection
Imaging showing sinusitis plus at least 1 of the following 3 signs:
Acute localized pain (including pain radiating to the eye)
Nasal ulcer with black eschar
Extension from the paranasal sinus across bony barriers, including into the orbit
CNS infection
1 of the following 2 signs:
Focal lesions on imaging
Meningeal enhancement on MRI or CT
Disseminated candidiasis[d]
At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:
Small, target-like abscesses (bull's-eye lesions) in liver or spleen
Progressive retinal exudates on ophthalmologic examination
Mycological criteria
Direct test (cytology, direct microscopy, or culture)
Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:
Presence of fungal elements indicating a mold
Recovery by culture of a mold (e.g., *Aspergillus*, *Fusarium*, Zygomycetes, or *Scedosporium* species)
Indirect tests (detection of antigen or cell-wall constituents)[e]
Aspergillosis
Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF
Invasive fungal disease other than cryptococcosis and zygomycoses
β-D-glucan detected in serum

NOTE. Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.

[a] Host factors are not synonymous with risk factors and are characteristics by which individuals predisposed to invasive fungal diseases can be recognized. They are intended primarily to apply to patients given treatment for malignant disease and to recipients of allogeneic hematopoietic stem cell and solid-organ transplants. These host factors are also applicable to patients who receive corticosteroids and other T cell suppressants as well as to patients with primary immunodeficiencies.

[b] Must be consistent with the mycological findings, if any, and must be temporally related to current episode.

[c] Every reasonable attempt should be made to exclude an alternative etiology.

[d] The presence of signs and symptoms consistent with sepsis syndrome indicates acute disseminated disease, whereas their absence denotes chronic disseminated disease.

[e] These tests are primarily applicable to aspergillosis and candidiasis and are not useful in diagnosing infections due to *Cryptococcus* species or Zygomycetes (e.g., *Rhizopus*, *Mucor*, or *Absidia* species). Detection of nucleic acid is not included, because there are as yet no validated or standardized methods.

Table 3. Criteria for the diagnosis of endemic mycoses.

Diagnosis and criteria
Proven endemic mycosis
In a host with an illness consistent with an endemic mycosis, 1 of the following:
Recovery in culture from a specimen obtained from the affected site or from blood
Histopathologic or direct microscopic demonstration of appropriate morphologic forms with a truly distinctive appearance characteristic of dimorphic fungi, such as *Coccidioides* species spherules, *Blastomyces dermatitidis* thick-walled broad-based budding yeasts, *Paracoccidioides brasiliensis* multiple budding yeast cells, and, in the case of histoplasmosis, the presence of characteristic intracellular yeast forms in a phagocyte in a peripheral blood smear or in tissue macrophages
For coccidioidomycosis, demonstration of coccidioidal antibody in CSF, or a 2-dilution rise measured in 2 consecutive blood samples tested concurrently in the setting of an ongoing infectious disease process
For paracoccidioidomycosis, demonstration in 2 consecutive serum samples of a precipitin band to paracoccidioidin concurrently in the setting of an ongoing infectious disease process
Probable endemic mycosis
Presence of a host factor, including but not limited to those specified in table 2, plus a clinical picture consistent with endemic mycosis and mycological evidence, such as a positive *Histoplasma* antigen test result from urine, blood, or CSF

NOTE. Endemic mycoses includes histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, sporotrichosis, and infection due to *Penicillium marneffei*. Onset within 3 months after presentation defines a primary pulmonary infection. There is no category of possible endemic mycosis, as such, because neither host factors nor clinical features are sufficiently specific; such cases are considered to be of value too limited to include in clinical trials, epidemiological studies, or evaluations of diagnostic tests.

in our understanding of *Coccidioides* serological characteristics. Consequently, the presence of coccidioidal antibody in CSF was considered to be sufficient to fulfill the criteria for proven coccidioidomycosis. Similarly, the presence of capsular antigen in CSF was considered to be sufficiently distinctive to establish a diagnosis of disseminated cryptococcosis [25]. Urinary *Histoplasma* antigen supports a diagnosis of probable endemic mycosis, in conjunction with appropriate host and clinical criteria (table 3), but cannot be considered sufficient evidence of proven histoplasmosis, because *Histoplasma* antigen is also found in urine and serum of patients with coccidioidomycosis and blastomycosis [26].

Probable IFD. Cases of probable IFD require that a host factor, clinical features, and mycological evidence be present, as outlined in tables 2 and 3.

Possible IFD. The category of possible IFD was retained but was defined more strictly to include only those cases with the appropriate host factors and with sufficient clinical evidence consistent with IFD but for which there was no mycological support (table 2). However, this category was not considered appropriate for endemic mycosis, because host factors and clinical features are not sufficiently specific and because such cases would be of value too limited to include in clinical trials, epidemiological studies, or evaluations of diagnostic tests.

COMMENTS

Implications of the revised category of possible IFD. After enrollment into an interventional or diagnostic study, every effort should be made to upgrade the certainty of diagnosis for patients with possible IFD to the category of proven or probable IFD. These definitions may be applied at different times during the period of risk. For example, although a case might not meet the definition of possible, probable, or proven IFD at the beginning of a period of high risk, during which prophylaxis is given, the case may continue to evolve, such that the criteria may be met later.

The overrepresentation of dubious cases that resulted from the application of the original definitions made it imperative to redress the balance and to capture more patients with a higher probability of IFD while excluding patients who are unlikely to have invasive mycosis. Some members even argued that the category of possible IFD, as defined in the original set of definitions, should be abolished altogether. However, such a decision would reduce dramatically the number of candidates eligible for clinical studies of fungal pneumonia, making randomized trials nearly impossible to conduct. The corollary of retaining a better-defined category of possible IFD, to reduce the number of doubtful cases, was that greater emphasis was placed on mycological evidence for the categories of proven and probable IFD. This allows the category of possible IFD to be reserved for clinical manifestations fully consistent with fungal etiology but for which there is no mycological evidence available, although a reasonable attempt has been made to exclude an alternative etiology.

Non–culture-based diagnostic tests. There was much discussion about indirect mycological tests, especially assays for detection of antigen and β-D-glucan. Since the first definitions were published [1], the FDA has approved the *Aspergillus* galactomannan EIA and, more recently, the assay for β-D-glucan, on the grounds that they were standardized, were validated, are available, and are fit to convey useful information [8, 19, 27]. However, controversy arose about the interpretation of the index for the galactomannan assay, which was originally set at 1.5 and was applied in Europe but which was lowered to 0.5

after review by the FDA. This cutoff value has been shown recently to improve the overall performance of the test for adult hematology patients [28]. Because the issue remains contentious, the decision was made to place the onus on the manufacturers of commercial tests and to adopt whatever threshold values they recommend.

We had hoped that nucleic acid–detection tests, such as PCR, would have improved enough to incorporate the results of these tests into the definitions. However, standardization and validation have not yet been attained for these platforms.

Limitations of the revised definitions. The revised definitions apply to immunocompromised patients but not necessarily to critically ill patients in the intensive care unit who, nonetheless, may develop possible or probable IFD [29]. The group recognized this as an omission but was unable to find a sufficient basis for identifying the appropriate host factors, even though there may be mycological evidence, such as recovery of *Aspergillus* species from bronchial secretions or a positive β-D-glucan test result. The group, therefore, concluded that the body of evidence supporting a diagnosis other than proven IFD is not sufficiently mature at present.

The definitions are not a substitute for complete clinicopathologic descriptions and classifications of IFD, as have been published recently for aspergillosis [21]. The failure to meet the criteria for IFD does not mean that there is no IFD, only that there is insufficient evidence to support the diagnosis. This is the most compelling reason for not employing these definitions in daily clinical practice.

We anticipate that the field of diagnosis will continue to evolve, so that there will come a time when the definitions may be formally evaluated for their sensitivity and specificity. Until then, additional revisions of the present set of definitions are likely, but they should be contemplated carefully. The words and phrases chosen here were selected on the basis of extensive debate and discussion. Seemingly, slight changes may have unexpectedly profound consequences in the design, implementation, and interpretation of clinical trials.

These revised definitions of IFD categories are intended to advance clinical and epidemiological research and, as such, may serve as a useful model for defining other infections in high-risk patients. The definitions are not meant to be used to guide clinical practice but must be applied consistently if they are to continue to achieve their primary goal of fostering communication, furthering our understanding of the epidemiology and evolution of IFD, and facilitating our ability to test the efficacy of therapeutic regimens and strategies.

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Appendix 3 Criteria for Diagnosis of Invasive Aspergillosis

In order to determine if a subject meets the modified 2008 EORTC/MSG consensus criteria for proven, probable, or possible invasive aspergillosis, use the criteria below.

A subject can be diagnosed as having…	**if they have:**
PROVEN Invasive Aspergillosis	One of the required criteria
PROBABLE Invasive Aspergillosis	One host factor AND One clinical criteria AND One mycological criteria
POSSIBLE Invasive Aspergillosis	One host factor AND One clinical criteria

Criteria for Proven Invasive Aspergillosis
• Tissue histopathologic, cytopathologic[a], or direct microscopic examination of a needle aspiration or biopsy specimen showing hyphal forms with evidence of associated tissue damage (either microscopically or as an infiltrate or lesion by imaging) OR • Recovery of *Aspergillus* species by culture from a sample obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL, cranial sinus cavity, and urine.
[a]: tissue and cells submitted for histopathology or cytopathology should be stained by Grocott-Gomori methenamine silver stain or by periodic acid Schiff stain to facilitate inspection of fungal structures. Where possible, wet mounts of specimens from foci related to invasive fungal infectious disease should be stained with a fluorescent dye (e.g., calcofluor or Blankophor).

Criteria for Probable and Possible Invasive Aspergillosis Host Factors[a]
• Recent history of neutropenia (0.5 x 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days[b]) temporally related to the onset of fungal disease • Receipt of an allogeneic HSCT • Treatment with other recognized T-cell immune suppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days. • Prolonged use corticosteroid (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks. • Inherited severe immunodeficiency (such as chronic granulomatous disease or several combined immunodeficiency)
[a]: Host factors are not synonymous with risk factors and are characteristics by which individuals predisposed to invasive fungal diseases can be recognized. They are intended primarily to apply to patients given treatment for malignant disease and to recipients of allogeneic hematopoietic stem cell and solid-organ transplants. These host factors are also applicable to patients who receive corticosteroids and other T cell suppressants as well as to patients with primary immunodeficiencies. [b]: Any duration of neutropenia is also acceptable for possible criteria in this study.

Criteria for Probable and Possible Invasive Aspergillosis Clinical Criteria[a]

• Lower respiratory tract fungal disease[b]
  ○ The presence of 1 of the following 3 signs on CT:
  ▪ Dense, well-circumscribed lesions(s) with or without a halo sign
  ▪ Air-crescent sign
  ▪ Cavity
 	
• Tracheobronchitis
  ○ Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
 	
• Sinonasal infection
  ○ Imaging showing sinusitis plus at least 1 of the following 3 signs:
  ▪ Acute localized pain (including pain radiating to the eye)
  ▪ Nasal ulcer with black eschar
  ▪ Extension from the paranasal sinus across bony barriers, including into the orbit
 	
• CNS infection1 of the following 2 signs:
  ▪ Focal lesions on imaging
  ▪ Meningeal enhancement on MRI or CT

[a]: Must be consistent with the mycological findings, if any, and must be temporally related to current episode. [b]: Every reasonable attempt should be made to exclude an alternative etiology.

Criteria for Probable Invasive Aspergillosis Mycological Criteria

• Direct test (cytology, direct microscopy, or culture)
  ○ Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:
  ▪ Presence of fungal elements indicating a mold
  ▪ Recovery by culture of a mold (e.g., *Aspergillus* species)
 	
• Indirect tests (detection of antigen or cell-wall constituents)
  ○ Aspergillosis
  Galactomannan antigen detected in serum or bronchoalveolar lavage (BAL) fluid
  (a positive test result defined as a cut-off index ≥1.0 [single result from serum or BAL] or ≥0.5 [2 consecutive results from serum samples])

Appendix 4 Child-Pugh Scoring and Classification

Child-Pugh Scoring

Measure	1 point	2 points	3 points
Total bilirubin, µmol (mg/dl)	<34 (≤2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
PT prologation (INR)	<4 seconds (<1.7)	4-6 seconds (1.71-2.30)	>6 seconds (>2.30)
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Child-Pugh Interpretation

Points	Class
6	A
7-9	B
10-15	C

NOTE: Patients with IA will often have low albumin scores due to their underlying conditions or the fungal infection itself. Hence, a patient who meets the criteria for Child-Pugh Class A or B based solely on a low albumin score without any other measure of hepatic insufficiency (i.e., albumin 2 or 3 points but no other hepatic measure above 1 point) should not be considered to have mild or moderate hepatic insufficiency, and, thus, such patients do not truly meet the mild or moderate hepatic insufficiency criterion to reduce the VOR dose.

Appendix 5 DNA Sampling and Pharmacogenetic Analysis Procedures

1. Definitions

   a. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug response.

   b. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug response.

   c. Genomic Biomarkers: A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions.

   d. DNA: Deoxyribonucleic acid.

   e. RNA: Ribonucleic acid.

2. Summary of Procedures for Pharmacogenetics

   f. Subjects for Enrollment: All subjects enrolled in the current clinical trials will be considered for enrollment.

   g. Consent

      Informed consent for biosamples (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at an outpatient visit, or during an inpatient stay by the investigator or his or her designate.

      Subjects are not required to participate in the pharmacogenetic sub-study in order to participate in the main trial.

3. Scope of Pharmacogenomic Study

   The DNA and serum samples collected in the current trial will be used to study various genetic causes for how subjects may respond to a drug. The DNA samples will be stored to provide a resource for future studies conducted by Merck focused on the study of genes responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease. All samples will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

4. Techniques to Collect Samples

   Blood samples will generally be obtained for all study participants. Blood samples for both DNA and RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

5. Confidential Subject Information for Pharmacogenomic Analysis

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

To maintain privacy of information collected from samples obtained for storage and future analysis, Merck has developed secure policies and procedures to maintain subject privacy. At the clinical site, a unique Code will be placed on the blood sample for transfer to the storage facility. The Code is a random number used only to identify the biosample of each subject. No other personal identifiers will appear on the sample tube. The first Code will be replaced with a Sample Code (e.g., Genetic Sample Code for DNA sample, Serum Sample code for serum sample) at the Central Laboratory or at the Merck designated facility. This sample is now a single coded sample. The Sample Code is stored separately from all previous sample identifiers. A secure code, hereinafter referred to as a "first coding key", will be utilized to match the Sample Code to the original blood code and subject number to allow clinical information collected during the course of the trial to be associated with the biosample. This "first coding key" will be transferred by the central laboratory or Merck designated facility under secure procedures to the Merck group designated as the entrusted keyholder to maintain confidentiality of the biosamples. The Sample Code will be logged into the primary biorepository database, 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 sample will be stored in a designated repository site with secure policies and procedures for sample storage and usage.

For DNA samples, a Storage Code will replace the Sample Code at the Merck designated facility. The DNA sample is now a double coded sample. This storage code will be stored separately from all previous sample identifiers. The second secure key referred to as a "second coding key" file will be transferred by the Merck designated facility under secure procedures to the Merck entrusted keyholder. Samples with the second code are sometimes referred to as de-identified samples. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both coding keys is needed to link any data or samples back to a subject identifier.

The "keys" could be utilized to reconstruct the link between genetic information and identifiable clinical information, at the time of analysis. This linkage would not be possible for the investigator conducting the analysis, but may only be done by the Merck entrusted keyholder under strict security policies and procedures. The Merck entrusted keyholder will link the information, conduct the analysis, then issue an anonymized data summary on the initially single or double coded samples to the investigator conducting the genetic analysis. The only circumstance by which genetic information would be linked to clinical information would be those situations mandated by health authorities

(e.g., EMEA, FDA), whereby this information would be directly transferred to the health authority. Once the link between subject's identifiers and the unique codes is deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding keys. Anonymization is intended to prevent subject re-identification.

6. Biorepository Sample Usage

Samples obtained for the Merck biorepository will be used for analyses using good scientific practices. Exploratory analyses will not be conducted under highly validated conditions. The scope of research performed on these samples is limited to the investigation of the variability in inherited biomarkers that may correlate with a clinical phenotype in subjects.

Genetic analysis utilizing the DNA samples may be performed by the sponsor, or an additional third party (e.g., a university investigator) designated by the sponsor. The investigator conducting the analysis will be provided with a double (single) coded sample. Reassociation of analysis results with corresponding clinical data will only be conducted by the Merck entrusted keyholder. Any contracted third party genetic analysis will conform to the specific genetic analysis outlined in the clinical protocol. DNA samples remaining with the third party vendor after genetic analysis will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

Consent form signed by the subject will be kept under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any samples, test results, or medical information once the specimens have been rendered de-identified. Laboratory personnel performing the genetic testing will not have access to the informed consent document, nor will they be able to identify subjects from the double (single) coded specimens. Specimens will be identified to the laboratory only by the Sample double (single) code. Subjects who decline to sign the informed consent document for the sub-study will not have the sample collected or stored, nor will they be discontinued from the main trial unless the pharmacogenetics sample is specifically required for trial enrollment.

A template of each site's informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate sample permissions. The tracking number on this document will be used to assign sample permissions for each sample in the entrusted keyholder's Sample Database.

7. Withdrawal From the Biorepository and Pharmacogenetic(-omic) Database

   Subjects may withdraw their consent to store the blood sample or the DNA or RNA derived from it. Subjects can also request that their sample be destroyed at any time. If samples can be identified in any way (i.e., are not anonymized samples), subjects may withdraw consent for banking samples at any time by contacting the investigator responsible for administering their initial informed consent. At that time, subject samples will be removed from the biorepository. Any DNA, RNA, or other biologic samples will be destroyed, destruction will be documented, and sample database information deleted. However, any analyses performed or data obtained from the samples prior to the subject withdrawing consent will not be deleted.

8. Retention of Data and Biosamples

   It is anticipated that data generated from processed samples collected during the course this trial will be retained for an indefinite period. DNA specimens will be maintained for potential analysis for 20 years from the acquisition. Samples will be destroyed according to Merck policies and procedures and this destruction will be documented in the repository database.

9. Data Security

   Pharmacogenetic and other research databases are accessible only to authorized sponsor and trial administrator research personnel and/or designated collaborators and are only stored and accessible as anonymized data. 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 key holder maintains control over access to all sample data. These data are collected for pharmacogenetic research purposes only as specified in the clinical protocol and will not be used for any other purpose without explicit consent from the research subject.

10. Reporting of 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 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 of data, limitations of predictive capability of research data, concerns of misinterpretation of data, absence of good clinical practices standards in exploratory research.

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

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 sites who participated in the Merck clinical trial, and post the 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 subjects may pursue genetic testing if they wish to do so.

11. 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 pharmacogenetic sampling. When studies with samples are conducted and subjects identified to serve as controls, every effort will be made to group samples from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

12. Risks Versus Benefits of Pharmacogenetic Testing

For pharmacogenetic testing, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood sample. This sample will be obtained at the time of routine blood samples drawn for clinical reasons.

Data privacy concerns of the subject have been strictly protected against with Merck security, policies and procedures. 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 reassociated to double (single) coded samples at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all samples will be stripped of subject identifiers. No information concerning results obtained from genotyping or biomarker studies conducted with samples from the biorepository 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.

13. Self-Reported Ethnicity

Subjects who participate in pharmacogenetic study will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in the pharmacogenetic study.

14. Questions

Any questions related to the genetic informed consent, genetic sampling, genetic sample handling, or genetic sample storage should be e-mailed directly to clinical.specimen.managment@merck.com.

Appendix 6 Summary of Imaging Charter

The imaging charter provides a comprehensive, detailed description of the imaging required as part of this protocol. The following elements are part of the imaging charter that was developed in collaboration with the central imaging laboratory used for this study. Please refer to the imaging charter and the Operations Manual for details regarding the imaging requirements.

1. Summary of Trial Design and Role of Imaging
2. Imaging Acquisition Standards
    a. Equipment standardization and operation
    b. Imaging drug standardization
3. Standards for Image Interpretation
    c. Image transfer, receipt, and quality assessment
    d. Image display and interpretation
4. Charter Modification Process
5. Imaging Data Transfer Process
6. Archiving of Images and Image Interpretation

Appendix 7 Additional Details on Statistical Methods

Miettinen and Nurminen's Asymptotic Confidence Interval

For the difference in the all-cause mortality rate of Posaconazole (POS) compared to Voriconazole (VOR), CIs will be calculated based on Miettinen and Nurminen's method [13]. The method is described as follows:

The two-sided 95% CI for a difference between 2 proportions is given by the roots for $\theta = P_1 - P_2$ of the following equation:

$$\chi_\alpha^2 = \frac{(\hat{p}_1 - \hat{p}_2 - \theta)^2}{\tilde{V}}$$

where

- χ_α^2 is the upper cut point of size α from the chi-square distribution with one degree of freedom (χ_α^2 =3.84 for 95% confidence interval);
- θ is the difference between two population proportions, i.e., $\theta = P_1 - P_2$;
- $\hat{p}_1$, $\hat{p}_2$ are the observed proportions (observed values of P_1 and P_2 , respectively) of POS and VOR groups, respectively;
- $\tilde{V} = \left[\frac{\tilde{p}_1(1-\tilde{p}_1)}{n_1} + \frac{\tilde{p}_2(1-\tilde{p}_2)}{n_2} \right] \frac{(n_1+n_2)}{(n_1+n_2-1)}$
- n_1 and n_2 are the sample sizes for POS treatment group and VOR, respectively;
- $\tilde{p}_1$ and $\tilde{p}_2$ are maximum likelihood estimates of P_1 and P_2 computed under the constraint $\tilde{p}_1 - \tilde{p}_2 = \theta$, respectively.

However, since there are no explicit solutions for θ, a numerical algorithm will be used to obtain the two roots (confidence interval) for θ. Details of programming the numerical algorithm can be found in Miettinen and Nurminen [13].

Appendix 8 Terminology Criteria for Adverse Events (CTCAE) lab grading criteria - Investigations System Organ Class. Please refer to the most recent complete CTCAE version and guidelines, if applicable.

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild 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 of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

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Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.					
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of corticotrophin in a blood specimen.					
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.					
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen.					
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow-up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	6 - 8 units below LLN; for follow-up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide.					
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin I in a biological specimen.					
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin T in a biological specimen.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of CD4 lymphocytes in a blood specimen.					
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen.					
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen.					

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Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.					
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Electrocardiogram QT corrected interval prolonged	QTc 450 - 480 ms	QTc 481 - 500 ms	QTc >= 501 ms on at least two separate ECGs	QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.					
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of fibrinogen in a blood specimen.					
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds.					
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.					
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen.					
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.					
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.					
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen.					

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Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.					
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

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Appendix 9 Estimated blood volumes collected during the Study

Estimated Blood Volumes

Study Procedures	Screening	Baseline	Treatment Phase						Follow-Up	Unscheduled	Total Estimated Volume (mL)
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7		Visit 9	U (Optional)	
Day Relative to First Dose of Study Drug	Days -7 to 1	Day 1	Day 3 (± 1 day)	Week 1 [Day 4 to 8]	Week 2 [Day 9 to 15]	Week 4 [Day 16 to 29]	Week 6 [Day 30 to 54]	Week 12 / EOT[a] [Day 84 (±4 weeks)]	30 Days Postthera py (±2 weeks)	Unscheduled	
Pharmacogenetics Sampling (optional)		8.5									8.5
Hematology*	2	2	2	2	2	2	2	2	2	4	22
Serum Chemistry*	6	6	6	6	6	6	6	6	6	6	60
Serum hCG Pregnancy Test (included in S. Chem)	X	X	X	X	X	X	X	X	X	X	X
Serum for *Aspergillus* Galactomannan EIA	3	3	3	3	3	3	3	3	3	3	30
Serum for Beta-D-Glucan Assay (Included in galactomannan EIA collection)	x	x	x	x	x	x	x	x	x	x	X
Mycology Testing	X	X	X	X	X	X	X	X	X	X	X
Blood for CYP 2C19 genotyping[I]		6									6
Plasma Pharmacokinetic Assessment		2		4±	2†	2†	2†	2†		2	4
Totals	**11**	**27.5**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**15**	**130.5**
											~9.5 Tablespoons

*Adolescent subjects will utilize mircotubes (if available), that collect approximately half the volume for these panels

†Adolescent subjects will have an additional peak steady state sample collected at this visit

± All subjects on IV therapy (adults and adolescents) will have an addiitonal Cmax PK sample collected

INVESTIGATOR SIGNATURE PAGE

Title	A Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis in Adults (Phase 3; Protocol No. MK-5592-069)
Sponsor	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Trial Physician/Director	PPD, MD MSPH Global Clinical Research, Infectious Diseases
Date of Finalization of This Current Version of the Protocol	07-FEB-2019 – PROTOCOL AMENDMENT#5
Previous Version(s) of the Protocol	01-AUG-2016– PROTOCOL AMENDMENT#4 08 JAN 2015 – Protocol Amendment#3 26 JUN 2013 – Protocol Amendment#2 12 DEC 2012 – Protocol Amendment #1 15 NOV 2012 – Initial Protocol

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Name and Degree of Sponsor Representative ***dd MMM yyyy***
Department of Sponsor Representative

I have read Protocol No. MK-5592-069-03 (also known as P06200) dated ***XX*** including all appendices, and agree to conduct the trial in accordance with the protocol. The protocol and trial documents must also be approved by the IRBs/IECs and regulatory authorities as appropriate, before implementation at the site. I agree to implement the protocol and trial documents only after all necessary approvals have been obtained and the sponsor has confirmed that it is acceptable to do so.

_____ _____ _____

Name, Degree, full mailing address of Investigator ***Site Number*** ***dd MMM yyyy***