

<b>Official Protocol Title:</b>	A Randomized, Comparative, Open-label Study to Assess the Safety and Efficacy of MK-5592 Compared with Voriconazole in Japanese Subjects with Deep-seated Fungal Infection
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One Merck Drive  
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**TITLE:**

A Randomized, Comparative, Open-label Study to Assess the Safety and Efficacy of MK-5592 Compared with Voriconazole in Japanese Subjects with Deep-seated Fungal Infection

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## SUMMARY OF CHANGES

### PRIMARY REASON(S) FOR THIS AMENDMENT:

This amendment is only applicable to [REDACTED] <sup>PPD</sup>. Primary reason for this amendment is to change the maximum treatment duration for the specific subjects with zygomycosis. Zygomycosis is a severe infection and amphotericin B formulation is an only option for the treatment in Japan at the moment. However, MK-5592 therapy would benefit the patients who cannot use these treatments. Therefore, MK-5592 therapy could be continued after finishing 84 day maximum treatment period in those patients with prior approval from Sponsor. During the study treatment over 84 days, adverse events should be monitored, and the information of study medication and adverse events should be recorded in the source documents and CRF(Routine safety laboratory should be also monitored and recorded in the source document). The study treatment period over 84 days in those zygomycosis subjects will be considered as extension period. All objectives in Section 3 will be performed for Cohort 2 only and [REDACTED]. Data from extension period will be excluded from the analysis.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	TRIAL SUMMARY		
2.1	Trial Design		
5.2.1.3	Treatment Duration	Added the possibility to join the extension period after main study period for the subject with zygomycosis.	Zygomycosis is a severe infection and amphotericin B formulation is an only option for the treatment in Japan at the moment. There is no option for the patients who cannot use these treatments.
1.0	TRIAL SUMMARY		
2.1	Trial Design		
3.0	OBJECTIVE(S) & HYPOTHESIS(ES)	Added to exclude data for extension period from the analysis for the subject with zygomycosis.	MK-5592 administration during the extension period for the subject with zygomycosis is an exceptional use, therefore the data is excluded from the analysis.
8.1	Statistical Analysis Plan Summary		
8.2	Statistical Analysis Plan		

<b>Section Number (s)</b>	<b>Section Title(s)</b>	<b>Description of Change (s)</b>	<b>Rationale</b>
4.2.3.3 6.0	Pharmacokinetic Endpoints TRIAL FLOW CHART (footnote 9)	Added and clarified not to collect the PK sampling during the extension period.	MK-5592 administration data and safety data is only collected during the extension period.
5.2.1.1 5.2.1.3 6.0	Dose Selection Treatment Duration TRIAL FLOW CHART (footnote 11)	Added to be able to switch the both formulation interactively (IV ↔ PO) during the extension period.	Zygomycosis is a severe infection and amphotericin B formulation is an only option for the treatment in Japan at the moment. There is no option for the patients who cannot use these treatments. In those cases, continuation of MK-5592 therapy would benefit the patients.
6.0	TRIAL FLOW CHART (footnote 13, 17)	Added and clarified the procedure during the extension period.	After the main study period, MK-5592 administration is for the exceptional use, therefore, MK-5592 administration data and safety data is only collected and procedures during the extension period are simplified.
7.1.2.9	Evaluation for Overall Response	Clarified not to evaluate the overall response during the extension period.	After the main study period, MK-5592 administration is for the exceptional use, therefore, MK-5592 administration data and safety data is only collected and procedures during the extension period are simplified.

## 1.0 TRIAL SUMMARY

Abbreviated Title	MK-5592 Phase III study for treatment of deep-seated fungal infection in Japanese subjects.
Trial Phase	Phase III
Clinical Indication	Treatment of deep-seated fungal infection
Trial Type	Interventional
Type of control	Active control with Voriconazole
Route of administration	Intravenous or Oral (or both)
Trial Blinding	Unblinded Open-label
Treatment Groups	MK-5592 treatment arm or Voriconazole treatment arm
Number of trial subjects	Approximately 112(Cohort 1: 22 subjects enrolled under protocol amendment 00-03, Cohort 2: 90 subjects enrolled under protocol amendment 04 and any subsequent amendment) subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 45 months(may extend due to zygomycosis subjects who join the extension period) from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for approximately 15 weeks at a maximum, from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 1 week, each subject will be receiving assigned treatment for approximately 12 weeks. After the end of treatment each subject will be followed for 14 days. However, if the subject is a patient with zygomycosis and joins the extension period, study period may be extended by necessary duration for the subject.
Randomization Ratio	A total of 112 subjects with Aspergillosis (approximately 112) will be randomized to MK-5592 treatment arm (approximately 75) or Voriconazole treatment arm (approximately 37) in a 2:1 ratio. [REDACTED] [REDACTED] and a new Cohort 2 which will include 90 patients with body weight $\geq$ 45 kg to receive 300 mg QD of MK-5592. Subject with invasive aspergillosis will be randomized to MK-5592 treatment arm or Voriconazole treatment arm in a 2:1 ratio using a classification (proven and probable / possible) at the randomization as a stratification factor. Subject with chronic pulmonary aspergillosis will be randomized to MK-5592 treatment arm or voriconazole treatment arm in a 2:1 ratio without stratification. Subject with fusariosis or zygomycosis will be assigned to MK-5592 treatment arm only.

All objective in Section 3 will be performed for Cohort 2 only and [REDACTED]. Data from extension period will be excluded from the analysis of Cohort 2.

## **2.0 TRIAL DESIGN**

### **2.1 Trial Design**

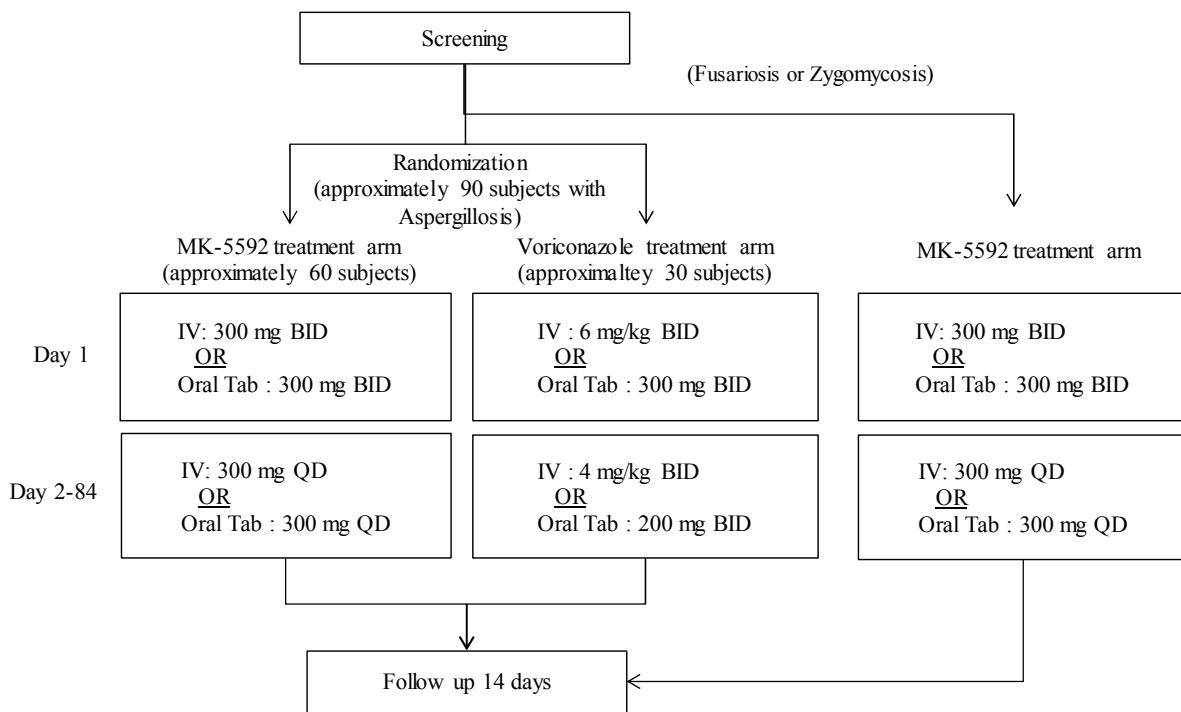
This is a randomized, active-controlled, parallel-group, multi-site, open-label trial of MK-5592 versus Voriconazole in Japanese subjects with deep-seated fungal infection to be conducted in conformance with Good Clinical Practices. Subjects with Fusariosis or Zygomycosis will be assigned to the MK-5592 treatment arm; approximately 112 subjects with Aspergillosis will be randomized to MK-5592 (approximately 75 subjects) or Voriconazole (approximately 37 subjects) in a 2:1 ratio. Subject with invasive aspergillosis will be randomized to MK-5592 treatment arm or Voriconazole treatment arm in a 2:1 ratio using a classification (proven and probable / possible) at randomization as a stratification factor. Subject with chronic pulmonary aspergillosis will be randomized to MK-5592 treatment arm or voriconazole treatment arm in a 2:1 ratio without stratification. Approximately 15 subjects with invasive aspergillosis as a target number will be enrolled. The target number of subjects is not set in the subjects with Fusariosis or Zygomycosis, and there will not be comparator arm for these subjects, because Fusarium and Zygomycota are rare fungi. MK-5592 or Voriconazole will be administered by oral and/or intravenous injection for 84 days as a general rule. After the end of treatment each subject will be followed for 14 days. The initial formulation will be selected based on the subjects' condition. For the voriconazole treatment arm, subjects for whom zygomycota is detected after voriconazole is initiated may be transitioned to MK-5592 treatment arm at the investigator's discretion after discontinuation of voriconazole treatment and completion of all applicable activities scheduled for the end of treatment visit. For the subjects with zygomycosis, restart of the study therapy after finishing 84 day maximum treatment period or extension of treatment period could be done under the extension period with the prior approval from the Sponsor and obtaining the signing of a new informed consent from the subject.

and additional 90 subjects who will be enrolled into updated version of the protocol (from version 04) are treated as cohort 2. Cohort 2 is the main cohort in this study and all objectives in Section 3 will be performed for Cohort 2 only. Data from extension period will be excluded from the analysis of Cohort 2.

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

### **2.2 Trial Diagram**

The trial design is provided in [Figure 1](#).



1. In the event that additional work-up does not result in a proven or probable IA diagnosis within 7 days of randomization, subjects should continue participation in the trial with possible IA.
2. 22 subjects already enrolled is treated as cohort 1. Additional 90 subjects will be newly enrolled as cohort 2.

Figure 1 Outline of Trial Design and Therapeutic Regimen for Cohort 2

### 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

### 3.1 Primary Objective(s) & Hypothesis(es)

1) Objective: To assess and compare the safety of MK-5592 and Voriconazole in Japanese subjects with Aspergillosis [Invasive aspergillosis and Chronic pulmonary aspergillosis (Chronic progressive pulmonary aspergillosis and Simple pulmonary aspergilloma)]

### 3.2 Secondary Objective(s) & Hypothesis(es)

- 1) Objective: To assess the overall response on Day 42 of MK-5592 and Voriconazole in Japanese subjects with Invasive aspergillosis.
- 2) Objective: To assess the overall response on Day 84 of MK-5592 and Voriconazole in Japanese subjects with Chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma)

- 3) Objective: To assess the overall response at EOT of MK-5592 and Voriconazole in Japanese subjects with Aspergillosis [Invasive aspergillosis or Chronic pulmonary aspergillosis (Chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma)]
- 4) Objective: To assess the safety and efficacy of MK-5592 in Japanese subjects with fusariosis and zygomycosis
- 5) Objective: To assess the pharmacokinetic profile of MK-5592 in Japanese subjects with deep-seated fungal infection.

An overall response criterion is defined in Section 4.2.3.1. Also, all objectives in Section 3 will be performed for Cohort 2 only.

## 4.0 BACKGROUND & RATIONALE

### 4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-5592.

#### 4.1.1 Pharmaceutical and Therapeutic Background

Fungal infections are classified as superficial mycoses due to dermatophyte and deep-seated fungal infections, as represented by *Candida* spp. and *Aspergillus* spp. Deep-seated fungal infections are recognized in patients in a broad area such as hematology, respiratory medicine, pediatrics and obstetrics and gynecology. The morbidity of deep-seated fungal infections is variable. There are some risk factors for deep-seated fungal infections such as latent or apparent infection due to highly infectious fungus and opportunistic infection under immuno-compromised conditions. The latter accounts for the overwhelmingly majority of cases in Japan [1] and most of the cases led to a poor prognosis. The important factors causing deep-seated fungal infections are neutropenia, immunosuppressive treatment, long-term steroid administration, indwelling of CV catheters, complication of graft versus host disease (GVHD), long-term antibiotics administration, diabetes and HIV et. Al [2]. The more usage of immunosuppressive treatment for organ or bone marrow transplantation, change of medical condition emerging antibody drug and immune compromised in aging patients are increasing [3], the higher the risk is for deep-seated fungal infections.

The fungi causing deep-seated fungal infection are eukaryotic organism existing in the body and environment, including *Candida* spp., *Aspergillus* spp. *Cryptococcus* spp and *Zygomycetes* spp. Since there is no comprehensive surveillance system regarding a deep-seated fungal infection, an epidemiological status of deep-seated fungal infection is mostly inferred by the information of pathology autopsy in Japan. According to the estimated number of deceased leukemic with deep-seated fungal infection, 20.9% of deceased leukemic have been infected by some fungi, in which majority of fungi is *Aspergillus* spp. (52.4%) and then *Candida* spp. (14.2%) and *Zygomycetes* spp. (12.0%). The rate of deep-seated fungal patients leading to serious medical conditions is 63.9% and the rate of serious medical

conditions in Zygomycetes spp., Aspergillus spp. and Candida spp. are 81.8%, 65.6% and 57.8%, respectively. Recently, fungal infection of Zygomycetes spp. is increasing [4] and it is reported that some patients displayed unfavorable response to conventional medications [5, 6]. Therefore there are high medical needs to develop an antifungal agent with broad spectrum against fungi.

Debridement therapy and treatment of antifungal agents for deep-seated fungal infection are generally performed and antifungal agent therapy are utilized as prophylactic for the onset of deep-seated mycosis. Amphotericin B has a broad spectrum against fungi, strong antifungal activity and acts in sterilization against Candida spp., Aspergillus spp. and Zygomycetes spp. However sufficient doses of amphotericin B are unable to be administrated due to adverse effects. Azole antifungal agents such as fluconazole are safer than amphotericin B but the azole class does not have necessarily satisfactory efficacy from the aspect of antifungal spectrum and pharmacokinetics. Voriconazole, approved in 2005, is effective against Aspergillus spp. and Candida spp. with resistance to fluconazole and has broad spectrum activity against fungi. In Japan, a Phase III study showed that the efficacy of voriconazole for Japanese subjects with deep-seated fungal infection was 27/39 (69.2%) for Aspergillosis. Voriconazole is utilized as a first line of empirical therapy and target therapy for Aspergillus infection and is more effective as compared to amphotericin B [7]. Photophobia, vision blurred and visual impairment related to voriconazole administration are observed with high-frequency. In some cases breakthrough infection due to Zygomycetes spp. during voriconazole administration were observed [8, 9]. At present, only amphotericin B is effective in both highly lethal Aspergillus infection and Zygomycetes infection. Conventional antifungal agent does not meet the medical needs so development of antifungal agents which have an effective broad spectrum and safer is needed.

MK-5592 is an antifungal agent in the azole class and inhibits ergosterol biosynthesis, the main component of fungal cell membrane by affecting the enzyme lanosterol 14-alpha demethylase (CYP51), which is the same mechanism as other azoles [10-12]. As a result, depletion of ergosterol and the accumulation of methylated intermediates occurs. This leads to the inhibition of growth of the fungal cell or cell death and show antifungal activity. Clinical studies targeting patients with deep-seated fungal infections demonstrated that MK-5592 oral suspension was effective against aspergillosis, candidiasis, pulmonary cryptococcosis, fusariosis, coccidioidomycosis, chromoblastomycosis and mycetoma and zygomycosis. Furthermore MK-5592 showed efficacy in zygomycosis patients with infections refractory or intolerant of the other antifungal treatments [5, 6]. In clinical studies targeting acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS) patients with neutropenia and patients with GVHD MK-5592 showed superiority or non-inferiority efficacy in reducing the incidence of deep-seated fungal infections as compared to itraconazole or fluconazole. For safety, specific adverse drug reactions are reported but generally well tolerated.

In the EU MK-5592 (oral suspension) was first approved in October 2005 and is currently registered and approved in more than 80 countries, such as the US, EU and Australia. MK-5592 is indicated for the treatment of invasive aspergillosis with disease that is refractory or intolerant of other antifungal agents, treatment of fusariosis, coccidioidomycosis,

chromoblastomycosis and mycetoma, treatment of oropharyngeal candidiasis and prophylaxis of invasive fungal infections. In addition MK-5592 has the indication for the treatment of zygomycosis in Australia. In Japan MK-5592 is expected to be effective for these fungal infections [13]. Thus, MK-5592 is an important alternative option for the treatment of deep-seated fungal infections as an antifungal agent with broad spectrum against fungi. The profile of MK-5592 oral suspension which is widely used in ex-Japan demonstrates that the pharmacokinetics of MK-5592 is affected by food and absorption is saturated at the highest dose. On the other hand, the formulation of MK-5592 which will be used in Japan (as of May 1<sup>st</sup> 2015, solid oral tablet is approved in US, EU, Canada, Australia, New Zealand, Switzerland, Taiwan and Korea, IV solution is approved in US, EU, Canada and Australia), has an improved pharmacokinetic profile compared to the oral suspension. MK-5592 solid oral tablet and IV solution ensures sufficient exposure regardless of food. MK-5592 PK parameter is similar between Japanese and non-Japanese when single doses of MK-5592 solid oral tablet and IV solution and multiple doses of MK-5592 solid oral tablet are administered.

Therefore, in Japan, the Sponsor has decided to develop the MK-5592 solid oral tablet and IV solution which is thought to be an important alternative option for the treatment of Japanese patients with deep-seated fungal infections.

#### **4.1.2 Clinical Trials**

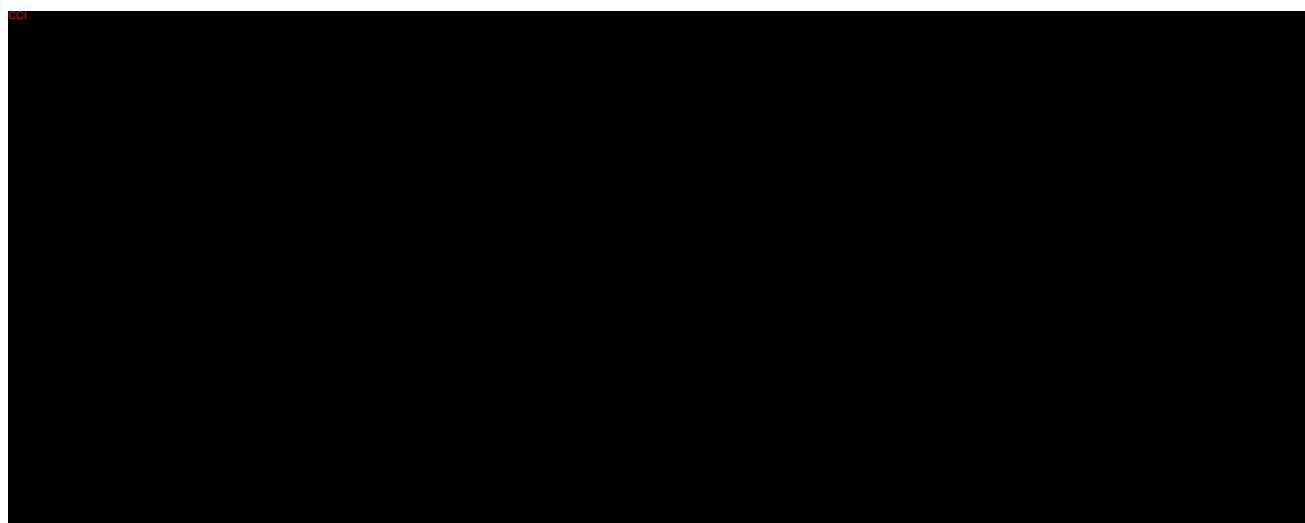
##### **4.1.2.1 Treatment Study (P00041 Study) and Prophylaxis Study (P01899 and C/I98-316)**

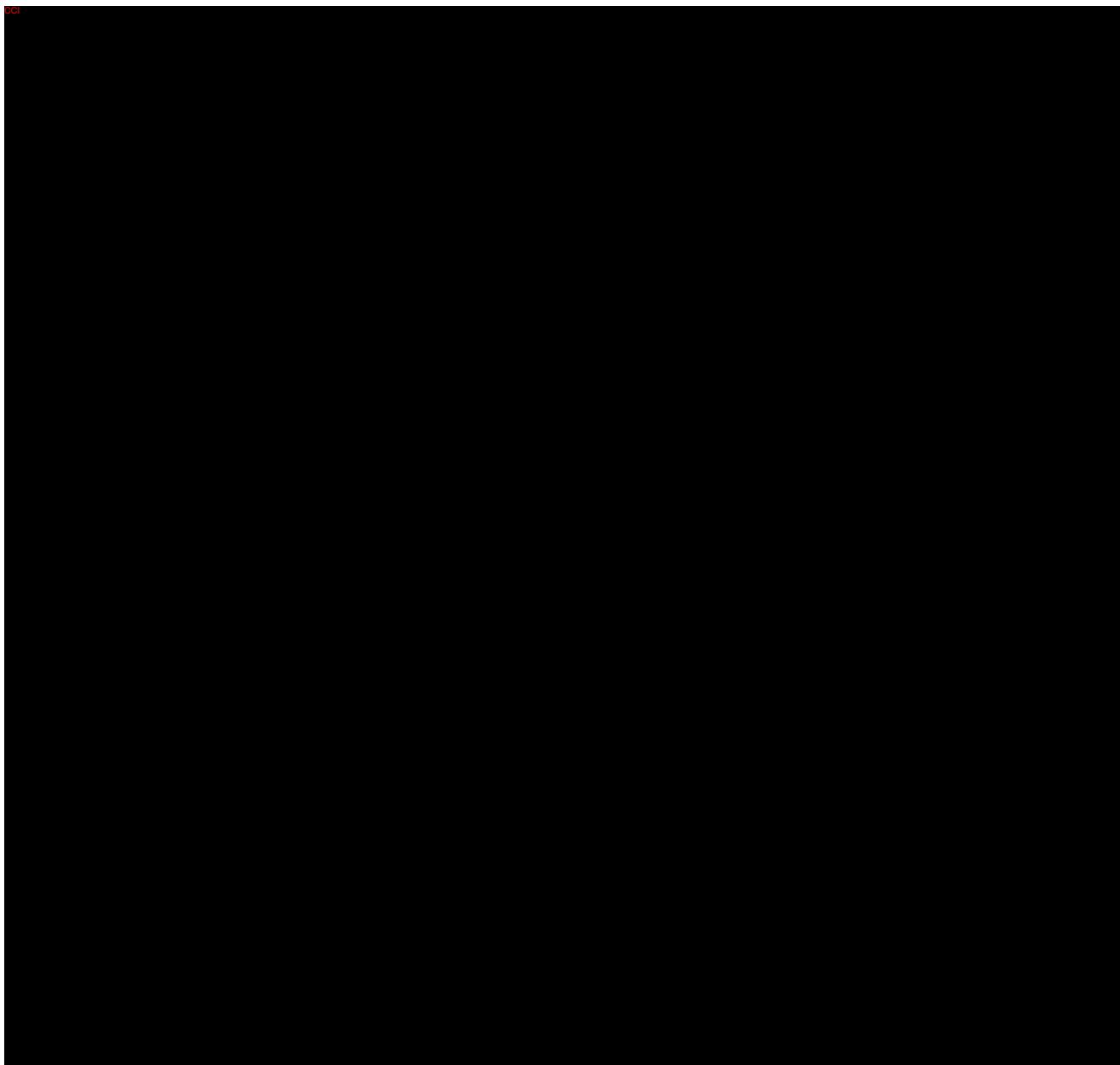
Merck has analyzed the correlation between the efficacy and exposure of MK-5592 oral suspension in clinical trials conducted in overseas (P00041, P01899 and C/I98-316 study) (Table 1). As a result, efficacy of lowest quartile was lower than that of control and efficacy was becoming almost constant to ~2500 ng/mL. Safety profile was similar within the exposure which was observed in clinical trial. From the efficacy and safety point of view, it was suggested that 500~2500 ng/mL of Cavg was targeted.

**Table 1 Correlation Between Efficacy (Treatment or Prophylaxis for Invasive Fungal Infection) and Mean Exposure (Cavg)**

	<b>P00041 (Aspergillosis)</b>		<b>P01899 (AML/MDS)</b>		<b>C/198-316 (GVHD)</b>	
	Range of Cavg (ng/mL)	Response N(%)	Range of Cavg (ng/mL)	Response N (%)	Range of Cavg (ng/mL)	Response N (%)
<b>MK-5592</b>	55-277	24(4/17)	90-322	45.3(24/53)	22-557	55.6(35/63)
	290-544	53(9/17)	322-490	63.0(34/54)	557-915	79.4(50/63)
	550-861	53(9/17)	490-734	53.7(29/54)	915-1563	82.5(52/63)
	877-2010	71(11/16)	734-2200	72.2(39/54)	1563-3650	82.5(52/63)

P00041 study : Treatment of invasive fungal infection (IFI) as an endpoint. Success is defined complete response and partial response at the end of treatment using overall response  
P01899 study : Prophylaxis of IFI as an endpoint, AML/MDS subjects as a target population  
C/198-316 study : Prophylaxis of IFI as an endpoint, GVHD subjects as a target population  
P01899 and C/198-316 study: Failure is defined occurrence of a proven or probable IFI, use of empiric antifungal therapy treatment with a systemic antifungal other than study treatment for 5 days or more and death from all causes and/or premature discontinuation of study treatment. Success is defined other than failure.

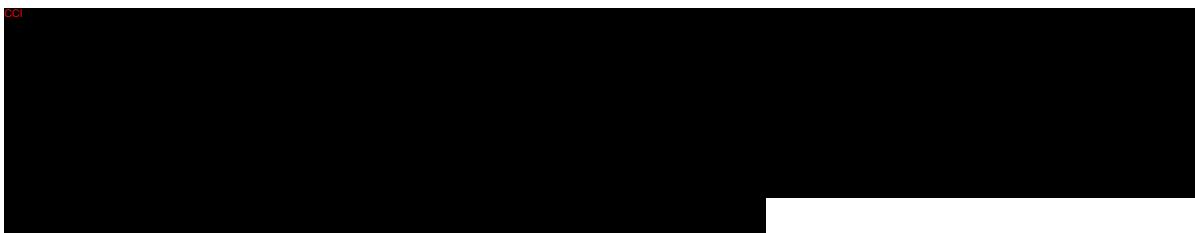




#### **4.1.2.3 P05520 Study**

P05520 study was conducted to evaluate the pharmacokinetics and safety in non-Japanese patients with acute myeloid leukaemia, myelodysplastic syndrome, and post allogeneic-HSCT patients when 200 mg or 300 mg of MK-5592 IV solution was administered via central vein. This study consisted of 4 cohorts (Cohorts 0, 1, 2, 3).

Overall, 94% (46/49) of subjects had  $C_{avg}$  values between 500 to 2500 ng/mL, meeting the PK exposure target specified in P05520 study. In Cohort 0, a single dose of MK-5592 IV solution 200 mg or placebo was administered via a central vein and its pharmacokinetic profile was evaluated in 21 subjects.



In Cohort 2, MK-5592 IV solution 300 mg was administered twice a day via a central vein on Day 1, once a day on Days 2 to 14, and MK-5592 oral suspension 400 mg was orally administered twice a day on Days 15 to 28 in 24 subjects with AML/MDS. Data (steady state) from 19 PK-evaluable subjects on Day 14 showed that mean  $C_{avg}$  of MK-5592 was 1410 ng/mL and  $C_{avg}$  of 95% (18/19) of subjects was within target exposure (500 to 2500 ng/mL), but  $C_{avg}$  of 5% (1/19) subjects was 2910 ng/mL (Table 4). Similar to the safety of MK-5592 IV solution 200 mg dose / MK-5592 oral suspension 400 mg dose, the safety of MK-5592 IV solution 300 mg dose / MK-5592 oral suspension 400 mg dose was also favorable at this dose. There is no new safety concern due to dose escalation of MK-5592. The Sponsor considered that a higher exposure is desirable in order to have enough efficacy and judged that 300 mg is the most appropriate dose for the IV solution in Cohort 3.

In Cohort 3, MK-5592 IV solution 300 mg was administered twice a day via a central vein on Day 1 and once a day on subsequent days for at least 4 days in 213 subjects with AML/MDS/HSCT to evaluate the safety, tolerability, and pharmacokinetics of the IV solution in a wider range of patients. From the point where the subject was judged eligible for oral administration up to Day 28, MK-5592 oral suspension was orally administered at 400 mg twice a day or 200 mg three times a day. Data from 31 serial PK-evaluable subjects receiving 300 mg of MK-5592 IV solution showed that mean  $C_{avg}$  in steady state was 1566 ng/mL on Day 10 and  $C_{avg}$  of 93% (28/30) of subjects was within the target exposure (500-2500 ng/mL), but  $C_{avg}$  of 7% (2/30) of subjects was between 2500 and less than 3650 ng/mL. Only one subject was above 3650 ng/mL. This subject was excluded from the analysis because this subject was dosed and the PK sample was collected through the same catheter. The mean  $C_{avg}$  at steady state from MK-5592 IV solution 300 mg dose for the pooled data from Cohorts 2 and 3 was 1500 ng/mL.

Table 4 Mean Pharmacokinetic Parameters of MK-5592 After Administration of IV Solution 200 or 300 mg BID (Day 1), Followed by 200 or 300 mg QD in High Risk Patients (Results of P05520)

Cohort	Dose (mg)	Day	n <sup>†</sup>	AUC( $\tau$ ) (ng•hr /mL)	$C_{avg}^{\$}$ (ng/mL)	n (%) of subjects $C_{avg}$ ≥500 ng/mL and <2500	
						%	subjects/n
1	200 QD	14	15	28200 (51)	1180 (51)	94	14/15
2	300 QD	14	19	33800 (42)	1410 (42)	95	18/19
3	300QD	10	30	37600 (31)	1566 (31)	93	28/30
2+3	300QD	10, 14	49	36100 (35)	1500 (35)	94	46/49

<sup>†</sup> PK-evaluable subject

<sup>§</sup>  $C_{avg}$  = AUC(interval) at steady state/dosing interval

#### 4.1.2.4 P05615 Study

A repeat dose study of the solid oral tablets 200 mg and 300 mg in non-Japanese patients with neutropenia or non-Japanese HSCT patients was conducted to evaluate the safety and pharmacokinetics of the solid oral tablet in patients (P05615). This study consisted of 3 parts (Part 1A, Part 1B, Part 2).

The pre-defined exposure target range was achieved at the 300 mg dose level.

In Part 1A, MK-5592 solid oral tablet 200 mg was orally administered twice a day on Day 1 and once a day on Days 2 to 28 in 20 AML or MDS patients with neutropenia. Data (steady state) from 18 serial PK-evaluable subjects showed that mean  $C_{avg}$  on Day 8 was 981 ng/mL and  $C_{avg}$  of 83% (15/18) of subjects was within target exposure (500-2500 ng/mL), but 17% (3/18) of subjects could not achieve the target exposure and their  $C_{avg}$  were between 200 to 500 ng/mL ([Table 5](#)).

In Part 1B, MK-5592 solid oral tablet 300 mg was administered in the same manner in 34 patients with patient characteristics similar to those in Part 1A, and in Part 2, MK-5592 solid oral tablet 300 mg was orally administered twice a day on Day 1 and once a day on Days 2 to 28 in 176 AML or MDS patients with neutropenia and HSCT patients, and the pharmacokinetics and safety were evaluated in a greater number of subjects. Based on Day 8 data (steady state) from serial PK-evaluable subjects with AML/MDS (33 patients) and HSCT (17 patients) receiving MK-5592 solid oral tablet 300 mg,  $C_{avg}$  were 1440 ng/mL and 1870 ng/mL, respectively and  $C_{avg}$  in HSCT serial PK-evaluable subjects was slightly higher than in the AML/MDS serial PK-evaluable subjects. AML/MDS and HSCT patients with  $C_{avg}$  between 500 ng/mL and 2500 ng/mL were 97% (32/33) and 76% (13/17), respectively. AML/MDS and HSCT patients with  $C_{avg}$  between 2500 ng/mL and 3750 ng/mL were 3% (1/33) and 24% (4/17), respectively. Based on the pooled data from part 1B and part 2,  $C_{avg}$  at steady state from MK-5592 solid oral tablet 300 mg dose was 1580 ng/mL and 90% (45/50) of patients attained  $C_{avg}$  between 500 ng/mL and 2500 ng/mL.

A linear regression model was created from the  $C_{min}$  obtained in Part 1A, 1B and Part 2. An estimated  $C_{avg}$  ( $pC_{avg}$ ) was calculated using this model and the results are shown in [Table 6](#). Among 186  $C_{min}$  PK-evaluable subjects with AML/MDS and HSCT subjects, the percentage of subjects with a steady-state  $pC_{avg}$  within target exposure (500-2500 ng/mL) were 90% (96/107) for AML/MDS subjects and 70% (55/79) for HSCT subjects. The percentage of subjects with a steady-state  $pC_{avg}$  within 2500 to 3750 ng/mL was 8% (9/107) for AML/MDS subjects and 23% (18/79) for HSCT subjects. HSCT subjects treated with MK-5592 solid oral tablet 300 mg attained somewhat higher concentrations as compared to AML/MDS patients.

With respect to the safety of MK-5592 solid oral tablet 300 mg in Part 1B and Part 2, the most frequently observed adverse events were gastrointestinal adverse reactions reported in 148 (70%) patients. Of those 148 subjects with events they were assessed as adverse drug reactions in 54 patients (26%), but no new safety concern was observed compared to administration at 200 mg. Results were generally comparable to those in the major overseas

studies of the oral suspension (oral suspension: P00041, P01899, C/I98-316), and increased exposure observed in this study was suggested to have no significant impact on the safety profile. This increased exposure will not affect the tendency of frequency of adverse events.

**Table 5** Mean Pharmacokinetic Parameters After Repeated Administration of the Solid Oral Tablet in High Risk Patients (Results of Parts 1 and 2, P05615)

Part	Dose(mg)	Day	n	Disease	AUC( $\tau$ ) (ng•hr /mL)	Cavg <sup>§</sup> (ng/mL)	n (%) of subjects Cavg $\geq 500$ ng/mL and $< 2500$	
							%	subject / n
1A	200 QD	8	18	AML/MDS	23500 (49)	981 (48)	83	15/18
1B	300 QD	8	33	AML/MDS	34300 (36)	1440 (36)	97	32/33
2	300 QD	8	17	HSCT	44800 (45)	1870 (45)	76	13/17
1B+2	300 QD	8	50	AML/MDS +HSCT	37900 (42)	1580 (42)	90	45/50

<sup>§</sup> Cavg = AUC(interval) at steady state/dosing interval

**Table 6** Estimated Cavg (pCavg) After Repeated Administration of 300 mg QD in High Risk Patients (Comparison of Results by Target Patients in Part 1B and Part 2, P05615)

	pCavg <sup>a</sup> (ng/mL)		
	AML/MDS+HSCT	AML/MDS	HSCT
N	186	107	79
Arithmeric Mean (%CV)	1970 (56)	1680 (41)	2370 (60)
Range	442-9520	442-3970	680-9520
n (%) of subjects pCavg $\geq 200$ ng/mL and $< 500$ ng/mL	1 (0.5%)	1 (1%)	0 (0%)
n (%) of subjects pCavg $\geq 500$ ng/mL and $< 2500$ ng/mL	151 (81%)	96 (90%)	55 (70%)
n (%) of subjects pCavg $\geq 2500$ ng/mL and $< 3750$ ng/mL	27 (15%)	9 (8%)	18 (23%)
n (%) of subjects pCavg $\geq 3750$ ng/mL	7 (4%)	1 (1%)	6 (8%)

a: pCavg was derived from linear regression model using observed Cmin on Day 8 from P05615 Parts 1 and 2 (pCavg= 228 +1.02·Avg\_Cmin)

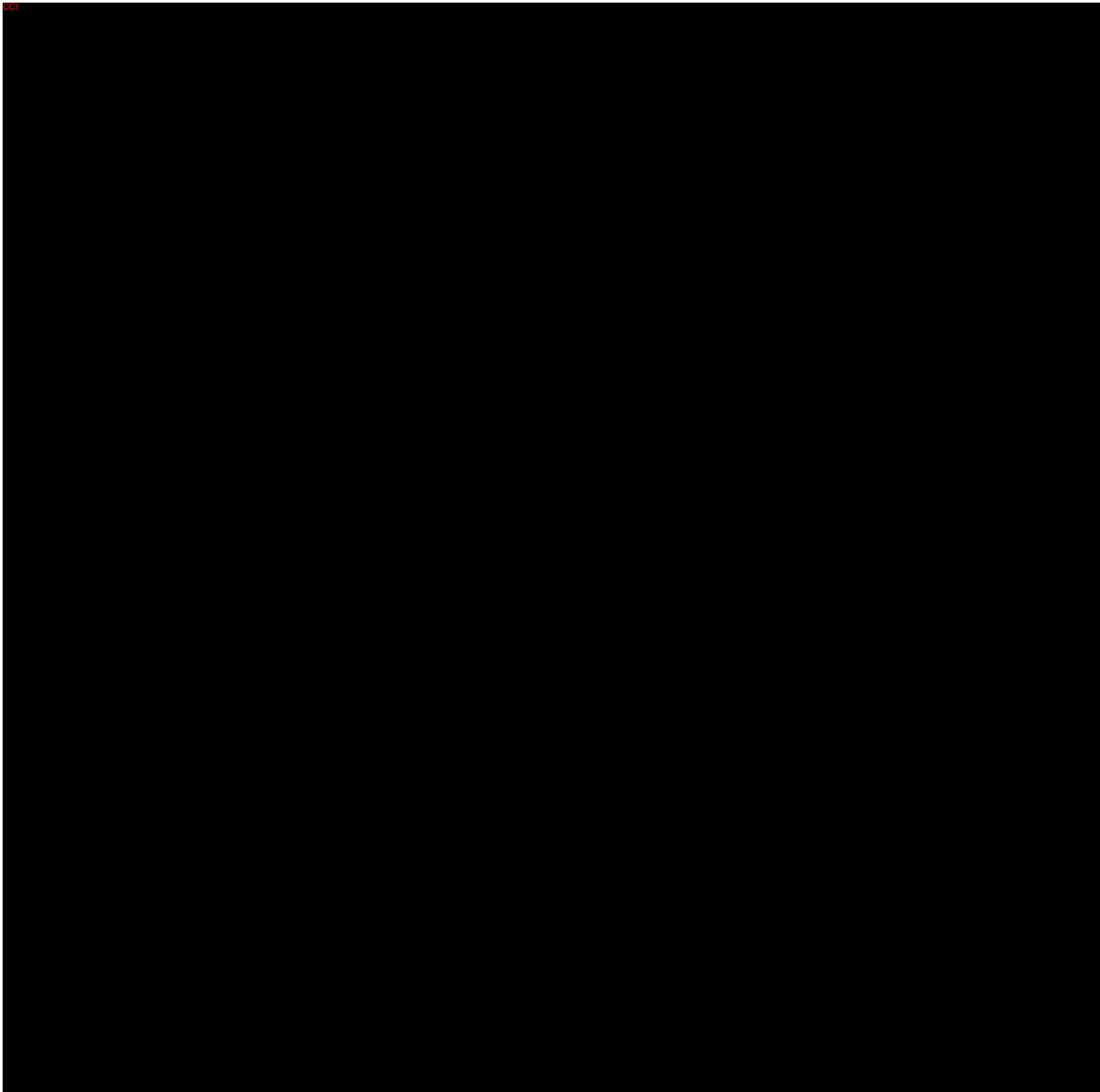
#### **4.1.3 Ongoing Clinical Trials**

##### **4.1.3.1 PN069**

PN069 is a randomized, double-blind phase III study to evaluate the efficacy, safety and tolerability of MK-5592 IV solution and solid oral tablet (300 mg QD, 300 mg BID on Day 1 only) versus voriconazole IV and solid oral formulation [IV: 6 mg/kg BID for loading dose and 4 mg/kg BID for maintenance dose, solid oral formulation: 300 mg BID for loading dose and 200 mg BID for maintenance dose] for the treatment of invasive aspergillosis in adults;

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## 4.2 Rationale

### 4.2.1 Rationale for the Trial and Selected Subject Population

The diagnosis of invasive fungal infections (IFI) is generally difficult and most of patients with IFI have serious underlying diseases. In most of cases the therapy for IFI is initiated prior to the diagnosis of IFI because the condition of patient is critical. The antifungal agents approved in Japan are not always effective depending on the IFI morbidity and it is reported that some patients displayed unfavorable response to the conventional medication. Therefore there are high medical needs to develop safe and effective antifungal agent with broad spectrum against fungi.

Amphotericin B has broad spectrum activity against fungi and has a strong antifungal activity, many adverse effects are observed due to strong toxicity. Antifungal agents such as azoles and echinocandins are superior to amphotericin B with regards to safety and pharmacokinetics profile, but antifungal spectrum is not entirely satisfactory.

MK-5592 is an antifungal agent in the azole class that inhibits ergosterol biosynthesis, a in the main component of the fungal cell membrane, by affecting the enzyme lanosterol 14-alpha demethylase (CYP51). Nonclinical and clinical studies (MK-5592 oral suspension) indicate that MK-5592 is effective against broad fungus including zygomycota that is refractory to voriconazole in addition to aspergillus. In safety profile, azole specific ADRs were observed, but well tolerated.

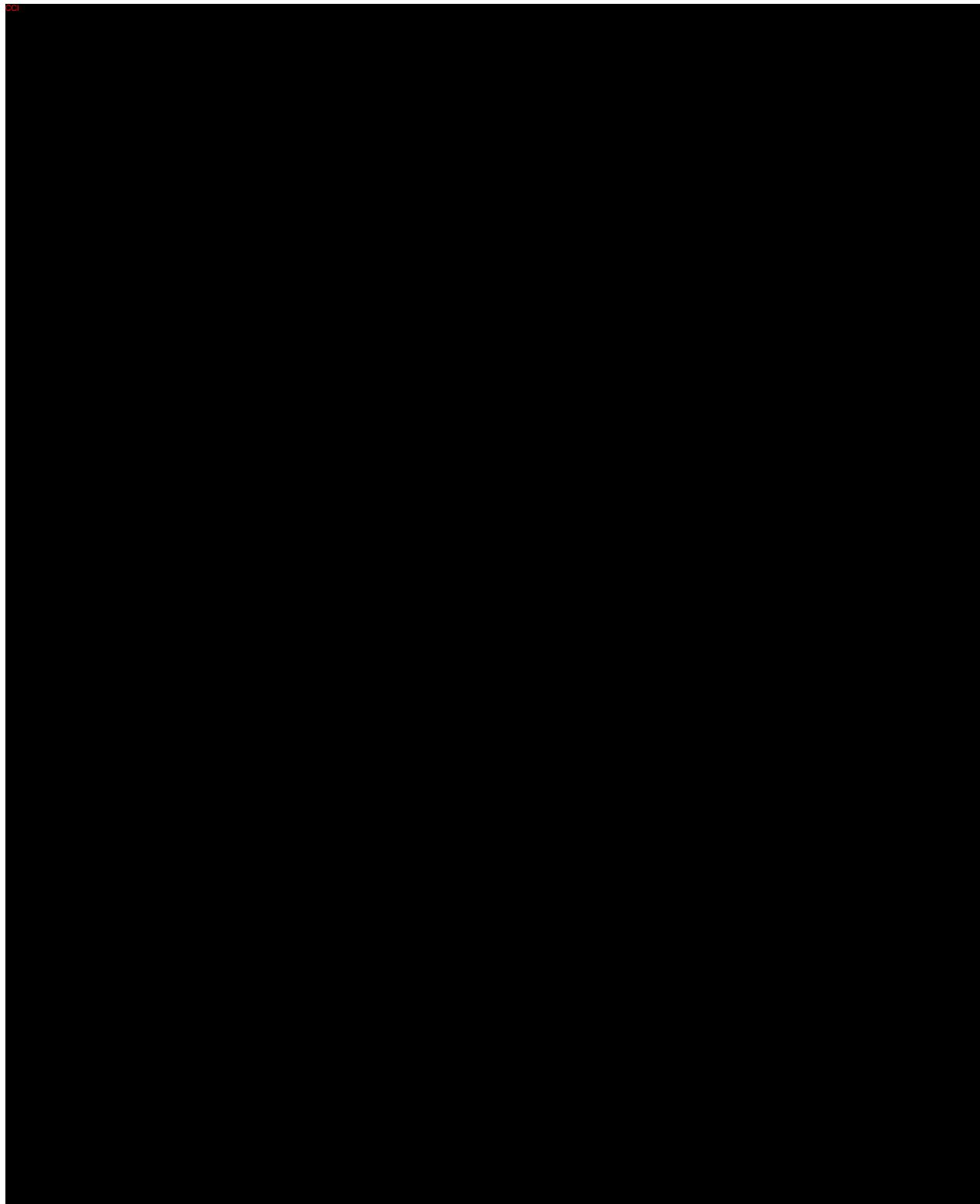
Based on the above, MK-5592 is expected to be safe and efficacious in the treatment of broad deep-seated fungal infections and should be considered as one option for the treatment of these deep-seated fungal infections to meet the current medical needs. This Phase 3 study is planned to assess the safety and efficacy of MK-5592 in patients with proven or probable deep-seated fungal infections in Japan using the criteria and endpoints referred to in the EORTC/MSG criteria [14, 15], endpoints of MK-5592 clinical study conducted outside Japan, endpoints of clinical study for chronic pulmonary aspergillosis conducted in and outside Japan [16, 17], and the guideline as antifungal drugs evaluation committee by Japan chemotherapy association March 2012 [18].

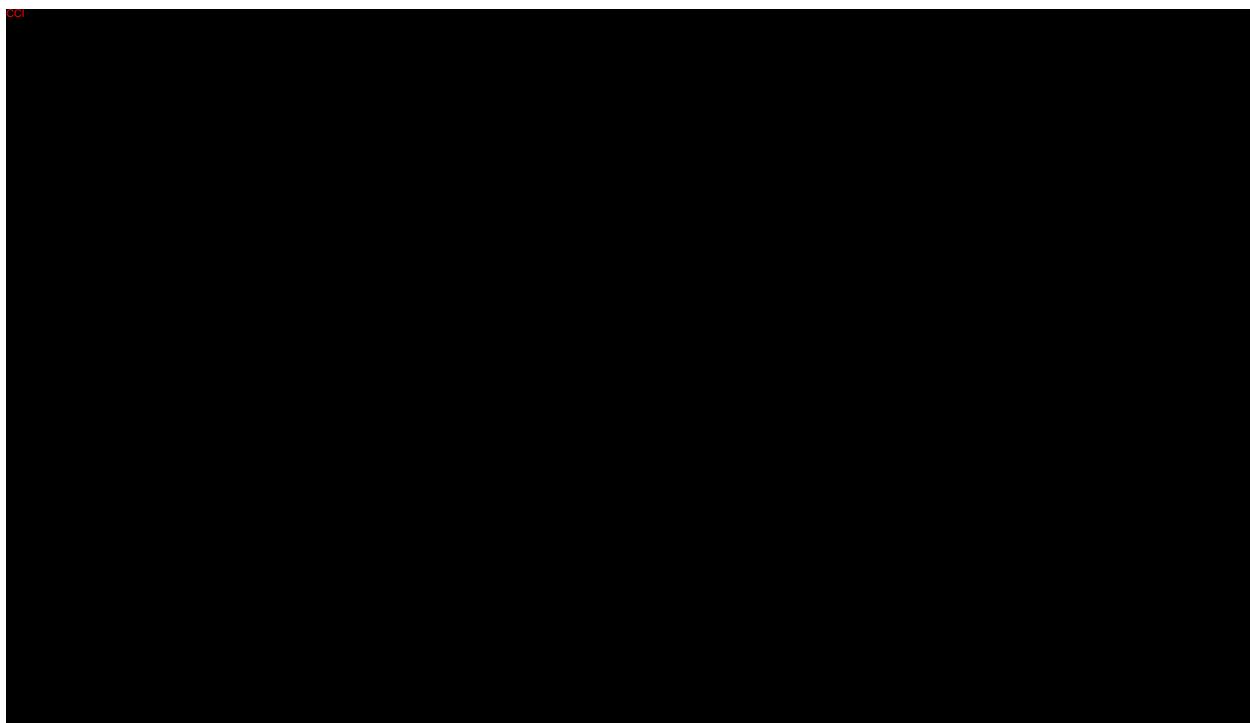
Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

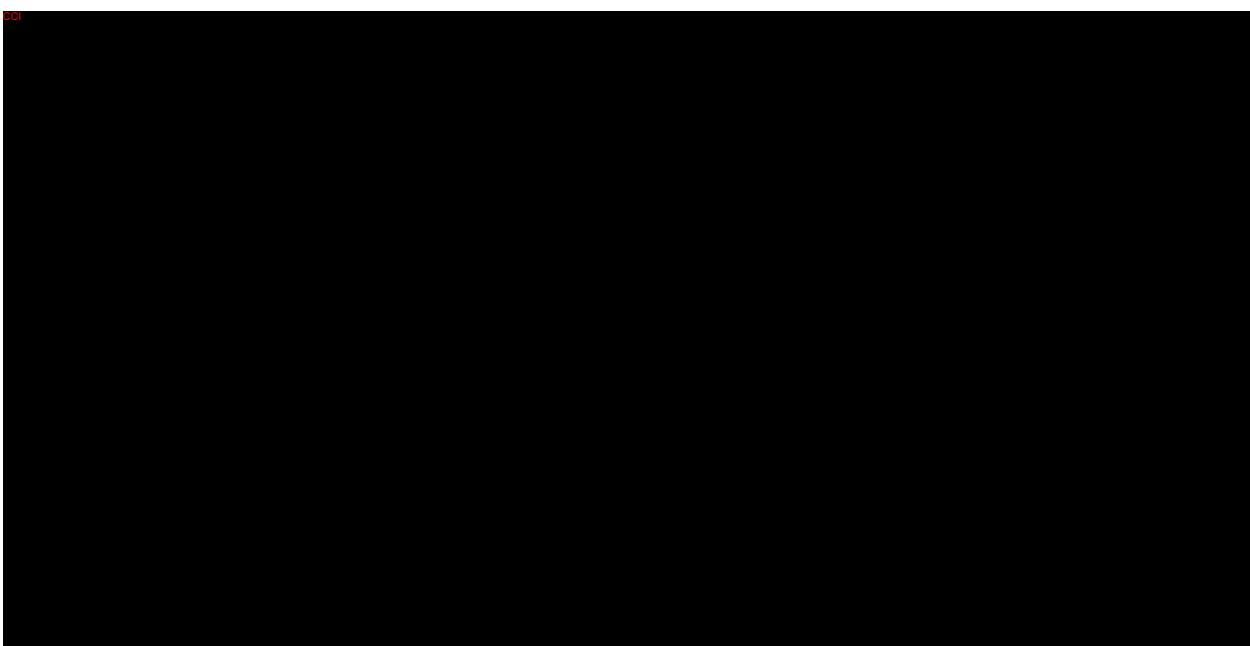
#### **4.2.2 Rationale for Dose Selection/Regimen/Modification**

##### **1) Rationale for MK-5592 dosage and administration**





**For Cohort 2**



2) Rationale for Voriconazole Dosage and Administration

Dosage of Voriconazole was chosen based on approved dosage of treatment for deep-seated fungal infection in Japan. Oral administration is 200 mg BID (300 mg BID on Day 1), IV infusion is 4 mg/kg BID (6 mg/kg BID on Day 1).

In JPC of voriconazole, ‘it is recommended that plasma concentration of voriconazole should be monitored during the treatment’ is stated. From the both efficacy and safety aspects, dosing adjustment based on the result of therapeutic drug monitoring (TDM) is recommended for voriconazole in Japan. Therefore, in this study, adjustment of voriconazole dosing should be performed based on the result of TDM, with the dose modified at the investigator’s discretion. The frequency of blood sampling for TDM is also left to the investigator’s discretion.

#### **4.2.3 Rationale for Endpoints**

Safety and efficacy endpoints in this study are based on the EORTC/MSG criteria [14, 15], endpoints of MK-5592 clinical study conducted outside Japan, endpoints of clinical study for chronic pulmonary aspergillosis conducted in and outside Japan [16, 17], and the guideline as antifungal drugs evaluation committee by Japan chemotherapy association March 2012 [18]. Deep-seated fungal infection is usually manifested in immunocompromised subjects with serious underlying diseases (such as HIV, organ transplantation, and cancer). For such infections, the assessment of efficacy usually takes into consideration a number of key variables, including the response to clinical signs and symptoms (Clinical Response), the response to mycological measures of the infection (Mycological Response), and the response to radiological evidence of the infection (Radiological Response). Therefore, an overall response, which encompasses many of these individual components, is routinely applied to the assessment of efficacy in these types of infections. Overall response criteria for invasive aspergillosis is set in 5 levels (complete response, partial response, stable response, progressive disease and unable to determine). Success is defined as complete response and partial response. Failure is defined as stable response, progressive disease and unable to determine. Overall response criteria for chronic pulmonary aspergillosis is set in 4 levels (favorable response, stable response, progressive disease and unable to determine). Success is defined as favorable response. Failure is defined as stable response, progressive disease and unable to determine. For chronic pulmonary aspergillosis, it is rare that ‘finding of imaging’ are resolved. Complete response and partial response are not set but favorable response is set in overall response. The overall response is evaluated by the investigator or sub-investigator according to the criteria. The overall response is finally evaluated by the clinical adjudication committee.

For subject with IA, we set the endpoint at Day 42 same as global study (069 study) in order to be able to confirm the efficacy between 101 and 069 study. For subject with CPA, we set the endpoint at Day 84 same as registration clinical studies conducted with using other anti-fungal drugs in the subject with CPA in Japan.

Pharmacokinetics endpoints were chosen to evaluate MK-5592 PK profile and will be able to compare to other clinical trials.

#### **4.2.3.1 Efficacy Endpoints**

##### **(1) Invasive aspergillosis**

Overall response for efficacy is evaluated based on clinical response, radiological response and mycological response.

##### **(2) Chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma)**

Overall response for efficacy is evaluated based on clinical response, radiological response.

##### **(3) Fusariosis and Zygomycosis**

Overall response for efficacy is evaluated based on clinical response, radiological response and mycological response.

##### **(4) Antifungal susceptibility testing**

Minimum inhibitory concentration (MIC) of MK-5592, voriconazole and representative anti-mycosis drugs will be measured in the isolated causative fungus from the subjects (pre-treatment, post-treatment).

Individual evaluation criteria and overall response criteria is defined as follows;

#### **Criteria for Each Evaluation Element**

Table 7 Criteria for Clinical Response

Response	Definition
Resolution <sup>†</sup>	Resolution of attributable signs and symptoms of disease
Improvement	Improvement of attributable signs and symptoms of disease <sup>‡</sup>
Stabilization	No change or minor improvement of attributable signs and symptoms of disease
Worsening	Worsening of attributable signs and symptoms of disease
Unable to Determine	Unable to determine
Clinical response is evaluated based on the clinical signs and symptoms related to mycosis (cough, dyspnea, sputum, hemoptysis, bloody sputum, pain, pyrexia and weight loss etc), with vital sign and shift of clinical laboratory (CRP etc) for reference during the trial.	
<sup>†</sup> : It does not use for chronic pulmonary aspergillosis	
<sup>‡</sup> : “Resolution or Improvement of attributable signs and symptoms of disease” for chronic pulmonary aspergillosis	

Table 8 Criteria for the Radiological Response

Response	Definition
Resolution <sup>†</sup>	Resolution of radiological lesions
Improvement <sup>‡</sup>	Major reduction of size of radiological lesions <sup>§</sup>
Stabilization	No change or minor reduction of size of radiological lesions
Worsening	Increase of size of existing lesion or new site with fungal infection
Unable to Determine	Unable to Determine

Imaging findings caused by fungus is evaluated.  
†: It does not use for chronic pulmonary aspergillosis  
‡: In the case of invasive aspergillosis, fusariosis, and mucormycosis, reduction of the longest diameter of lesions on imaging by 25% or more; for chronic pulmonary aspergillosis, whether lesions have been improved or not is judged by considering change in size and quality of lesions on imaging comprehensively.  
§: “Resolution or improvement of radiological lesions” for chronic pulmonary aspergillosis

Table 9 Criteria for Mycological Response

Response	Definition
Eradication	Fungus detected from culture or microscopy at the screening is eradicated at the time of evaluation(including presumed eradication <sup>†</sup> )
Stabilization	“Fungus detected from culture or microscopy at the screening is detected at the time of evaluation” or “Fungus at the screening is not detected at the time of screening and evaluation”
Worsening	Fungus is not detected at the screening but fungus or newly infected site is detected at the time of evaluation.
Unable to Determine	Unable to determine

†: It is difficult to obtain the sample due to eradication of infection site (etc.) but it is clinically judged to eradicate the infected fungus.

**Criteria for Overall Response**

Table 10 Overall Response Criteria for Invasive Aspergillosis, Zygomycosis and Fusariosis

		Clinical Response				
		Resolution	Improvement	Stabilization	Worsening	Unable to determine
Radiological Response	Resolution	Complete Response	Partial Response	Partial Response	Progressive Disease	Unable to determine
	Improvement	Partial Response	Partial Response	Partial Response	Progressive Disease	Unable to determine
	Stabilization	Partial Response	Partial Response <sup>†</sup> / Stable response <sup>†</sup>	Stable Response	Progressive Disease	Unable to determine
	Worsening	Progressive Disease	Progressive Disease	Progressive Disease	Progressive Disease	Progressive Disease
	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Progressive Disease	Unable to determine

<sup>†</sup>: Assessment based on the Mycological Response in below

- In case of “Detected at Screening” and “Undetected at the Evaluation”, Mycological Response and Overall Response are “Resolution” and “Partial Response”, respectively.
- In case of “Undetected at Screening” and “Undetected at the Evaluation”, Mycological Response and Overall Response are “Stabilization” and “Stable Response”, respectively.
- In case of “Detected at Screening” and “Detected at the Evaluation”, Mycological Response and Overall Response are “Stabilization” and “Stable Response”, respectively.
- In case of “Undetected at Screening” and “Detected at the Evaluation”, Mycological Response and Overall Response are “Worsening” and “Stable Response”, respectively.

Table 11 Overall Response Criteria for Chronic Pulmonary Aspergillosis

		Clinical Response			
		Improvement	Stabilization	Worsening	Unable to determine
Radiological Response	Improvement	Favorable Response	Favorable Response	Progressive Disease	Unable to determine
	Stabilization	Favorable Response	Stable Response	Progressive Disease	Unable to determine
	Worsening	Progressive Disease	Progressive Disease	Progressive Disease	Progressive Disease
	Unable to determine	Unable to determine	Unable to determine	Progressive Disease	Unable to determine

Table 12 Overall Response Criteria for in Case of Zygomycosis and Fusariosis Without Imaging

		Clinical Response				
		Resolution	Improvement	Stabilization	Worsening	Unable to determine
Mycological Response	Eradication	Complete Response	Partial Response	Stable Response	Progressive Disease	Unable to determine
	Stabilization	Partial Response	Stable Response	Stable Response	Progressive Disease	Unable to determine
	Worsening	Progressive Disease				
	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Progressive Disease	Unable to determine

#### 4.2.3.2 Safety Endpoints

Safety endpoints are evaluated based on physical findings, clinical symptoms and signs, vital signs, 12-lead ECG and laboratory measurements. Adverse events are collected through the study duration from the subjects.

#### 4.2.3.3 Pharmacokinetic Endpoints

Steady-state pharmacokinetic profile of MK-5592 in Japanese patients with mycosis will be explored using population PK approach. The PPK analysis plan will be prepared separately.

*For MK-5592 treatment arm, plasma samples for PK evaluation will be collected at the following time points:*

For IV administration: Thirty minutes before the treatment, just before the end of first infusion, 6 to 10 hours after the initiation of the infusion and just before the treatment of second infusion on Day 1[Blood sampling after the first dosing on Day 1 (or second dosing) should be performed at least 3 hours apart among these sampling points (6 to 10 hours after the treatment and just before the second treatment)]. Thirty minutes before the treatment on Day 3, 14, 28, 42 and end of treatment<sup>a, b</sup>. Thirty minutes before the treatment, just before the end of the infusion, 2 to 3 hours after the initiation of infusion, 8 to 10 hours after the initiation of infusion on Day 8 and thirty minutes before the treatment of the next day (on Day 9).

For oral administration: Thirty minutes before the treatment, 2 to 4 hours after the first treatment, 6 to 10 hours after the treatment and just before the second treatment on Day 1[Blood sampling after the first dosing on Day 1 (or second dosing) should be performed at least 3 hours apart among these sampling points (6 to 10 hours after the treatment and just before the second treatment)]. Thirty minutes before the treatment on Day 3, 14, 28, 42 and end of treatment<sup>a, b</sup>. 30 minutes before the treatment and 2 to 6 hours after the treatment on after 7 days of switching formulation (Only for the subjects who switch from IV to oral<sup>a</sup>). Thirty minutes before the treatment, 2 to 3 hours after the treatment, 4 to 6 hours after the treatment, 8 to 10 hours after the treatment on Day 8 and 30 minutes before the treatment of the next day (on Day 9).

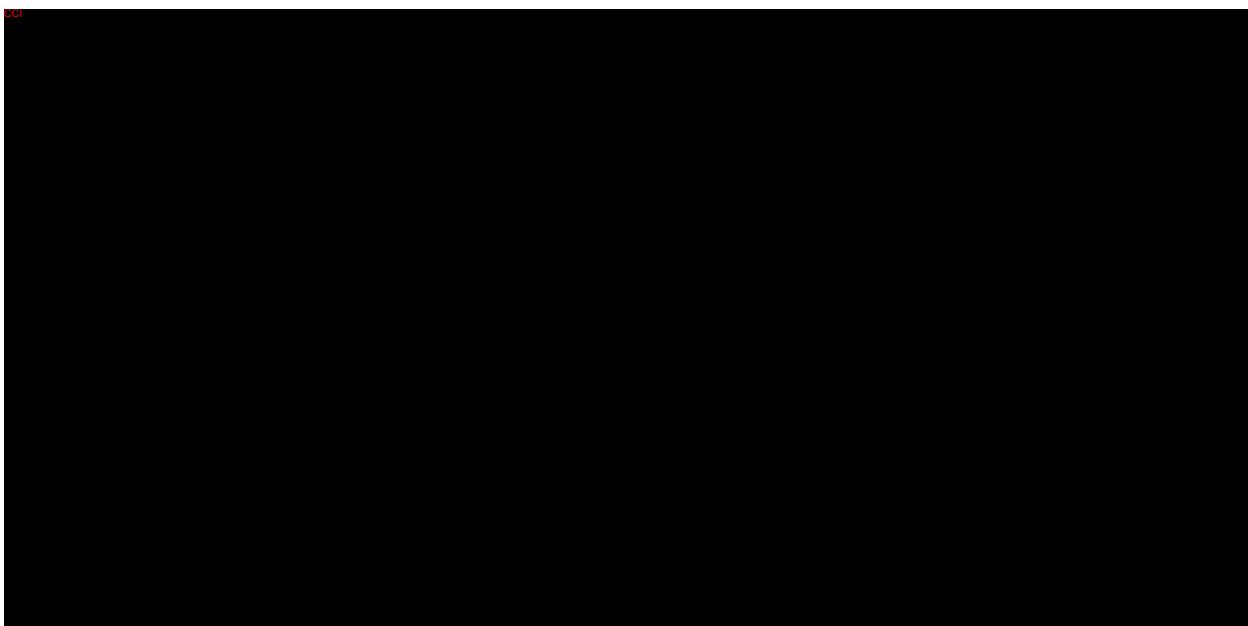
For both formulations: At the time of interruption<sup>a</sup> or discontinuation<sup>a</sup> due to adverse events, or at the incidence of serious adverse events<sup>a</sup> by MK-5592 administration.

<sup>a</sup>: The plasma samples for PK evaluation in the subjects with zygomycosis during the extension period will not be needed.

<sup>b</sup>: The plasma samples for PK evaluation in the subjects with zygomycosis must be collected at EOT before the transition to the extension period.

#### **4.2.3.4 Future Biomedical Research**

The Sponsor will conduct Future Biomedical Research on DNA (blood) specimens collected during this clinical trial.



## **5.0 METHODOLOGY**

### **5.1 Entry Criteria**

#### **5.1.1 Diagnosis/Condition for Entry Into the Trial**

Male/Female subjects with deep-seated mycosis of at least 18 years of age will be enrolled in this trial.

### **5.1.2 Subject Inclusion Criteria**

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

1. The subject whose written consent is obtained prior to the study. If the subject is incompetent, the written consent of an appropriate attorney\* must be obtained. If the subject is infirm, the written consent/assent of a subject and an appropriate attorney\* must be obtained. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

\* Appropriate attorney includes those persons who can consider the best benefit of the subject judging from the livelihood or mental relationships with the subject, such as a spouse, parent, legal guardian or other person pursuant to those persons.

2. Male or female Japanese subject aged 18 years and over at the time when informed consent is obtained, and subject with body weight greater than or equal to 45 kg at the randomization.
3. The subject who can take investigational medical products [he/she can take tablet via oral or he/she can take IV formulation via central vein (he/she has central venous catheter or he/she can obtain a central venous catheter)]
4. The subject (only female) who has a negative pregnancy test at screening visit. Female subjects of child-bearing potential who agree to continue using proper combination of barrier method of birth control (e.g. condom, pessary, oral contraceptive, intrauterine device (IUD), hormonal implant, vasectomy) during the study period. Female subjects of non-child-bearing potential are defined as having none of following three items.
  - (1) 12 months of spontaneous amenorrhea with no alternative medical cause
  - (2) 6 month or more post surgical bilateral oophorectomy with or without hysterectomy
  - (3) Bilateral tubal ligation
5. As a result of screening test within 7 days prior to Day 1, subject met the following criteria for 1 of the 4 listed fungal infections.
  - (1) Invasive Aspergillosis

Subject meets the following criteria for proven, probable or possible IA

- (a) Proven IA: the subject meets the following criteria 1) or 2)

- 1) Tissue histopathologic, cytopathologic\*, or direct microscopic examination of a needle aspiration or biopsy specimen obtained within 14 days prior to Day 1 showing hyphal forms with evidence of associated tissue damage (either microscopically or as an infiltrate or lesion by imaging)

\*: 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).

- 2) 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 obtained within 14 days prior to Day 1, excluding BAL, cranial sinus cavity, and urine.

(b) Probable IA: the subject meets one host factor, one clinical criteria and one mycological criteria, respectively

- 1) Host factors\*

- i. Recent history of neutropenia ( $0.5 \times 10^9$  neutrophils/L [ $<500$  neutrophils/mm<sup>3</sup>] for  $>10$  days) temporally related to the onset of fungal disease
- ii. Receipt of an allogeneic HSCT
- iii. Treatment with other recognized T-cell immune suppressants, such as cyclosporine, TNF- $\alpha$  blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days.
- iv. 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.
- v. Inherited severe immunodeficiency (such as chronic granulomatous disease or several combined immunodeficiency)

- vi. Host factor which matches to develop invasive aspergillosis (In this case the pre-approval of the sponsor is required and subject meets one clinical criteria and one mycological criteria)

\*: 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.

2) Clinical criteria\*

- i. For lower respiratory tract fungal disease\*\*, the presence of 1 of following 3 signs: 1) dense, well-circumscribed lesions(s) with or without a halo sign, 2) air-crescent sign or 3) cavity on CT
- ii. For tracheobronchitis, tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
- iii. For sinonal infection, Imaging showing sinusitis plus at least 1 of the following 3 signs: 1) Acute localized pain (including pain radiating to the eye), 2) Nasal ulcer with black eschar or 3) Extension from the paranasal sinus across bony barriers, including into the orbit
- iv. CNS infection 1 of the following 2 signs: 1) Focal lesions on imaging, 2) Meningeal enhancement on MRI or CT

\* : Must be consistent with the mycological findings, if any, and must be temporally related to current episode.

\*\*: Every reasonable attempt should be made to exclude an alternative etiology.

3) Mycological criteria

- i. For direct test (cytology, direct microscopy, or culture), Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples obtained within 14 days prior to Day 1, indicated by 1 of the following: 1) Presence of fungal elements indicating a mold or 2) Recovery by culture of a mold (e.g., Aspergillus species)
- ii. For indirect tests (detection of antigen or cell-wall constituents), Galactomannan antigen detected in serum or bronchoalveolar lavage (BAL) fluid [a positive test result defined as a cut-off index  $\geq 1.0$  (single result from serum or BAL) or  $\geq 0.5$  (2 consecutive results from serum samples)]

(c) Possible IA: the subject meets one host factor (vi is not applicable for this criteria) and one clinical criteria, respectively. Of the subject who is enrolled as possible IA, if the subject meets the criteria for proven IA or probable IA

within 7 days of randomization, it is treated as proven IA or probable IA respectively.

(2) Chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis or simple pulmonary aspergilloma)

The subject meets host factor, clinical criteria and mycological criteria with active chronic pulmonary aspergillosis.

(a) Host factors:

The subject has one of the risk factor of chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis or simple pulmonary aspergilloma) (obsolete pulmonary tuberculosis, COPD, bronchiectasis, cavity formulation including cyst, pulmonary nontuberculous mycobacteriosis, interstitial pneumonia or history of chest surgery etc)

(b) Clinical criteria: subject meets the all of following criteria

- 1) The subject has attributable chronic signs and symptoms [e.g. cough, sputum (bloody sputum or hemoptysis etc), dyspnea, pyrexia, weight decrease etc]
- 2) The subject has a shadow [enhancement of cavity, thickness of cavity wall (enhancement of cavity consolidation), fungus ball-like shadow, progression of pleural thickening or niveau etc.] by chest imaging (CT) and it is judged that other causes are negative.

(c) Mycological criteria: the subject meets one of following criteria by mycological testing or serological testing

- 1) Fungal element of Aspergillus species is detected by direct microscopy in biopsy specimen (bronchial mucosa or lung etc.), BAL, sputum, sputum with transtracheal aspiration, pleural effusion or a sample obtained within 14 days prior to Day 1 using any other appropriate method, or recovery of Aspergillus species by culture of samples obtained within 14 days prior to Day 1 (Proven case)
- 2) Aspergillus species is detected by histopathological testing of samples obtained within 14 days prior to Day 1 (Proven case)
- 3) Galactomannan antigen is detected in serum or bronchoalveolar lavage (BAL) fluid [a positive test result defined as a cut-off index  $\geq 1.0$  (single result from serum or BAL) or  $\geq 0.5$  (2 consecutive results from serum samples)], or aspergillus antibody is detected in serum or BAL (Probable case) Aspergillus antibody within 28 days before the initiation of study therapy, it can be used as a screening result.

- (3) Zygomycosis (The subject is assigned to the MK-5592 treatment arm); Fungal infection is strongly suspected based on clinical symptom and/or characteristic imaging findings and meets at least one of the following criteria: If data of (a) and (b) comes from within 14 days before initiation of study therapy, it can be used as a screening result.
  - (a) Fungal elements of *Zygomycota* spp (*Rhizopus*, *Absidia*, *Rhizomucor*, *Mucor*, *Cunninghamella*, etc.) mold in biopsy sample (bronchial mucosa, lung etc.), broncho-aleveolar lavage fluid, sputum, sputum with transtracheal aspiration, pleural effusion, blood and any other appropriate sample by direct microscopy or *Zygomycota* spp. are observed by culture test.
  - (b) *Zygomycota* spp. is detected by histopathologic test.
- (4) Fusariosis (The subject is assigned to the MK-5592 treatment arm); Fungal infection is strongly suspected based on clinical symptom and/or characteristic imaging findings etc. and met at least one of the following criteria: If data of (a) and (b) comes from within 14 days before initiation of study therapy, it can be used as a screening result.
  - (a) Fungal elements of *Fusarium* spp. mold in biopsy sample (bronchial mucosa, lung etc.), broncho-aleveolar lavage fluid, sputum, sputum with transtracheal aspiration, pleural effusion, blood and any other appropriate sample by direct microscopy or *Fusarium* spp. are observed by culture test.
  - (b) *Fusarium* spp. is detected by histopathologic test.

### **5.1.3 Subject Exclusion Criteria**

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

1. The subject is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with the trial.
2. The subject has fungal infection other than *Aspergillus* spp., Zygomycetes (including *Mucor* spp.) and *Fusarium* spp. infection.
3. The subject has allergic bronchopulmonary aspergillosis, allergic sinusitis of aspergillosis or aspergillosis of the eye.
4. The subject with long-term inactive aspergilloma which are not expected to develop the radiological response and clinical response by investigational product.
5. The subject is not expected to survive for this study duration.

6. The subject with an underlying disease, complication(e.g. bacterial pneumonia which is difficult to be distinguished from study target infection or aspiration pneumonia) or systemic condition which makes it difficult to evaluate the efficacy and safety of the study drug.
7. The subject has received any systemic antifungal therapy for the treatment of this infection who cannot discontinue this treatment or has improve/tend improve for this infection (The subject whose fungal infection does not improve/tend to improve can switch from existing medication to study drug).
8. The subject is expected to need prohibited medications in the following durations.

Table 13 Prohibited Medications

Prohibited Medications	Duration
Systemic antifungal therapy (oral, intravenous or inhaled) for treatment of this infection. Note that new antifungal therapy must not be started during the study medication for this infection.	Randomization to end of treatment
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.	Prior 28 days of Day 1 to end of treatment
Prophylaxis of deep-seated fungal infection with systemic antifungal drugs.	Randomization to end of treatment
Medications that are known to interact with azole and may lead to life-threatening side effects (QT prolongation, ventricular arrhythmia including torsades de pointes etc.) : ebastine, pimozide and quinidine.	Prior 24 hours of Day 1 to end of treatment
Ergot alkaloids (ergotamine, dihydroergotamine or other licensed or investigational members of this class).	Prior 2 days of Day 1 to end of treatment
Medications that are known to result in a false positive galactomannan EIA (Aspergillus antigen) result: amoxicillin/clavulanate	From the date of informed consent to end of treatment
Medications known to lower the serum concentration/efficacy of azole antifungals: barbiturates <sup>a</sup> , carbamazepine, isoniazid, phenytoin, rifabutin, rifampicin <sup>b</sup> , and St John's Wort <sup>a</sup> (hypericum perforatum).	Prior 24 hours of Day 1 to end of treatment
Cyclophosphamide	Prior 24 hours of Day 1 to end of treatment
Ritonavir <sup>a</sup> and efavirenz	Prior 24 hours of Day 1 to end of treatment
Vinca Alkaloids	Prior 24 hours of Day 1 to end of treatment
Triazolam <sup>a</sup>	Prior 24 hours of Day 1 to end of treatment
HMG-CoA reductase inhibitors metabolized via CYP3A4 <sup>c</sup>	Prior 24 hours of Day 1 to end of treatment

<sup>a</sup>: After randomization, it is applicable to only the subject assigned to voriconazole treatment arm.

<sup>b</sup>: After randomization, it is applicable to the subject assigned to voriconazole treatment arm, but in case of co-administration in subject assigned to MK-5592 treatment arm, refer to the recommendation (Section 5.5.1).

<sup>c</sup>: After randomization, it is applicable to the subject assigned to MK-5592 treatment arm, but in case of co-administration in subject assigned to voriconazole treatment arm, refer to the recommendation (Section 5.5.1)

9. The subject meet the following criteria;
  - (1) The subject has received MK-5592.
  - (2) The subject has received voriconazole\* for this infection in the past, and has deep-seated fungal infection which is not effective for this treatment.
  - (3) The subject has intolerance for azole fungal treatment.
  - (4) The subject who is receiving two or more systemic antifungal combination therapy for chronic pulmonary aspergillosis at the time when informed consent is obtained.
10. The subject has known hypersensitivity including serious drug allergy, shock or anaphylaxis to any medication [including hypersensitivity to azole agents or rash (regardless of seriousness) caused by these agents].
11. The subject has any known history of Torsade de Pointes, a history of recent myocardial infarction within 90 days of study entry, or subject has a congenital or acquired long QT interval syndrome (including administration of drug which prolongs QT interval) or have a unstable cardiac arrhythmia.
12. The subject has QTc interval  $\geq$  450 msec on electrocardiogram performed at screening.
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 on screening labs) at the time of randomization.
14. The subject has liver cirrhosis or cholestasis at the time of randomization.
15. The subject has renal insufficiency (estimated creatinine clearance  $<$  30 mL/min.) or on hemodialysis at the time of randomization or is likely to require dialysis during the study.  
In subject with estimated creatinine clearance of 30~50 mL/min and who receive IV formulation of MK-5592 or voriconazole, serum creatinine is carefully monitored. If serum creatinine is increased, switching to the oral therapy should be considered. Worsening of renal impairment may be occur due to accumulation of sulfobutylether-beta-cyclodextrine sodium.(creatinine clearance should be calculated by using Cockcroft-Gault Equation)
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 or melanoma at the time of randomization or a prior history of malignant melanoma within 5 year of study entry\*.
19. A subject has known or suspected Gilbert's disease at the time of randomization\*.
20. The female subject is pregnant, intends to become pregnant during 14 days from the end of study treatment, or is nursing at the time of randomization.
21. The subject has previously enrolled in this study.
22. The subject in the judgment of the investigator/sub investigator, is unfit for entry into this study.

\*: It is not applicable to the subject with zygomycosis or fusariosis.

## **5.2 Trial Treatments**

The treatments to be used in this trial are outlined below in [Table 14](#).

**Table 14 Trial Treatment**

Drug	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-5592 (any one of oral tablet or IV solution must be selected)					
oral tablet	300 mg	QD (BID on Day 1)	Oral	84 days as a general rule	deep-seated fungal infection
IV solution	300 mg	QD (BID on Day 1)	Central intravenous		deep-seated fungal infection
Voriconazole (any one of oral tablet or IV formulation must be selected)					
oral tablet	200 mg (300 mg on Day 1)	BID	Oral	84 days as a general rule	deep-seated fungal infection
IV formulation	4 mg/kg(6 mg/kg on Day 1)	BID	intravenous		deep-seated fungal infection
If formulation is switched during the study, loading dose must not be administered again. From the date of switching formulation, maintenance dose administration should be continued.					

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

### **5.2.1 Dose Selection/Modification**

#### **5.2.1.1 Dose Selection**

Investigator / sub-investigator will select the initial formulation according to the subject's condition. Subjects who have central intravenous catheter or are judged to be able to administer via central venous at the timing of randomization by investigator will start with MK-5592 IV solution or voriconazole IV. Administration of MK-5592 IV solution or

voriconazole IV need to be considered for the subjects who present with or are expected to have intolerance to oral study drug administration (e.g. conditions which may interfere with oral intake or absorption of study drug such as vomiting or oral mucosal disorders). Subjects who are judged to be able to take the tablet at the timing of randomization by investigator will start with MK-5592 solid oral tablet or voriconazole tablet.

After the initiation of the IV formulation, transition from IV to oral therapy on or after Day 9 may occur when the subject is considered clinically stable and able to take oral administration by investigator's discretion. When switching the formulation, the investigator must evaluate the overall response. In case that subject who started using oral formulation cannot continue to receive the oral formulation during the treatment, investigator must evaluate the overall response at that time and conduct the discontinuation procedure. Data gathered on the day of switching formulation or preceding day can be used as an overall response at the switching formulation [However, if the subject is a patient with zygomycosis and joins the extension period, the switch of the formulation(iv↔tablet) could be done based on the subject's condition but dose modification of MK-5592 must not be allowed and the investigator does not need to evaluate the overall response at the timing of switching the formulation].

For subjects with estimated creatinine clearance of 30~50 mL/min who receive IV formulation of MK-5592 or voriconazole, serum creatinine is carefully monitored. If serum creatinine is increased, switching to the oral therapy should be considered. Worsening of renal impairment may occur due to accumulation of sulfobutylether-beta-cyclodextrine sodium.

#### 5.2.1.1.1 MK-5592 IV Solution

[Table 15](#) provides the dosing of MK-5592 for subjects randomized to the MK-5592 treatment arm if on IV therapy.

MK-5592 IV infusions will be prepared in 5% dextrose in water or saline. See the procedure separately for detail of MK-5592 IV formulation preparation. MK-5592 IV infusion is prepared as the time of use, but if necessary, the IV infusions may be prepared up to 18 hours prior to administration and stored at 2°C to 8°C refrigerated. The IV infusions should return to room temperature prior to administration.

MK-5592 IV will be given every 12 hours on Day 1, with infusions being not less than 9 hours or no more than 15 hours apart. The subsequent MK-5592 IV infusions will be administered once daily at approximately the same time every day with 24 hours apart, with infusions being not less than 21 hours or no more than 27 hours apart (infusions on Day 2 should not be less than 9 hours or no more than 15 hours apart). IV infusions should be administered for approximately 1.5 hours via a peripherally inserted central catheter or a dedicated lumen of a central venous catheter. Starting and stopping time of every infusion must be correctly recorded. Before and after infusion, investigator/sub-investigator will observe at the subject's infusion site.

If the dosing of study medication is delayed, the dose should be administered as soon as possible. Regarding the dose on or after Day 2, 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 source documentation and eCRF.

Exceptionally, first dose could be in the night on Day 1. In case that the first dose is in the night, second dose could be in the morning on Day 2 approximately 12 hours apart from the first dose, third dose could be in the night on Day 2 approximately 12 hours apart from the second dose, and following doses from Day 3 could be in the night at approximately the same time every day with 24 hours apart with dosing being not less than 21 hours or no more than 27 hours apart. Also, if the dosing time need to be changed due to subject's schedule or operational handling (e.g., from QD dosing in pm to QD dosing in am), the dosing time could be adjusted within the range of allowance (scheduled time -/+3 hours). However, approximate dosing time needs to be fixed by Day 5(e.g. QD dosing is done at approximately 9:00am every day from Day 5).

Table 15 Dosing for MK-5592 IV Therapy for Cohort 2

	Day 1	Day 2-84*
Dose	300 mg BID	300 mg QD
Volume	250 mL (150 mL can be acceptable as needed)	
Infusion duration	1.5 hr	

\*: It should be conducted on or after Day 9 if subject need to switch the formulation of study drug.

### 5.2.1.1.2 MK-5592 Solid Oral Tablet

**Table 16** provides the dosing of MK-5592 for subjects randomized to the MK-5592 treatment arm if on oral therapy.

MK-5592 oral tablet will be given every 12 hours on Day 1, with being not less than 9 hours or no more than 15 hours apart, and will be given once daily at approximately the same time every day with 24 hours apart on or after Day 2, with doses being not less than 21 hours or no more than 27 hours apart (doses on Day 2 should not be less than 9 hours or no more than 15 hours apart). MK-5592 solid oral tablet can be administered with or without the food, investigator instructs that all cases should be properly documented in the administration diary (dosage amount, and food intake data within 2 hours before or within 1 hour after taking study drug etc.).

If the dosing of study medication is delayed, the dose should be taken as soon as possible. Regarding the dose on or after Day 2, if it is more than 12 hours since the missed dose, the missed dose should be skipped and the next dose should be administered at the regularly scheduled time. If a subject vomits within 15 minutes of MK-5592 solid oral administration, the dosing should be repeated as soon as possible, following appropriate antiemetic treatment. Any missed doses should be properly documented in the subject's source documentation and eCRF.

Exceptionally, first dose could be in the night on Day 1. In case that the first dose is in the night, second dose could be in the morning on Day 2 approximately 12 hours apart from the first dose, third dose could be in the night on Day 2 approximately 12 hours apart from the second dose, and following doses from Day 3 could be in the night at approximately the same time every day with 24 hours apart with dosing being not less than 21 hours or no more than 27 hours apart. Also, if the dosing time need to be changed due to subject's schedule or operational handling (e.g., from QD dosing in pm to QD dosing in am), the dosing time could be adjusted within the range of allowance (scheduled time -/+3 hours). However, approximate dosing time needs to be fixed by Day 5 (e.g. QD dosing is done at approximately 9:00am every day from Day 5).

Table 16 Dosing for MK-5592 Oral Therapy for Cohort 2

	Day 1	Day 2-84
Dose	300 mg(3 tablets) BID	300 mg(3 tablets) QD

### 5.2.1.1.3 Voriconazole IV

[Table 17](#) provides the dosing of voriconazole for subjects randomized to the Voriconazole treatment arm if on IV therapy.

Voriconazole IV infusions will be prepared in 5% dextrose in water or saline. See the procedure separately for detail of Voriconazole IV formulation preparation. Voriconazole IV infusion is prepared at the time of use, and it should be administered promptly after the preparation.

Initial dosage is decided based on the weight on the day of registration. Voriconazole IV will be administered 6 mg/kg BID on Day 1 (approximately 12 hour intervals with being not less than 9 hours or no more than 15 hours apart) and followed by 4 mg/kg BID (at approximately the same time every day with 12 hours apart with approximately 12 hour intervals being not less than 9 hours or no more than 15 hours apart). The infusions should not run faster than 3 mg/kg/hr. Starting and stopping time of every infusion must be correctly recorded. Before and after infusion, investigator/sub-investigator will observe at the subject's infusion site.

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 source documentation and eCRF.

Exceptionally, first dose could be in the night on Day 1. In case that the first dose is in the night, second dose could be in the morning on Day 2 approximately 12 hours apart from the first dose, third dose could be in the night on Day 2 approximately 12 hours apart from the second dose, and following BID doses from Day 3 could be in the morning and night at approximately the same time every day with 12 hours apart with dosing being not less than 9 hours or no more than 15 hours apart. Also, if the dosing time need to be changed due to subject's schedule or operational handling, the dosing time could be adjusted within the range of allowance (scheduled time -/+3 hours). However, approximate dosing time needs to be fixed by Day 5.

Table 17 Dosing for Voriconazole IV Therapy

	Day 1	Day 2-84*
Dose	6 mg/kg BID	4 mg/kg BID
Volume	The final concentration is not less than 0.5 mg/mL nor greater than 5 mg/mL	
Infusion duration	The infusion should not run faster than 3 mg/kg/hr.	

\* : It should be conducted on or after Day 9 if subject need to switch the formulation of study drug. Dose adjustment may be performed based on the trough concentration of voriconazole.

#### 5.2.1.1.4 Voriconazole Oral Tablet

Table 18 provides the dosing of voriconazole for subjects randomized to the Voriconazole treatment arm if on oral therapy.

Voriconazole tablets will be administered as a 300 mg dose BID on Day 1 (approximately 12 hour intervals with being not less than 9 hours or no more than 15 hours apart) and followed by 200 mg dose BID (at approximately the same time every day with approximately 12 hour intervals being not less than 9 hours or no more than 15 hours apart). Voriconazole oral tablets SHOULD NOT BE TAKEN WITH A MEAL, and all cases should be taken at least one hour before or one hour following a meal. Investigator should instruct subject that all doses should be properly documented in the administration diary (dosage amount, and food intake data within 1 hour before or within 1 hour after taking study drug etc.). 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. 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.

If a subject vomits within 15 minutes of Voriconazole oral administration, the dosing should be repeated as soon as possible, following appropriate antiemetic treatment. Any missed doses should be properly documented in the subject's source documentation and eCRF.

Exceptionally, first dose could be in the night on Day 1. In case that the first dose is in the night, second dose could be in the morning on Day 2 approximately 12 hours apart from the first dose, third dose could be in the night on Day 2 approximately 12 hours apart from the second dose, and following BID doses from Day 3 could be in the morning and night at approximately the same time every day with 12 hours apart with dosing being not less than 9 hours or no more than 15 hours apart. Also, if the dosing time need to be changed due to subject's schedule or operational handling, the dosing time could be adjusted within the range of allowance (scheduled time -/+3 hours). However, approximate dosing time needs to be fixed by Day 5.

Table 18 Dosing for Voriconazole Oral Tablet

	Day 1	Day 2-84*
Dose	300 mg (6 tablets) BID	200 mg (4 tablets) BID

\* : Dose adjustment may be performed based on the trough concentration of voriconazole.

### 5.2.1.2 Dose Modification (Escalation/Titration/Other)

Dose modification of MK-5592 must not be allowed. On the other hand, during the study treatment, measurement of voriconazole concentration in plasma and subsequent TDM is recommended to be performed. The frequency of blood sampling for TDM is judged by the investigator's discretion. Based on the result of voriconazole concentration in plasma, in case of concern about safety and efficacy, dose adjustment of voriconazole should be performed based on the result of TDM, with the dose modified at the investigator's discretion. In case of adjustment of dosage, TDM must be performed. Voriconazole concentration in plasma is recommended between  $\geq 1$ -2  $\mu\text{g}/\text{mL}$  and  $\leq 4$ -5  $\mu\text{g}/\text{mL}$  from efficacy and safety point of view. In this case, upper limit of dosing is 6 mg/kg BID for IV formulation and 300 mg BID for oral formulation. If dose adjustment is performed, voriconazole concentration in plasma should be appropriately monitored after the dose adjustment. Any dose adjustment and voriconazole concentration in plasma should be properly documented in the subject's source documentation and eCRF.

In case of interruption due to adverse event, a temporary interruption of no more than 3 sequential days without study medication will be allowed with resumption of treatment.

### 5.2.1.3 Treatment Duration

As a general rule, the treatment duration of all diseases is 84 days (77-84 days with considering the final treatment allowance). [However, for the subjects with zygomycosis, restart of the study therapy after finishing 84 day maximum treatment period or extension of treatment period could be done under the extension period with the prior approval from the Sponsor and obtaining the signing of a new informed consent from the only subject who have responded to the study therapy without intolerant toxicity if the investigator thinks that continuation of MK-5592 therapy would benefit the subjects with ample consideration of the MK-5592 profile and no alternative treatment in Japan (e.g. failure or intolerant to amphotericin B formulation). In addition to the above, in case of restart of the study therapy after the finishing 84 days, it can be done for the only subjects with same zygomycosis episode from the main study therapy (not new episode). The switch of the formulation (iv $\leftrightarrow$ tablet) could be done based on the subject's condition during the extension period but dose modification of MK-5592 must not be allowed. However, the study therapy must be discontinued when MK-5592 is marketed or the development of MK-5592 is discontinued in Japan. As a general rule, study medication information and adverse events are recorded (routine safety laboratory should be also monitored and recorded in the source document) during the study treatment over 84 days but refer to the specific procedure relating this matter including the details of information that should be recorded in CRF.] However, the treatment may be completed earlier if the subject does not need the therapy any longer by the investigator's discretion (e.g. cure of the target infection). The therapy may also be discontinued prematurely if the investigator decides that the patient is not capable of receiving further therapy (e.g. adverse event) although the investigator feels that the patient requires further treatment for the condition under study (refer to section 5.8 for discontinuation criteria).

In the event that the additional work-up does not result in a proven or probable IA diagnosis within 7 days of randomization, subjects should continue participation in the trial with possible IA.

### **5.2.2 Timing of Dose Administration**

MK-5592 will be administered twice a day (12 hours interval) on Day 1 and will be administered every 24 hours on or after Day 2. Voriconazole will be administered twice a day (12 hours interval), however, voriconazole oral tablet should be taken at least one hour before (or at least more than one hour after) a meal.

### **5.2.3 Trial Blinding/Masking**

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

## **5.3 Randomization or Treatment Allocation**

Randomization will occur centrally using an treatment registration center. There are 2 treatment arms. Subjects will be assigned randomized treatment in an 2:1 ratio to MK-5592 treatment arm and Voriconazole treatment arm, respectively. Subjects with fusariosis or zygomycosis will be assigned to the MK-5592 treatment arm. Recruitment is completed when 112 subjects' are randomized (excluding subjects with fusariosis or zygomycosis). Approximately 15 subjects with invasive aspergillosis as a target number will be enrolled.

## **5.4 Stratification**

Randomization will be stratified according to the subject's disease status at the time of randomization following three categories:

1. Proven/probable Invasive aspergillosis at randomization
2. Possible Invasive aspergillosis at randomization
3. Chronic pulmonary aspergillosis at randomization

Within each of these three categories of disease status, subject will be randomized in a 2:1 ratio to the MK-5592 and Voriconazole treatment arms, respectively. Note that chronic pulmonary aspergillosis includes subjects with chronic progressive pulmonary aspergillosis and subjects with simple pulmonary aspergilloma.

## **5.5 Concomitant Medications/Vaccinations (allowed & prohibited)**

Medications or vaccinations specifically prohibited in exclusion criterion 8 are not allowed during the specified period during the trial. Listed below are some specific restrictions for concomitant therapy or vaccination during the course of the trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during

the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the local Clinical Monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

### **5.5.1 Concomitant Medications, Supplements, and Other Substances Allowed During the Trial**

Both MK-5592 and voriconazole are potent inhibitors of CYP3A4. Coadministration of MK-5592 or voriconazole with CYP3A4 substrates may result in large increases in exposure of CYP3A4 substrates. Caution is advised during coadministration of MK-5592/voriconazole 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.

Voriconazole is also metabolized by CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these enzymes may increase or decrease Voriconazole 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 co-administration.

Table 19 Allowed Concomitant Medications and Recommendations

<b>Drug/Drug Class</b>	<b>Recommendations for Drug Dosage Adjustment/Comments</b>
Cyclosporine Tacrolimus	When initiating therapy with study drug follow with monitoring of blood levels of these drugs. Blood level of these drug will be increased when coadministered with MK-5592 or voriconazole. Nephrotoxicity and leukoencephalopathy (including death) have been reported due to elevation of these drugs' concentration in blood. When study drug is discontinued, concentrations must be frequently monitored and the dose adjusted as necessary.
Temsirolimus	When initiating therapy with study drug follow with monitoring of blood levels of this drug. When study drug is discontinued, concentrations must be frequently monitored and the dose adjusted as necessary.
Methadone	Monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.
Fentanyl <sup>a</sup> Oxycodone <sup>a</sup>	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 <sup>a</sup>	Monitoring for adverse events and toxicity related to NSAIDs. Dose reduction of NSAIDs may be needed.

Drug/Drug Class	Recommendations for Drug Dosage Adjustment/Comments
Oral Contraceptives containing ethinyl estradiol and norethisterone <sup>a</sup>	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 <sup>a</sup>	Monitor PT or other suitable anticoagulation tests. Adjustment of warfarin dosage may be needed.
Omeprazole <sup>a</sup>	Monitoring for adverse events is recommended during coadministration.
Antiretroviral therapy other than ritonavir and efavirenz (e.g., fosaprenavir, NNRTIs <sup>a,b</sup> )	Monitoring for adverse events and toxicity related to antiretroviral therapy. Adjustment of antiretroviral therapy dosage may be needed.
Benzodiazepines	Monitoring for adverse events and toxicity (i.e., prolonged sedation) related to benzodiazepines metabolized by CYP3A4 (e.g., midazolam, alprazolam, diazepam <sup>a</sup> ). Adjustment of benzodiazepine dosage may be needed.
Calcium Channel Blockers	Monitoring for adverse events and toxicity related to calcium channel blockers. Adjustment of calcium channel blocker dosage may be needed.
Oral hypoglycemics <sup>a</sup>	Monitoring of blood glucose and for signs and symptoms of hypoglycemia. Adjustment of oral hypoglycemic drug dosage may be needed.
HMG-CoA reductase inhibitors metabolized via CYP3A4 <sup>c</sup>	Monitoring for adverse events and toxicity related to HMG-CoA reductase inhibitors metabolized by CYP3A4. Adjustment of HMG-CoA reductase inhibitors dosage may be needed.
Zorpidem <sup>a</sup>	Monitoring for adverse events and toxicity related to zorpidem. Adjustment of zorpidem dosage may be needed.
Digoxin	Monitoring for adverse events and toxicity related to digoxin. Adjustment of digoxin dosage may be needed.
Theophylline	Monitoring for adverse events and toxicity related to theophylline. Adjustment of theophylline dosage may be needed.
Rifampicin <sup>d</sup>	Carefully monitoring for patient condition because plasma concentration of MK-5592 may be decreased.

<sup>a</sup> It is applicable to the subject who is randomized to voriconazole treatment arm

<sup>b</sup> Non-Nucleoside Reverse Transcriptase Inhibitors

<sup>c</sup> It is applicable to the subject who is randomized to voriconazole treatment arm. It is a prohibited medication to the MK-5592 treatment arm.

<sup>d</sup> It is applicable to the subject who is assigned (or transitioned) to MK-5592 treatment arm. It is a prohibited medication to the voriconazole treatment arm.

### 5.5.2 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.

### 5.6 Rescue Medications & Supportive Care

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

## **5.7 Diet/Activity/Other Considerations**

### **Diet**

Voriconazole tablet should not be taken with a meal, therefore taking a meal should be completed at least one hour before or at least one hour following a dosing.

## **5.8 Subject Withdrawal/Discontinuation Criteria**

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Subject with a prolonged QTc interval of their post baseline ECG: greater than 500 msec.
- Subject who develops clinically indicated visual problems (Grade 3 or more)
- Subject who develops an exfoliative cutaneous reaction, develops a skin lesion consistent with squamous cell carcinoma or melanoma.
- Subject who, during the course of the study, is determined to have an infection caused by an organism that may be insufficiently covered by the current study therapy or some other appropriate concomitant medications.
- Subject who cannot (or don't need to) continue the study therapy (e.g. pregnancy).
- Subject who develop the grade 4 AE with causality related to the study drugs.
- Subject who experiences adrenal insufficiency with associated electrolyte disturbances and related blood pressure grading

## **5.9 Subject Replacement Strategy**

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

## **5.10 Beginning and End of the Trial**

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

## **5.11 Clinical Criteria for Early Trial Termination**

The clinical trial may be terminated early 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. In addition, further recruitment in the trial or at (a) particular trial 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.

## 6.0 TRIAL FLOW CHART

Trial Period:	Screening	Treatment								Post-treatment	Extension <sup>17</sup>
		In-patient <sup>16</sup>			In-patient/Out-patient						In-patient/ Out-patient
Visit Number/Title:	1 Screening	2 Day 1	3 Day 3	4 Day 8	5-8 After Day 8	9 Day 42	10, 11 After Day 42	12 End of treatment or discon <sup>13</sup>	X Day of formulation switch	13 14 days after end of treatment	X
Scheduled Day.:	-7 to -1	1	3	8	14, 21, 28, 35	42	56, 70	84	X	14	X
Scheduling Window Days	-	-	+2	+/-1	+/-3	-3 to +7	+/-6	+2	-1	+7	-
<b>Administrative Procedures</b>											
Informed Consent	x <sup>14</sup>										
Informed Consent for Future Biomedical Research	x										
Subject Identification Card	x										
Inclusion/Exclusion Criteria	x										
Medical History	x										
Prior and Concomitant Medication Review	x	Continuing to confirm									
Physical Examination (clinical finding)	x	x <sup>1</sup>	x	x	x	x	x	x	x	x	
Assessment of Clinical signs and symptom of deep-seated mycosis	x	x <sup>1</sup>	x	x	x	x	x	x	x	x	
Vital signs and weight	x	x <sup>1, 12</sup>	x	x	x	x	x	x	x	x	
Height	x										
12-Lead Electrocardiogram <sup>2</sup>	x	x	x	x		x		x	x	x	
Diagnostic imaging (CT, MRI etc.)	x <sup>4</sup>					x		x	x	x	
Mycology test (culture testing, direct microscopy or histopathological examination etc.) <sup>3</sup>	x <sup>4</sup>					x		x		x	
Serology testing <sup>3</sup>	x <sup>4</sup>		x <sup>5</sup>			x		x	x	x	
Hematology	x	x <sup>1</sup>	x	x	x	x	x	x	x	x	
Serum Chemistry	x	x <sup>1</sup>	x	x	x	x	x	x	x	x	
Serum Pregnancy testing (only for potency of child-bearing female)	x <sup>15</sup>					x		x			
Treatment Allocation/Randomization		x <sup>1, 12</sup>									
Collection of sample to measure MK-5592 plasma concentration (MK-5592 treatment arm) <sup>6,7,8,9</sup>		x	x	x	x	x		x	x <sup>7</sup>		
Blood for Future Biomedical Research <sup>10</sup>		x									
MK-5592, Voriconazole Administration		Everyday									x
Switching the formulation of study drug <sup>11</sup>									x		

Trial Period:	Screening	Treatment								Post-treatment	Extension <sup>17</sup>
		In-patient <sup>16</sup>			In-patient/Out-patient						In-patient/Out-patient
Visit Number/Title:	1 Screening	2 Day 1	3 Day 3	4 Day 8	5-8 After Day 8	9 Day 42	10, 11 After Day 42	12 End of treatment or discon <sup>13</sup>	X Day of formulation switch	13 14 days after end of treatment	X
Scheduled Day.:	-7 to -1	1	3	8	14, 21, 28, 35	42	56, 70	84	X	14	X
Scheduling Window Days	-	-	+2	+/-1	+/-3	-3 to +7	+/-6	+2	-1	+7	-
Dispensing and collecting of study drug, confirmation for number of study drug		x								x	x
Issuing, collecting and confirming the medication diary (oral administration)		x								x	x
Assessment of overall response (including clinical response, radiological response, and mycological response) <sup>11</sup>					xx	x	xx	x	x		
Adverse Events Monitoring		← Continuing to confirm →									x

x: must be done

xx: will be done as needed

1. Procedure must be done before the initiation of study therapy. If conducted on a same date, measurement and evaluation is not needed 2 times.
2. 12-lead ECG is tried to perform at the timing of maximum serum drug concentration. Recommended timing is as follows;
  - MK-5592 IV solution: just after the end of treatment
  - MK-5592 solid oral tablet: 3 to 5 hours after the treatment
  - Voriconazole IV: just after the end of treatment
  - Voriconazole oral tablet: 1 to 2 hours after the treatment
3. Subjects enrolled with a part of these testings, mycology testing and mycological serology testing (aspergillus antigen, antibody and β-D-glucan) must be performed. Mycological testings must be performed during the treatment and EOT excluding eradication of the sample enable to collect. Aspergillus antibody is performed for the subject with chronic pulmonary aspergillosis and is performed at the screening only. Serology testing is no need for subjects with Zygomycosis and Fusariosis
4. Data comes from within 7 days before initiation of study therapy, it can be used as a screening result. For the mycology test (culture testing, direct microscopy or histopathological examination etc.), data comes from within 14 days before initiation of study therapy can be used as a screening result. Aspergillus antibody testing, data comes from within 28 days before initiation of study therapy can be used as a screening result. Mycology test shroud be done by following 7.1.2.6 Mycology Testing and the isolated fungus should be provided to the central laboratory.
5. Only for the subject with invasive aspergillosis.
6. Intravenous treatment (The plasma samples for PK evaluation in the subjects with zygomycosis during the extension period will not be needed)
  - a: Day 1;30 minutes before the treatment, just before the first treatment, 6 to 10 hours after the initiation of the infusion and just before the treatment of second infusion. Blood sampling after the treatment on Day 1 (just before the end of first infusion, 6 to 10 hours after the initiation of the infusion and just before the treatment of second infusion) can be performed after the second dosing if it is difficult to perform the blood sampling after the first dosing.
  - b: Day 3, Day 14, Day 28, Day 42 and end of treatment; 30 minutes before the treatment
  - c: Day 8; 30 minutes before the treatment, just before the end of infusion, 2 to 3 hours after the initiation of infusion, 8 to 10 hour after the initiation of treatment and 30 minutes before the next day treatment.
  - d: At the time of interruption or discontinuation due to adverse events, or at the incidence of serious adverse events by MK-5592 administration.

7. Oral administration (The plasma samples for PK evaluation in the subjects with zygomycosis during the extension period will not be needed)
  - a: Day 1; 30 minutes before the treatment, 2 to 4 hour after the first treatment, 6 to 10 hours after the treatment and just before the second treatment. Blood sampling after the treatment on Day 1 (2 to 4 hours after the first treatment, 6 to 10 hours after the treatment and just before the second treatment) can be performed after the second dosing if it is difficult to perform the blood sampling after the first dosing
  - b: Day 3, Day 14, Day 28, Day 42 and end of treatment; 30 minutes before the treatment
  - c: Day 8; 30 minutes before the treatment, 2 to 3 hour after the treatment, 4 to 6 hours after the treatment, 8 to 10 hour after the treatment and 30 minutes before the next day treatment.
  - d: At the time of interruption or discontinuation due to adverse events, or at the incidence of serious adverse events by MK-5592 administration.
  - e: After 7 days of switching formulation; 30 minutes before the treatment and 2 to 6 hour after the treatment (only for the subject who switch from IV to oral)
8. Early discontinuation subjects who has discontinued this study before Day 8 or Day 9 PK sample collection, PK sample should have collected regulation point Day 8 and/or Day 9 sample on study discontinuation if possible (Oral administration; 30 minutes before the treatment, 2 to 3 hour after the treatment, 4 to 6 hours after the treatment, 8 to 10 hour after the treatment and 30 minutes before the next day treatment., intravenous administration; 30 minutes before the treatment, just before the end of infusion, 2 to 3 after the initiation of infusion, 8 to 10 hour after the initiation of treatment and 30 minutes before the next day treatment.).
9. Early discontinuation subject cannot collect sample of 30 minutes before the final treatment, PK sample should be collected on as at discontinuation if possible. If PK sample collected on discontinuation day, the other PK sample does not require. Also, PK sample should be collected on day of interruption due to adverse events or at the incidence of serious adverse events by MK-5592 administration, but if PK sample are collected on the same day, the other PK sample for interruption or serious adverse events is not required (However, the plasma samples for PK evaluation in the subjects with zygomycosis during the extension period will not be needed).
10. Informed consent for future biomedical research 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.
11. At the switching formulation (from IV to PO), investigator must evaluate the overall response (including clinical response, radiological response, and mycological response). Data conducted on the day of switching formulation or preceding day can be used as an overall response at the switching formulation. In case that subject who started using oral formulation cannot continue to receive the oral formulation during the treatment, investigator must evaluate the overall response at that time and conduct the discontinuation procedure [However, if the subject is a patient with zygomycosis and joins the extension period, the switch of the formulation(iv↔tablet) could be done based on the subject's condition but dose modification of MK-5592 must not be allowed and the investigator does not need to evaluate the overall response at the timing of switching the formulation].
12. Weight measurement and Treatment Allocation may be conducted between Day -1 and Day 1. Treatment allocation and weight measurement should be conducted on the same date. Weight used for treatment allocation should be considered as basis of the dosing calculation. When conducting the Visit 2 weight measurement on Day -1, weight measurement does not need to be repeated on Day 1.
13. As a general rule, treatment duration of all disease is 84 days (77-84 days with considering the treatment allowance). At the EOT (completion and discontinuation) visit before the transition to the extension period, procedure other than dose administration should be conducted within EOT +2 days. At the end of treatment or discontinuation, procedure at EOT should be conducted before starting other systemic antifungal therapy[However, if the subject is a patient with zygomycosis and joins the extension period, procedure at visit 12/EOT does not need to be conducted at the last dose of MK-5592 therapy in the extension period].
14. Informed Consent could be obtained prior 28 days of Day 1.
15. Urine pregnancy testing can be conducted. Even though urine pregnancy testing is conducted, serum pregnancy testing should be conducted as a screening testing.
16. Hospitalization is required until all procedures other than study drug administration are completed on Day 9 (9 days and 8 nights after the initiation of study drug). To closely monitor the subject's safety especially at the beginning of the study in addition to the all study periods. At the discretion of the investigator, subjects may be requested in remain in the investigator's site longer.
17. [REDACTED]

## **7.0 TRIAL PROCEDURES**

### **7.1 Trial Procedures**

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

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

#### **7.1.1 Administrative Procedures**

##### **7.1.1.1 Informed Consent**

The investigator must obtain documented consent from each potential subject prior to participating in a clinical trial or Future Biomedical Research.

###### **7.1.1.1.1 General Informed Consent**

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

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

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

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

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

#### **7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research**

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

#### **7.1.1.2 Inclusion/Exclusion Criteria**

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial. Diagnosing the deep-seated fungal infection and identifying the infected site will be appropriately recorded in the source document and eCRF.

#### **7.1.1.3 Subject Identification Card**

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

#### **7.1.1.4 Medical History**

A medical history will be obtained and recorded by the investigator or qualified designee.

#### **7.1.1.5 Prior and Concomitant Medications Review**

##### **7.1.1.5.1 Prior Medications**

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record the anti-fungal drug taken by the subject within 30 days before starting the study treatment, anti-bacterial drug taken by the subject within 14 days before starting the study treatment and record any other prior medication taken by the subject within 3 days before starting the study treatment.

##### **7.1.1.5.2 Concomitant Medications**

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

#### **7.1.1.6 Assignment of Screening Number**

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

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

#### **7.1.1.7 Assignment of Randomization Number**

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

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

#### **7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)**

Interruptions from the protocol specified treatment plan for 4 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

In case of administration of trial medication (IV formulation), administration will be witnessed by the investigator and/or trial staff.

In case of administration of trial medication (oral formulation), the way of the administration of trial medication will be informed to the subjects by the investigator and/or designee. The investigator and/or designee provides the direction that trial medication and meal should be recorded in the medication diary. The subjects bring the medication diary when subjects visit the hospital, and the medication diary will be confirmed by the investigator and/or designee. The medication diary is stored at the study site after the clinical trial. All the information of trial medication and meal should be recorded in the source document and eCRF.

### **7.1.2 Clinical Procedures/Assessments**

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

#### **7.1.2.1 Physical Examination**

Physical examination is performed at the specified visit and recorded in the source document. In case of abnormal physical findings compared to the baseline after the initiation of study treatment, the investigator/sub-investigator assesses and records whether the physical findings are adverse event, or not in the source document and eCRF.

#### **7.1.2.2 Clinical Signs and Symptoms of Deep-Seated Fungal Infection**

Attributable clinical signs and symptoms of deep-seated fungal infection [cough, dyspnea, sputum, bloody sputum, hemoptysis, pain, pyrexia and weight decreased etc.] are identified, and assessed through the existence and severity of vital signs and shifts of clinical laboratory

values (CRP etc.) for reference and recorded in the source document and eCRF at the scheduled visit. Intensity is evaluated in the following criteria.

Absense: There is no symptom or observation.

Mild: Grade 1 symptom or observation defined by the CTCAE grading (version 4.0).

Moderate: Grade 2 symptom or observation defined by the CTCAE grading (version 4.0).

Severe: Grade 3(or more) symptom or observation defined by the CTCAE grading (version 4.0).

#### **7.1.2.3 Vital Signs**

Temperature (oral, axilla or archo), pulse, blood pressure, weight and SpO<sub>2</sub> will be measured and recorded in the source document and eCRF at the scheduled visit. If it is difficult to measure these testing based on the subject's condition, it may not be done. Temperature recorded should be highest (maximum temperature) in each day. In principle, measuring method is same throughout the study. If the temperature is measured other than scheduled visit during the study, all of these data should be recorded in the source document and eCRF.

#### **7.1.2.4 12-Lead Electrocardiogram**

12-lead electrocardiogram is performed using standard equipment that can be measured for ventricular rate, RR, PR, QRS, QT and QTc interval. 12-lead electrocardiogram is performed at the scheduled or unscheduled visit and tried to measure at the time of the highest plasma concentration. Serum electrolytes (K, Ca, Mg) must be measured on the same day and recorded in the source document and eCRF, in case an unscheduled 12-lead electrocardiogram is performed. Clinically abnormal findings in the electrocardiogram will be followed up until recovering to the baseline value or stabilization appropriately. If QTc interval is greater than 500 msec, study treatment must be discontinued.

#### **7.1.2.5 Diagnostic Imaging**

The type of imaging used (e.g. CT or MRI) will depend on the site of infection. For pulmonary sites of infection, 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. Imaging must be performed at the scheduled visit and all imaging must be recoded and stored at the study site appropriately, and masked imaging is provided to the sponsor or the designated imaging facility. In case of performing imaging at the unscheduled visit, the masked imaging may be provided to the sponsor or the designated imaging facility by the direction of clinical adjudication committee or trial physician for the assessment. The imaging at the unscheduled visit also must be recoded and stored at the study site appropriately. In addition, imaging performed in the time when the subject condition was good and antifungal treatment was not needed may be provided to the sponsor or the designated imaging facility after being masked by the direction of clinical adjudication committee or trial physicians for the assessment.

#### **7.1.2.6 Mycology Testing**

Mycology testing is performed and fungal infection is observed by using the appropriate method. Even if causative fungus is identified by mycological serology testing, direct microscopy or histopathological examination, culture testing must be performed. Causative fungus is isolated from culture sample and its genus is identified at the study site. Fungal infection is followed throughout the trial by repeating the same mycology testing based on subjects' condition in principle. The fungus isolated by culture testing is provided to the central laboratory and its species is identified and minimum inhibitory concentration (MIC) testing is performed at the central laboratory. At the study site, isolated fungus is appropriately stored until identification of species. If the fungus isolated by culture testing done at the time other than the specified visit in the protocol, this is also provided to the central laboratory and isolated fungus is appropriately stored at the study site until identification of species.

If the microorganisms other than fungus are isolated by culture testing, all of these data should be recorded in the source document and eCRF appropriately.

#### **7.1.2.7 Serology Testing (Aspergillus Antigen, Aspergillus Antibody and $\beta$ -D-Glucan)**

Aspergillus antigen, antibody and  $\beta$ -D-glucan are measured at the scheduled visit and their result is recorded in the source document and eCRF appropriately. Aspergillus antibody is measured at the screening only. If the aspergillus antigen and  $\beta$ -D-glucan are measured at the unscheduled visit, all of these data should be recorded in the source document and eCRF appropriately. This testing does not need to be measured for the subjects with fusariosis and zygomycosis.

#### **7.1.2.8 Sample Collection for Plasma Concentration of MK-5592 (MK-5592 Treatment Arm)**

Blood sample for plasma concentration of MK-5592 is collected on the scheduled visit. Volume of the blood sampling is 2 mL/time. Blood sampling must be collected via other location different from the location of study administration. Regarding the sampling points of just before the end of first infusion on Day 1 and 8 for MK-5592 IV solution, blood sampling should be done before flushing. From the feasibility point of view, blood sampling after the treatment on Day 1 (IV solution: just before the end of first infusion, 6 to 10 hours after the initiation of the infusion and just before the treatment of second infusion, solid oral tablet: 2 to 4 hours after the first treatment, 6 to 10 hours after the treatment and just before the second treatment) can be performed after the second dosing if it is difficult to perform the blood sampling after the first dosing (e.g. in case that the first dose is in the night). If it is difficult to perform the blood sampling at the just before the second treatment/infusion, it may not be done but the reason for not performing the blood sampling must be recorded in the source document and eCRF. Blood sampling after the first dosing on Day 1 (or second dosing) should be performed at least 3 hours apart among these sampling points (IV solution: 6 to 10 hours after the initiation of the infusion and just before the treatment of second infusion, solid

oral tablet: 6 to 10 hours after the treatment and just before the second treatment). Sampling date and time must be correctly recorded in the source document and eCRF.

#### **7.1.2.9 Evaluation for Overall Response**

The individual response assessment (Clinical Response, Radiological Response, Mycological Response and Clinical Laboratory Response) in subjects with deep-seated fungal infection will be evaluated at Day 42, EOT(before the transition to the extension period) and switching formulation according to the criteria described in 4.2.3.1, and Overall Response is assessed based on these individual responses (However, if the subject is a patient with zygomycosis and joins the extension period, the individual response assessment at switching formulation or the last dose of MK-5592 therapy in the extension period does not need to be done). Overall response assessed by investigator and information are provided to the Clinical adjudication committee. CAC assessed the overall response according to the same criteria. The assessment by CAC is used as a Primary efficacy endpoint.

#### **7.1.2.10 Guidance for Treatment of adverse event**

When a subject shows an adverse event, the investigators should always consider the necessity of treatment of adverse events as soon as possible regardless of the relationship to study drugs. The investigators should carefully monitor all testing results including those that are not usually done in the routine medical examination in the sites and treat the adverse events as soon as possible before they have an effect on subjects or lead to study discontinuations. Considering the safety profile of the study drugs, the following treatment may be considered but not limited to these adverse events or treatments. It is always important to consider the treatment of adverse events first.

- Pyrexia

Most of these adverse events reported in previous clinical studies were mild to moderate and reversible. Pyrexia is one of the major signs of infection, and it is important to identify the cause of pyrexia. Thus, if pyrexia is not related to target infection of the study, any clinical testing and assessment need to be attempted to identify the cause of pyrexia such as bacterial infection. Antibacterials, antipyretics or any other appropriate treatment should be considered based on the clinical testing.

- Gastrointestinal events (nausea, vomiting, abdominal pain or diarrhea)

Most of these adverse events reported in previous clinical studies were mild to moderate and reversible. Appropriate antiemetic or antiflatulent treatment should be considered.

- Hepatic events (including asymptomatic elevations in transaminases and/or bilirubin)

Most of hepatic adverse events reported in previous clinical studies were mild to moderate and reversible. Interruption of suspicious concomitant drugs and/or adding hepatic function improving drugs should be considered.

- Visual disturbance

Most of these adverse events reported in previous clinical studies were mild to moderate and reversible without treatment.

If adverse events relate to study medication and they become a major issue in spite of the above attempt, interruption of study drugs should be considered before study drug discontinuation.

### **7.1.2.11 Domiciling**

Hospitalization is required until all procedures other than study drug administration are completed on Day 9 (9 days and 8 nights after the initiation of study drug). At the discretion of the investigator, subjects may be requested to remain in the investigator's site longer.

### **7.1.3 Laboratory Procedures/Assessments**

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory testing is performed in the local laboratory (or its outsourcing). Laboratory testing is performed at the timing of dosage in scheduled visit. The total amount of blood to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4. If abnormal laboratory findings are observed, its abnormality is appropriately followed up until stabilization or recovery to baseline.

#### **7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)**

Laboratory tests for hematology, chemistry are specified in [Table 20](#) to [Table 22](#).

Table 20 Laboratory Tests (Hematology)

Red blood cell count (RBC)
Hemoglobin
Hematocrit
Platelet count
White blood cell count (WBC)
WBC differential (neutrophil, eosinophil, basophil, lymphocyte, monocyte)

Table 21 Laboratory Tests (Blood Chemistry)

Total protein	Blood Urea Nitrogen
Albumin	Creatinine
Aspartate aminotransferase (AST)	Uric acid
Alanine aminotransferase (ALT)	CRP
Alkaline phosphatase	Calcium
LDH	Chloride
Total Bilirubin	Potassium
Direct Bilirubin	Sodium
	Magnesium

Table 22 Laboratory Test (Other)

Serum hCG (Total hCG or $\beta$ -hCG): female subjects of childbearing potential
Aspergillus antibody (only for subject with Chronic pulmonary aspergillosis): perform at Screening visit only
Galactomannan antigen (ELISA): perform for the subject with aspergillosis only
$\beta$ -D-Glucan: perform for the subject with aspergillosis only

Serum electrolytes (K, Ca, Mg) must be measured on the same day and recorded in the source document and eCRF, in case an unscheduled 12-lead electrocardiogram is performed. In case adrenal insufficiency is observed, serum electrolytes (K, Ca, Mg) must be measured, evaluated and recorded in the source documents and eCRF.

If CRP is measured at the unscheduled visit, all of these data are recorded in the source document and eCRF appropriately.

Urine pregnancy testing can be conducted for confirmation of subject eligibility and it is not required to record in the eCRF. Even though urine pregnancy testing is conducted, serum pregnancy testing should be conducted as a screening testing and it is recorded in the source document and eCRF appropriately.

### 7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

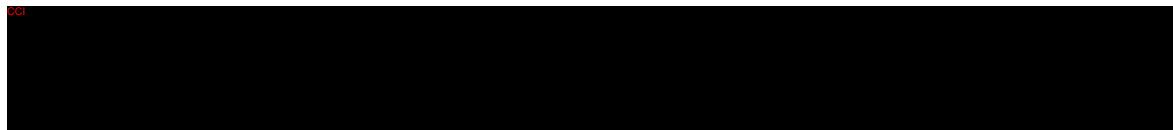
Measurement for PK analysis will be performed in collected samples.

#### 7.1.3.2.1 Blood Collection for Plasma MK-5592

Sample collection, storage and shipment instructions for plasma samples will be provided separately.

### **7.1.3.3 Future Biomedical Research**

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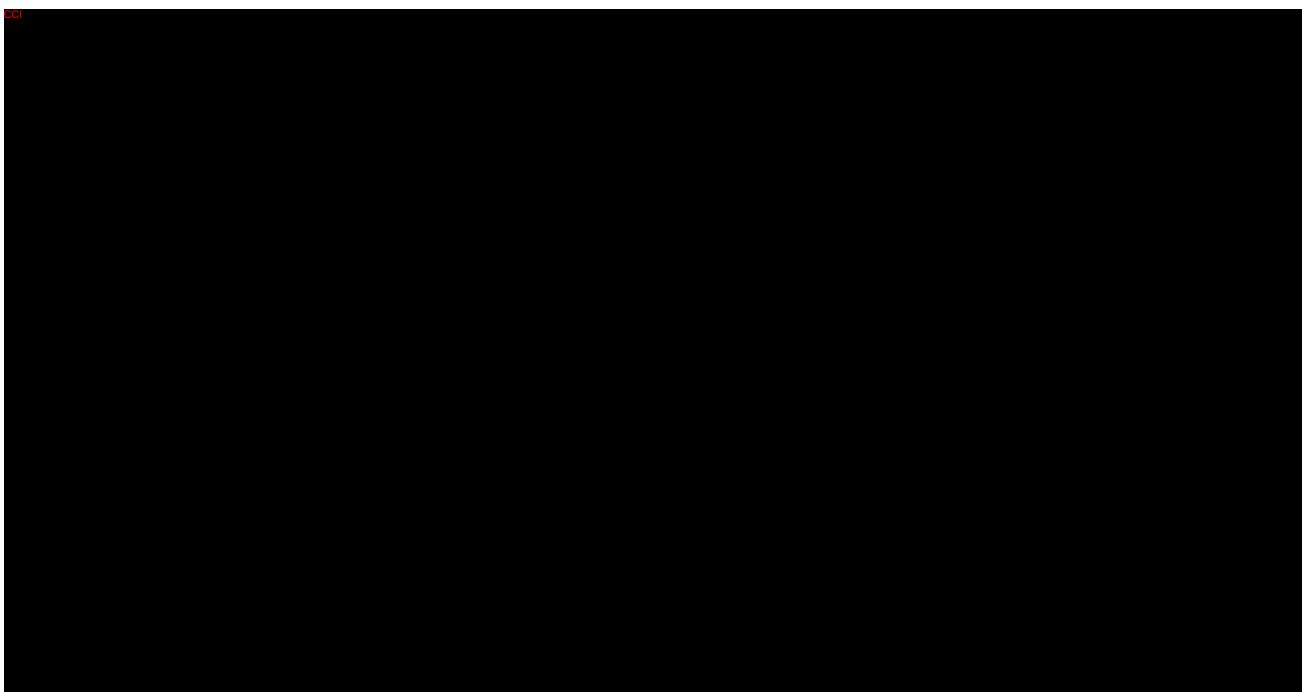
### **7.1.4 Other Procedures**

#### **7.1.4.1 Withdrawal/Discontinuation**

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

##### **7.1.4.1.1 Withdrawal From Future Biomedical Research**

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##### **7.1.4.2 Blinding/Unblinding**

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

### **7.1.5 Visit Requirements**

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

### **7.1.5.1 Procedure of MK-5592 Treatment for Subjects in case That Zygomycete are Observed During the Treatment Period in Voriconazole Treatment Arm**

Subjects in whom zygomycetes are detected during the treatment period in the voriconazole treatment arm can receive the MK-5592 by investigator's discretion after the discontinuation of voriconazole treatment. MK-5592 dosing can be initiated after performing all observations, testing and evaluations at the end of treatment and the signing of a new informed consent.

## **7.2 Assessing and Recording Adverse Events**

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

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

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

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

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

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

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

In this trial, an overdose is any dose higher than the dose below for cohort 2.

MK-5592 solid oral tablet and IV solution: 300 mg/time and 300 mg/day (600 mg/day on Day 1).

Voriconazole IV: 6 mg/kg/time and 12 mg/kg/day on Day 1, 4 mg/kg/time and 8 mg/kg/day after Day 1

Voriconazole oral tablet: 300 mg/time and 600 mg/day on Day 1, 200 mg/time and 400 mg/day after Day 1

In case of higher than the above criteria, overdose is not applicable when the voriconazole dosage is adjusted based on the TDM, however overdose is any higher than 6 mg/kg for IV and 300 mg for oral tablet as a single dose.

In case of higher than the above criteria, overdose is not applicable when the MK-5592 and voriconazole daily dosage is exceeded according to the allowance of dosing interval by Day 5.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

### **7.2.2 Reporting of Pregnancy and Lactation to the Sponsor**

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 14 days of completing the trial. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth

must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

### **7.2.3 Immediate Reporting of Adverse Events to the Sponsor**

#### **7.2.3.1 Serious Adverse Events**

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

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

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

- Is a cancer;
- Is associated with an overdose.

Refer to [Table 23](#) for additional details regarding each of the above criteria.

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

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the

investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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

### **7.2.3.2 Events of Clinical Interest**

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

Events of clinical interest for this trial include:

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

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

### **7.2.4 Evaluating Adverse Events**

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

**Table 23 Evaluating Adverse Events**

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

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

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

### **7.2.5 Sponsor Responsibility for Reporting Adverse Events**

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

## **7.3 TRIAL GOVERNANCE AND OVERSIGHT**

### **7.3.1 Clinical Adjudication Committee**

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 8.0 – Statistical Analysis Plan.

- 1) Diagnosis of deep-seated fungal infection [For subjects with all queries closed, validity of deep-seated fungal infection diagnosed by investigators is assessed]
- 2) Overall Response [For subjects with all queries closed, validity of Overall Response assessed by investigator is assessed (Overall Response, Clinical Response, Radiological Response, Mycological Response)]

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.

## **8.0 STATISTICAL ANALYSIS PLAN**

### **8.1 Statistical Analysis Plan Summary**

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

The primary population of statistical analysis is cohort 2 and the analysis plan described in this section will be conducted in cohort 2. Data from extension period will be excluded from the analyses of Cohort 2.   


#### **8.1.1 Efficacy Analyses**

The primary endpoints, primary analysis population, and statistical method that will be employed for the efficacy analyses are presented in [Table 24](#) below.

The primary efficacy endpoint is the overall response assessed by CAC. The overall response rates (the proportion of subjects with “success” assessment [see Section 8.2.3.3]) for invasive aspergillosis at Day 42 and for chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma) at Day 84 and their 95% confidence intervals will be computed by treatment. Subjects with solid oral tablet, IV solution and switch from IV solution to solid oral tablet for the MK-5592 treatment arm will

be pooled for the analyses due to the fact that it reflects clinical practice and the different routes of administration achieve targeted plasma concentration level of MK-5592. Likewise, subjects with oral tablet, IV solution and switch from IV solution to oral tablet for the Voriconazole treatment arm will be pooled for the analyses.

The overall response for the subjects with fusariosis and zygomycosis will be listed for MK-5592 treatment arm since the enrollment of these infections will be very limited.

Table 24 Analysis Strategy for Primary Efficacy Endpoint

Endpoint/Variable (Description, Timepoint)	Statistical Method	Analysis Population	Missing Data Approach
Overall response rates for invasive aspergillosis at Day 42 and for chronic pulmonary aspergillosis at Day 84	95% CI with Clopper-Pearson Exact Method	FAS	Carry Forward

### 8.1.2 Safety Analyses

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized patients who received at least one dose of study treatment. Invasive aspergillosis and chronic pulmonary aspergillosis will be pooled for the analyses but subject with fusariosis and zygomycosis will be separately evaluated. In this study, the prespecified events of interest (Tier-1 events) are not defined.

### 8.1.3 Power and Sample Size

This study initially planned to enroll a total of 90 subjects but due to the modification in protocol such as inclusion and exclusion criteria, an additional 90 subjects will be enrolled as cohort 2, [REDACTED] The cohort 2 will enroll subjects as initially planned for this protocol:

This study will randomize 60 subjects into the MK-5592 treatment arm and 30 into the Voriconazole treatment arm. A total number of 90 subjects were set with consideration of recruitment feasibility based on the past experiences (See Section 8.2.7 for details). A total of 90 subjects include those with all aspergillosis for safety analyses, and among them 15 subjects with invasive aspergillosis as a target number will be enrolled. Subjects with fusariosis and zygomycosis will be assigned to the MK-5592 treatment arm and their target number of recruitment is not set.

### 8.1.4 Interim Analyses

Formal interim analyses are not planned in this study. Safety and PK data will be reviewed by the sponsor on an ongoing basis. No alpha adjustment is needed since no hypothesis is tested in this study.

## **8.2 Statistical Analysis Plan**

The primary population of statistical analysis is cohort 2 and the analysis plan described below will be conducted in cohort 2. Data from extension period will be excluded from the analyses of Cohort 2. Safety and PK data in cohort 1 will be separately summarized from cohort 2.

### **8.2.1 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 trial is being conducted as an open-label study, i.e., patients, investigators, and SPONSOR personnel will be aware of patient treatment assignments after each patient is enrolled and treatment is assigned.

The Clinical Biostatistics department or designee will generate the randomized allocation schedule for study treatment assignment. Randomization will be implemented by registration center.

This trial is being conducted as an open-label study but the diagnosis and overall response will be assessed by CAC in a blinded manner based on data with masked information such as treatment assignment.

### **8.2.2 Hypotheses/Estimation**

Objectives and hypotheses of the study are stated in Section 3.0. The hypothesis is not set since the main objective of this study is safety assessment.

### **8.2.3 Analysis Endpoints**

Efficacy and safety endpoints are listed below.

#### **8.2.3.1 Efficacy Endpoints**

##### **8.2.3.1.1 Primary Efficacy Endpoint**

The Primary efficacy endpoint is the overall response for invasive aspergillosis at Day 42 and for chronic pulmonary aspergillosis at Day 84 assessed by CAC.

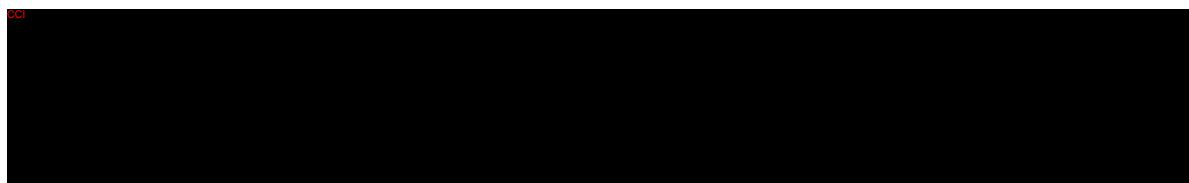
##### **8.2.3.1.2 Secondary Efficacy Endpoints**

The following endpoints assessed by CAC will be secondary efficacy endpoints:

- Overall response for invasive aspergillosis at Day 84
- Overall response for chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma) at Day 42

- Overall response for all aspergillosis [invasive aspergillosis and chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma)] at EOT
- Overall response for fusariosis and zygomycosis at Day 42 and Day 84
- Clinical response for invasive aspergillosis and chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma) at Day 42 and Day 84
- Radiological response for invasive aspergillosis and chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma) at Day 42 and Day 84
- Mycological response for invasive aspergillosis and chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma) at Day 42 and Day 84

In addition, overall response for invasive aspergillosis at Day 42 and for chronic pulmonary aspergillosis at Day 84 assessed by investigators/sub-investigators will be evaluated as a secondary efficacy endpoint.



### 8.2.3.2 Safety Endpoints

Refer to Section 7.0 for safety endpoints.

### 8.2.3.3 Derivations of Efficacy Endpoints

The overall response will be assessed by CAC using clinical, radiological and mycological response data. The data for assessing the overall response and criteria of efficacy judgment are presented in the [Table 25](#) and criteria for overall response is presented in Section 4.2.3.1.

Data will be submitted to CAC with masked Information such as treatment assignment and CAC will assess the overall response in a blinded manner.

**Table 25 The Data for Assessing the Overall Response and Criteria of Efficacy Judgment**

Disease Category	Information for assessing the overall response	Efficacy Assessment	
		Success	Failure
Invasive aspergillosis <sup>†</sup>	Clinical response Radiological response Mycological response	Complete Response Partial Response	Stable Response Progression of disease Unable to determine
Chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma)	Clinical response Radiological response	Favorable Response	Stable Response Progression of disease Unable to determine
Fusariosis and zygomycosis	Clinical response, Radiological response and Mycological response Or Clinical response and Mycological response	Complete Response Partial Response	Stable Response Progression of disease Unable to determine

<sup>†</sup>Subjects with possible invasive aspergillosis may also be enrolled into the study with further evaluation of proven or probable invasive aspergillosis, which must be confirmed by 7 days post-randomization to be included in the FAS analysis.

## 8.2.4 Analysis Populations

### 8.2.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS for a given endpoint consists of all randomized subjects in cohort 2 who:

- Diagnosed as target disease (proven or probable) by CAC
- Receive at least one dose of study treatment
- Have a baseline observation for the analysis endpoint

Subjects with possible invasive aspergillosis may also be enrolled into the study with further evaluation of proven or probable invasive aspergillosis, which must be confirmed by 7 days post-randomization to be included in the FAS analysis.

An Intention To Treat (ITT) population is defined as all randomized subjects in cohort 2 who received at least one dose of study treatment, and the analysis of the primary efficacy endpoint will be performed.

A supportive analysis using the Per-Protocol population in cohort 2 will be also performed for the primary efficacy endpoint. The Per-Protocol population excludes patients due to important deviations from the protocol that may substantially affect the results of the primary efficacy endpoint. Potential violations that may result in the exclusion of a patient from the Per-Protocol population include:

- Subjects with cases that affect the results of the primary efficacy endpoint, confirmed by CAC

The final determination on protocol violations, and thereby the composition of the Per-Protocol population, will be made prior to the final lock of the database and will be documented in a separate memo.

Patients will be included in the treatment group to which they are randomized for the analysis of efficacy data using both the FAS, ITT and Per-Protocol populations. Details on the approach to handling missing data are provided in Section 8.2.5.1.4.

#### **8.2.4.2 Safety Analysis Populations**

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this study. Randomized subjects with invasive aspergillosis and chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma) will be pooled for the analyses but subjects with fusariosis and zygomycosis, not randomized subjects, will be separately evaluated. The ASaT population consists of all randomized subjects in cohort 2 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 ASaT population.

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.

#### **8.2.5 Statistical Methods**

The main objective of this study is assessment of safety and the formal hypothesis testing for efficacy endpoints will not be conducted. Nominal p-values and confidence intervals will be presented at the  $\alpha=0.05$  (2-sided) level.

##### **8.2.5.1 Statistical Methods for Efficacy**

###### **8.2.5.1.1 Primary Efficacy Analysis**

The primary efficacy endpoint is the overall response assessed by CAC. The overall response rates (the proportion of subjects with “success” assessment) for invasive aspergillosis at Day 42 and for chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma) at Day 84 and their 95% confidence intervals will be computed by treatment. Subjects with solid oral tablet, IV solution and switch from IV solution to solid oral tablet for the MK-5592 treatment arm will be pooled for the analyses due to the fact that it reflects clinical practice and the different routes of administration achieve targeted plasma concentration level of MK-5592. Likewise, subjects with oral tablet, IV solution and switch from IV solution to oral tablet for the Voriconazole treatment arm will be pooled for the analyses. The 95% confidence intervals will be estimated with the Clopper-Pearson method.

### 8.2.5.1.2 Secondary Efficacy Analysis

The overall response rates for invasive aspergillosis at Day 84 and for chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma) at Day 42 will be provided by treatment ([Table 26](#)).

The overall response rate for all aspergillosis (invasive aspergillosis and chronic pulmonary aspergillosis are pooled) at EOT will be provided by treatment.

Clinical, radiological and mycological response rates for invasive aspergillosis and for chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma) at Day 42 and Day 84 will be provided by treatment.

The overall response for the subjects with fusariosis and zygomycosis will be listed for MK-5592 treatment arm since the enrollment of these infections will be very limited.

As a sensitivity analysis, the overall response rates for invasive aspergillosis at Day 42 and for chronic pulmonary aspergillosis at Day 84 will be provided by treatment in the PP population. For the PP analysis, a subject with missing post-treatment response data or with 'unable to determine' response will be excluded. In addition, the overall response rates will be provided in the ITT population and also the overall response rates by investigators/sub-investigators will be provided in the FAS population.

Table 26 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Methods	Analysis Population	Missing Data Approach
<b>Primary</b>				
Overall response rates for invasive aspergillosis at Day 42 and for chronic pulmonary aspergillosis at Day 84	P	95% CI with Clopper-Pearson Exact Method	FAS	CF <sup>†</sup>
	S	Point Estimate	PP	CF <sup>†</sup>
	S	Point Estimate	ITT	CF <sup>†</sup>
	S	Point Estimate: Assessment by investigators/sub-investigators	FAS	CF <sup>†</sup>
<b>Secondary</b>				
Overall response rates for invasive aspergillosis at Day 84 and for chronic pulmonary aspergillosis at Day 42	P	Point Estimate	FAS	CF <sup>†</sup>
Overall response rate for all aspergillosis at EOT (invasive aspergillosis and chronic pulmonary aspergillosis are pooled)	P	Point Estimate	FAS	CF <sup>†</sup>
Clinical response rates, radiological response rates and mycological response rates for invasive aspergillosis and for chronic pulmonary aspergillosis at Day 42 and Day 84	P	Point Estimate	FAS	CF <sup>†</sup>

<sup>†</sup>CF: Carried-forward method

#### 8.2.5.1.3 [REDACTED]

[REDACTED]

[REDACTED]

#### 8.2.5.1.4 Accounting for Missing Data

For the primary analyses in FAS and ITT (overall response rates for invasive aspergillosis at Day 42 and for chronic pulmonary aspergillosis at Day 84), missing data will be imputed by a carried-forward method. Baseline values will not be carried forward and if there is no data after treatment, the missing data will be considered as failure. Data with ‘unable to determine’ will be considered as failure as well. For the overall response rates for invasive aspergillosis at Day 84 and for chronic pulmonary aspergillosis at Day 42, and also clinical, radiological and mycological response rates at Day 42 and Day 84 for both aspergillosis, the missing data will be imputed likewise.

For the analyses in PP population, a subject with missing post-treatment response data or with ‘unable to determine’ response will be excluded.

#### 8.2.5.2 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 27](#)) but tier 1 events are not defined in this protocol. The tiers differ with respect to the analyses that will be performed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3. In addition, the broad clinical and laboratory AE categories consisting of the percentage of patients with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. 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.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will include zero when both treatment groups 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 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.

Table 27 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint <sup>†</sup>	p-value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Not defined in this protocol	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs (incidence $\geq 4$ of patients in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs <sup>‡</sup> (incidence $<4$ of patients in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

### 8.2.5.3 Summary 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 patients screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

### 8.2.6 Multiplicity

No multiplicity adjustment is necessary since no hypothesis is tested in this study.

### 8.2.7 Sample Size and Power Calculations

This study initially planned to enroll a total of 90 subjects, but due to the modification in protocol such as inclusion and exclusion criteria, an additional 90 subjects will be enrolled as

cohort 2 [redacted]

[redacted]. The cohort 2 will enroll subjects as initially planned for this protocol as follows:

The target number of subjects for the safety analyses will be 90 subjects (MK-5592 treatment arm: 60 subjects, Voriconazole treatment arm: 30 subjects) in this study. From past experiences of the sponsor as well as information of competitors a total number of 90 subjects were set as a target number with consideration of recruitment feasibility.

A total of 90 subjects include subjects with invasive aspergillosis and chronic pulmonary aspergillosis (chronic progressive pulmonary aspergillosis and simple pulmonary aspergilloma). In order to obtain MK-5592 data as much as possible with a limitation of the sample size, the allocation ratio was set 2 to 1. 15 subjects with invasive aspergillosis as a target number will be enrolled. Fusariosis and zygomycosis are very rare deep-seated fungal infections and it is reported that Voriconazole is not effective for treatment of zygomycosis, so subjects with those infections will not be randomized and will be enrolled in the MK-5592 treatment arm without a target number of enrollment.

According to clinical database of Posaconazole Oral Suspension, which is approved and available in the markets of Europe and the United States, as well as clinical studies of MK-5592 in the new formulations up to date, the incident rates of frequently observed adverse experiences (pyrexia, diarrhea, nausea, headache, vomiting and cough) are expected to be approximately 10% - 20%. Assuming that incident rates of the MK-5592 arm and Voriconazole arm are comparable, the half-width of the 95% confidence interval for the difference of the incidence rates will be 14.6% - 17.9% with 60 subjects of the MK-5922 arm and 30 subjects of the Voriconazole arm (Table 28). If a particular adverse experience is not observed in any of the 60 patients in the MK-5592 treatment arm, the true incidence rate for the particular adverse experience is less than 2.6% with 80% confidence. For efficacy assessment, assuming that response rate of 60% (80%), the lower limits of confidence interval for MK-5922 arm will be 46.5% (67.7%) with the sample size of 60.

Table 28 95% Confidence Interval for Difference of the Incidence Rates for Adverse Events

Incident Rates for both arms (difference of 0%)	95% Confidence Interval		
	Lower Bound	Upper Bound	A half-width of the 95% CI
10%	-12.5	16.8	14.6%
15%	-15.9	16.4	16.1%
20%	-16.3	19.5	17.9%

Incidence Rates for the MK-5592 and Voriconazole treatment arm are assumed to be equal.  
(MK-5592: 60 subjects, Voriconazole: 30 subjects)  
95% confidence interval was calculated with the Miettinen and Nurminen method.

### **8.2.8 Subgroup Analyses and Effect of Baseline Factors**

To determine whether the treatment effect is consistent across various subgroups, the treatment effect for the primary endpoint will be estimated by the disease category in the following factors:

- Sex (female, male)
- Age (<65 vs.  $\geq$ 65 years)
- Weight (<60,  $\geq$ 60 kg)
- Fungal species
- Route of administration (oral, IV, switch)
- Diagnosis (proven, probable)

### **8.2.9 Interim Analysis**

Formal interim analyses are not planned in this study. Safety and PK data will be reviewed by the sponsor on an ongoing basis. No alpha adjustment is needed since no hypothesis is tested in this study.

### **8.2.10 Compliance (Medication Adherence)**

In this study, as part of the routine recording of the amount of study treatment taken by each patient, the volume of injection and the number of tablets remaining in study packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate patient compliance.

#### **8.2.10.1 IV Route**

Drug accountability data for MK-5592 and Voriconazole will be collected during the study. Compliance with protocol-directed MK-5592 and Voriconazole will be measured by patients: (1) receiving unscheduled study agent infusions, (2) missing an infusion, (3) receiving incorrect study agent dose, and (4) receiving an infusion at rate greater than a rate specified in the protocol. Numbers and percentages of patients with any deviation in these measures will be reported by treatment for the FAS and ASaT population.

Compliance will be assessed using the off-drug therapy records. On each day, each patient should take a certain infusion dosage. The compliance rate for each patient will be computed as follows:

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

Study period is defined as the number of days that the patient has been in the active treatment phase of the trial.

### **8.2.10.2 Oral Therapy**

A day within the study will be considered an “On-Therapy” day if the patient takes the required number of tablets. 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. For a patient who discontinued from the study permanently, the “Number of Days Should be on Therapy” is the total number of days from randomization to the earlier/later date of the last dose of study medication.

For each patient, percent compliance will then be calculated using the following formula:

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

Summary statistics will be provided on percent compliance by treatment group for the FAS and ASaT.

### **8.2.11 Extent of Exposure**

The extent to 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.

## **9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES**

### **9.1 Investigational Product**

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

Clinical Supplies will be provided by the Sponsor as summarized in [Table 29](#).

Table 29 Product Descriptions

<b>Product Name &amp; Potency</b>	<b>Dosage Form</b>
MK-5592 18 mg/mL, 300 mg/vial	IV solution for injection
MK-5592, 100 mg	Tablet
Voriconazole, 200 mg/vial	Lyophilized Powder
Voriconazole, 50 mg	Tablet

## **9.2 Packaging and Labeling Information**

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

MK-5592 IV solution will be supplied as kits containing one vial. MK-5592 tablets will be supplied as bottles containing 30 tablets. No kitting is required. Voriconazole Lyophilized Powder will be supplied as kits containing ten vials. Voriconazole tablets will be supplied as kits containing 50 tablets in PTP sheets. All of clinical supplies will be supplied as open label.

## **9.3 Clinical Supplies Disclosure**

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

## **9.4 Storage and Handling Requirements**

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

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

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

## **9.5 Returns and Reconciliation**

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

# **10.0 ADMINISTRATIVE AND REGULATORY DETAILS**

## **10.1 Confidentiality**

### **10.1.1 Confidentiality of Data**

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and

employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

#### **10.1.2 Confidentiality of Subject Records**

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

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

#### **10.1.3 Confidentiality of Investigator Information**

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

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

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

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

#### **10.1.4 Confidentiality of IRB/IEC Information**

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

### **10.2 Compliance With Financial Disclosure Requirements**

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

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

### **10.3 Compliance With Law, Audit and Debarment**

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

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

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

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

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

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

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

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

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

#### **10.4 Compliance With Trial Registration and Results Posting Requirements**

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

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

#### **10.5 Quality Management System**

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

## 10.6 Data Management

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

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

## 10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings.<sup>101</sup>

Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

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

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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## 12.0 APPENDICES

### 12.1 Merck Code of Conduct for Clinical Trials

**Merck\***  
**Code of Conduct for Clinical Trials**

#### I. Introduction

##### A. Purpose

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

##### B. Scope

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

#### II. Scientific Issues

##### A. Trial Conduct

###### i. Trial Design

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

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

###### ii. Site Selection

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

###### iii. Site Monitoring/Scientific Integrity

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

##### B. Publication and Authorship

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

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

**III. Subject Protection**

**1. IRB/ERC review**

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

**2. Safety**

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

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

**3. Confidentiality**

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

**4. Genomic Research**

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

**IV. Financial Considerations**

**• Payments to Investigators**

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

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

**• Clinical Research Funding**

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

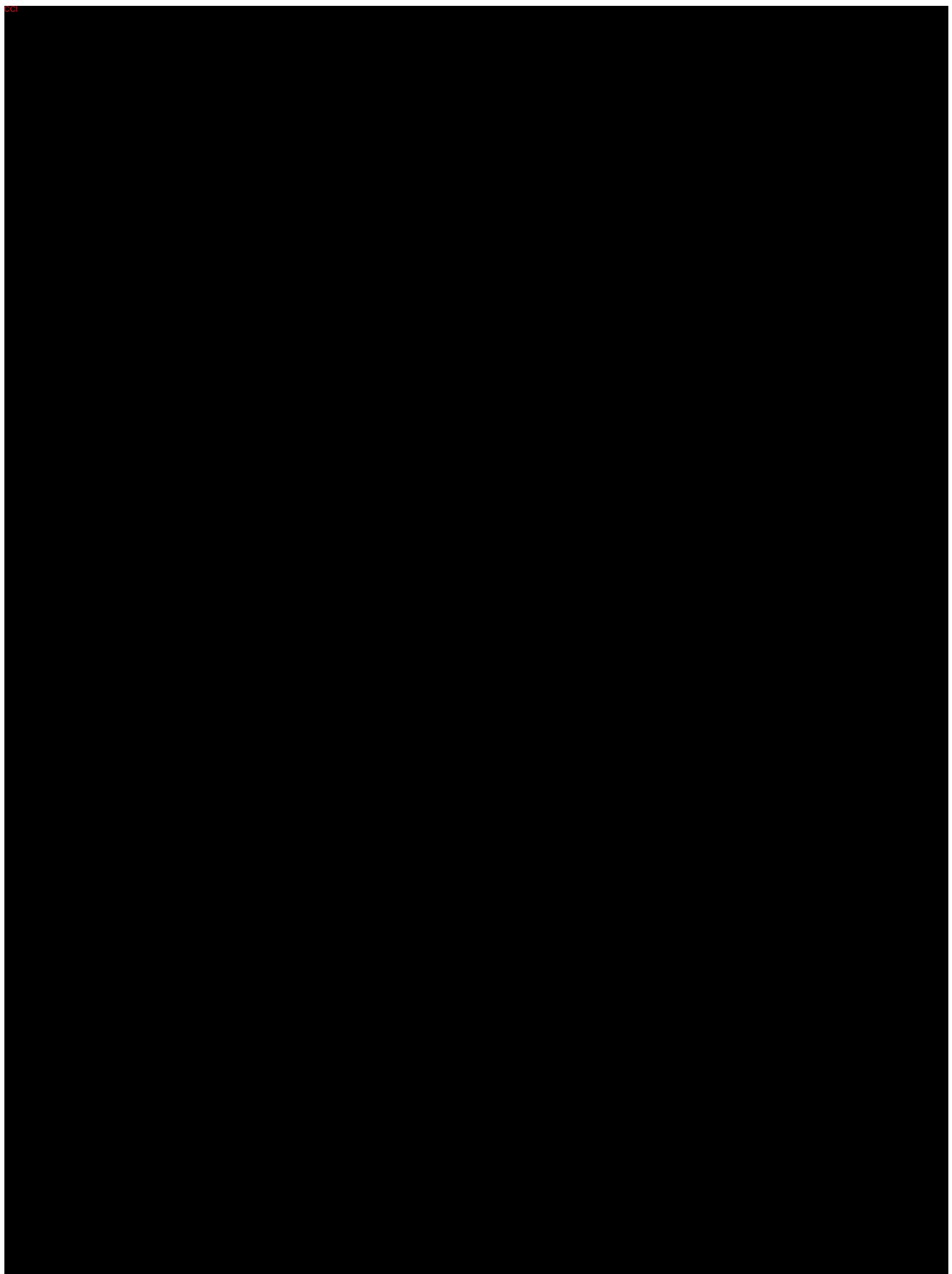
**• Funding for Travel and Other Requests**

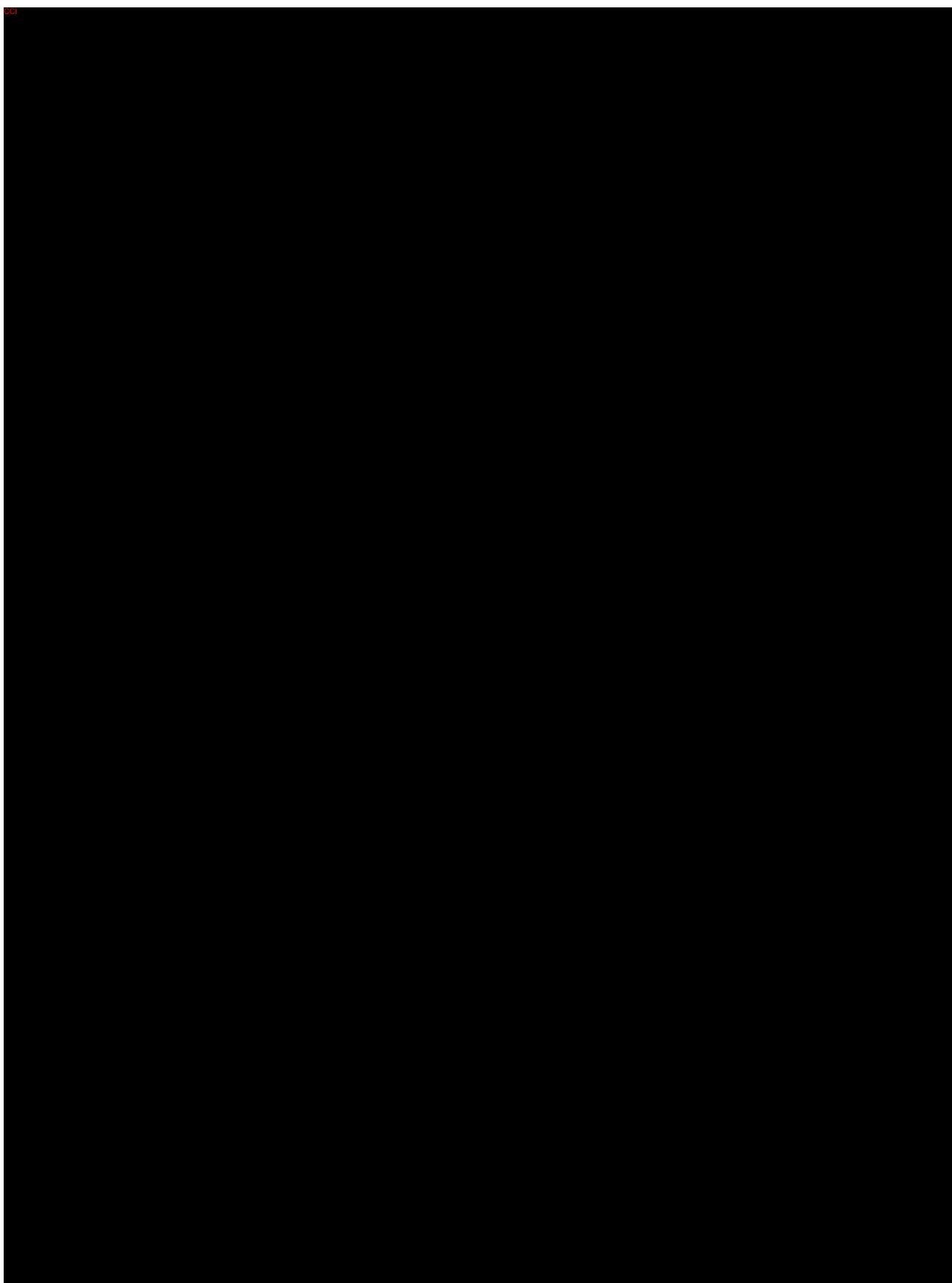
Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

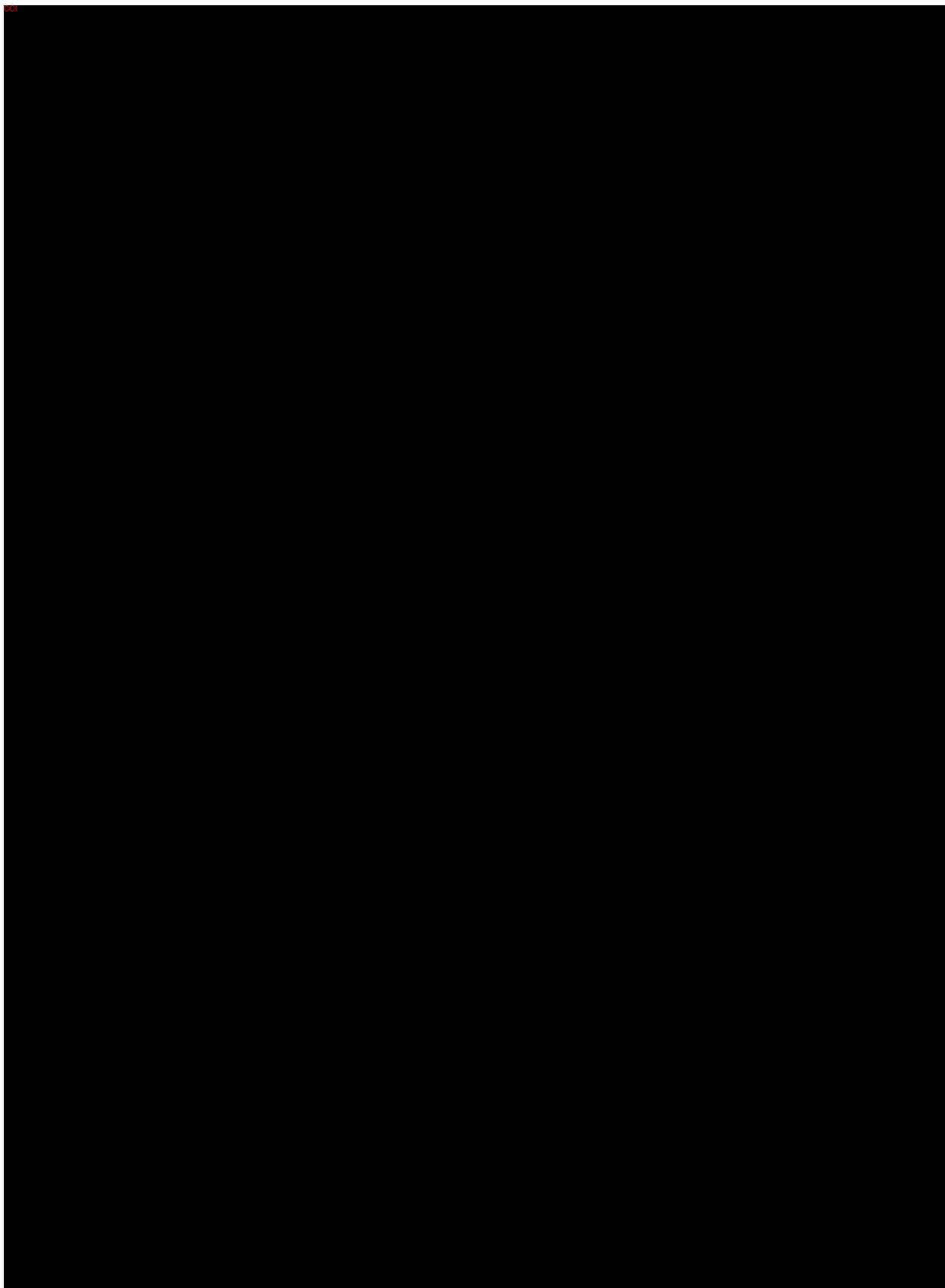
**V. Investigator Commitment**

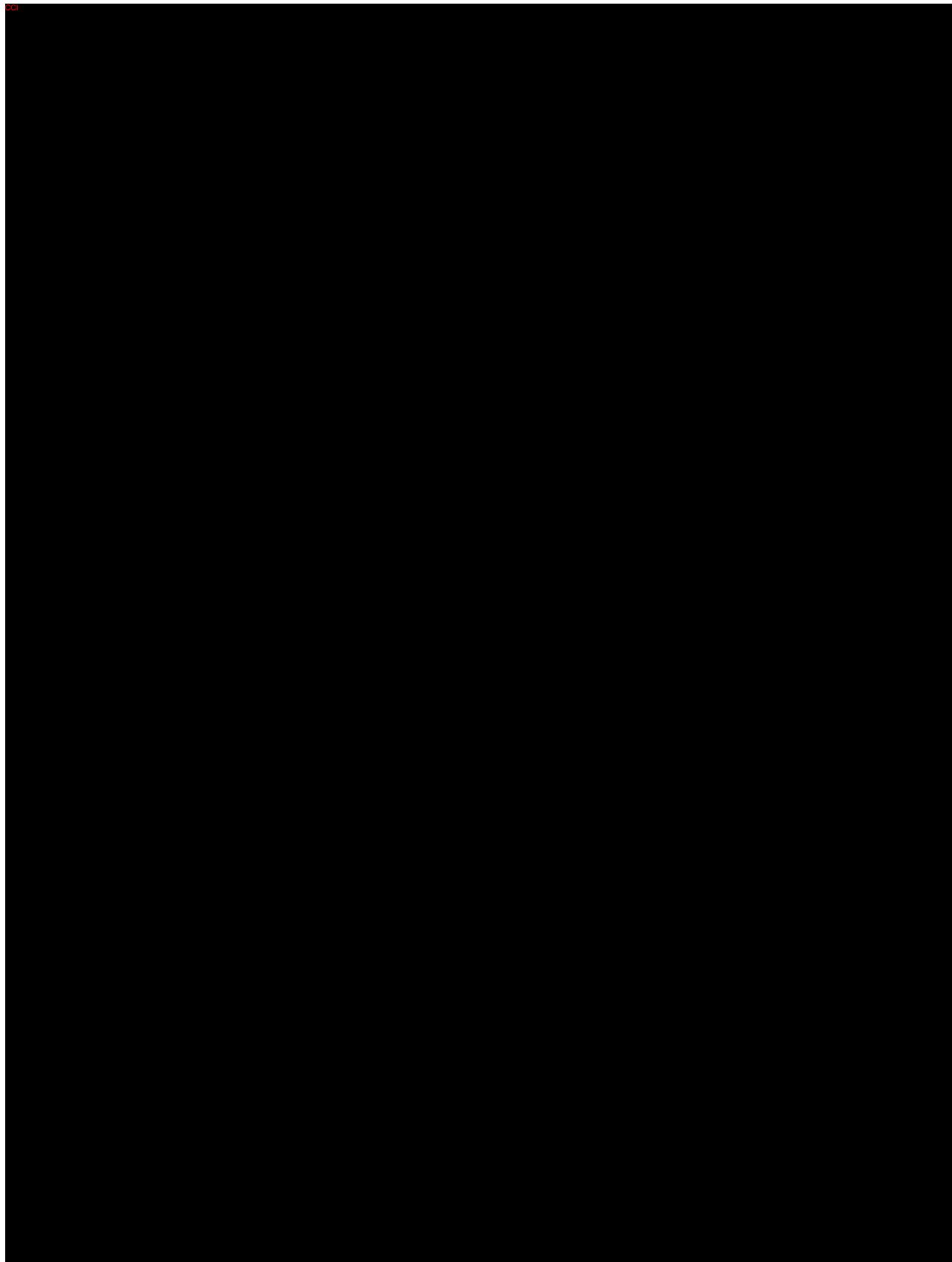
Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

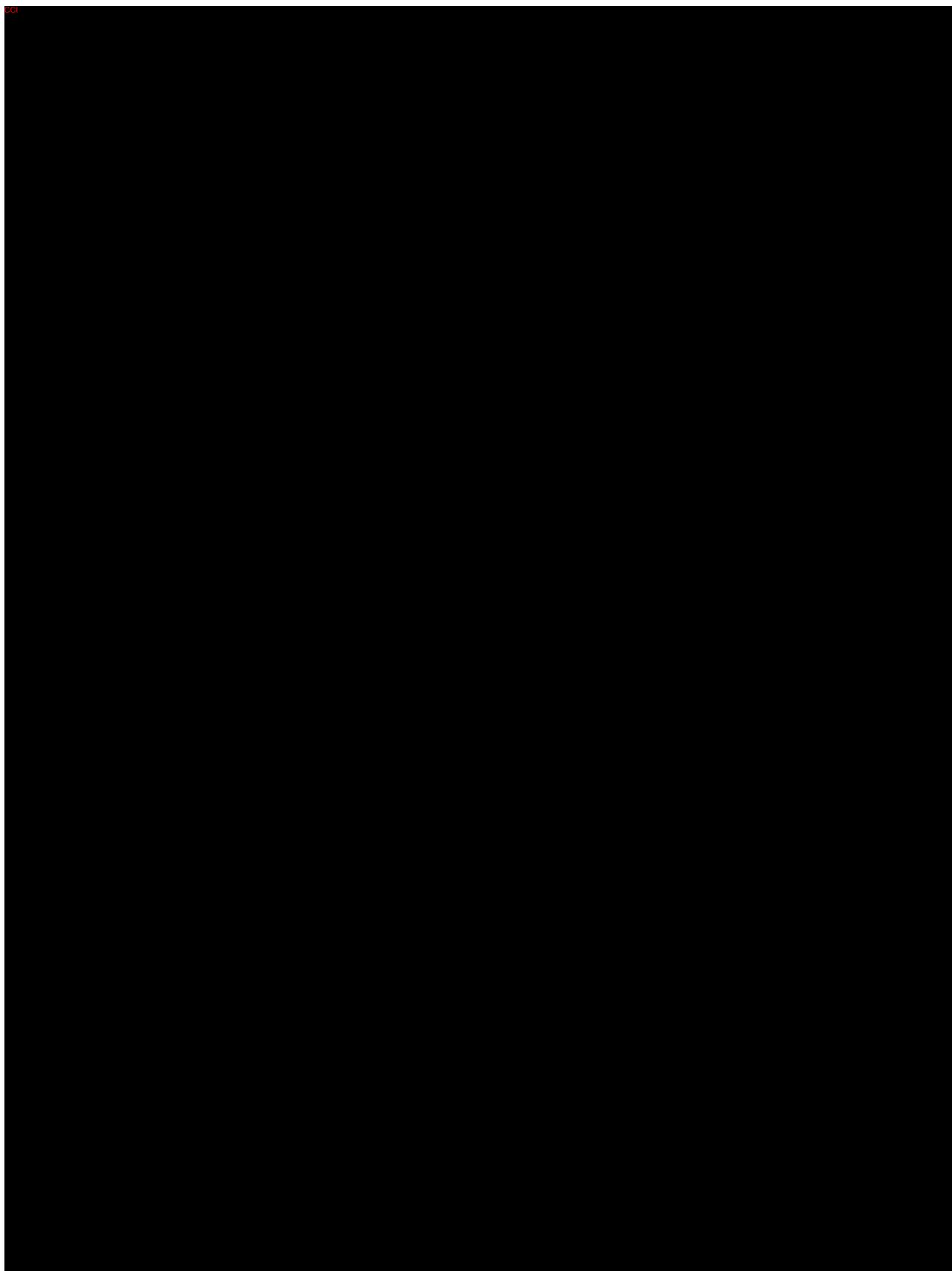
\* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc.\*

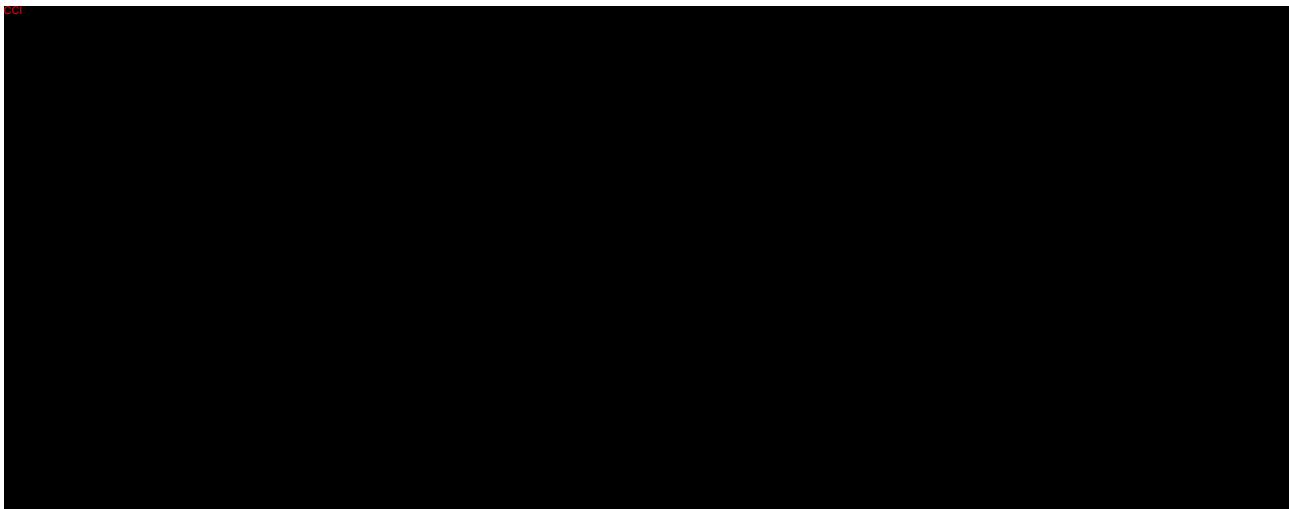








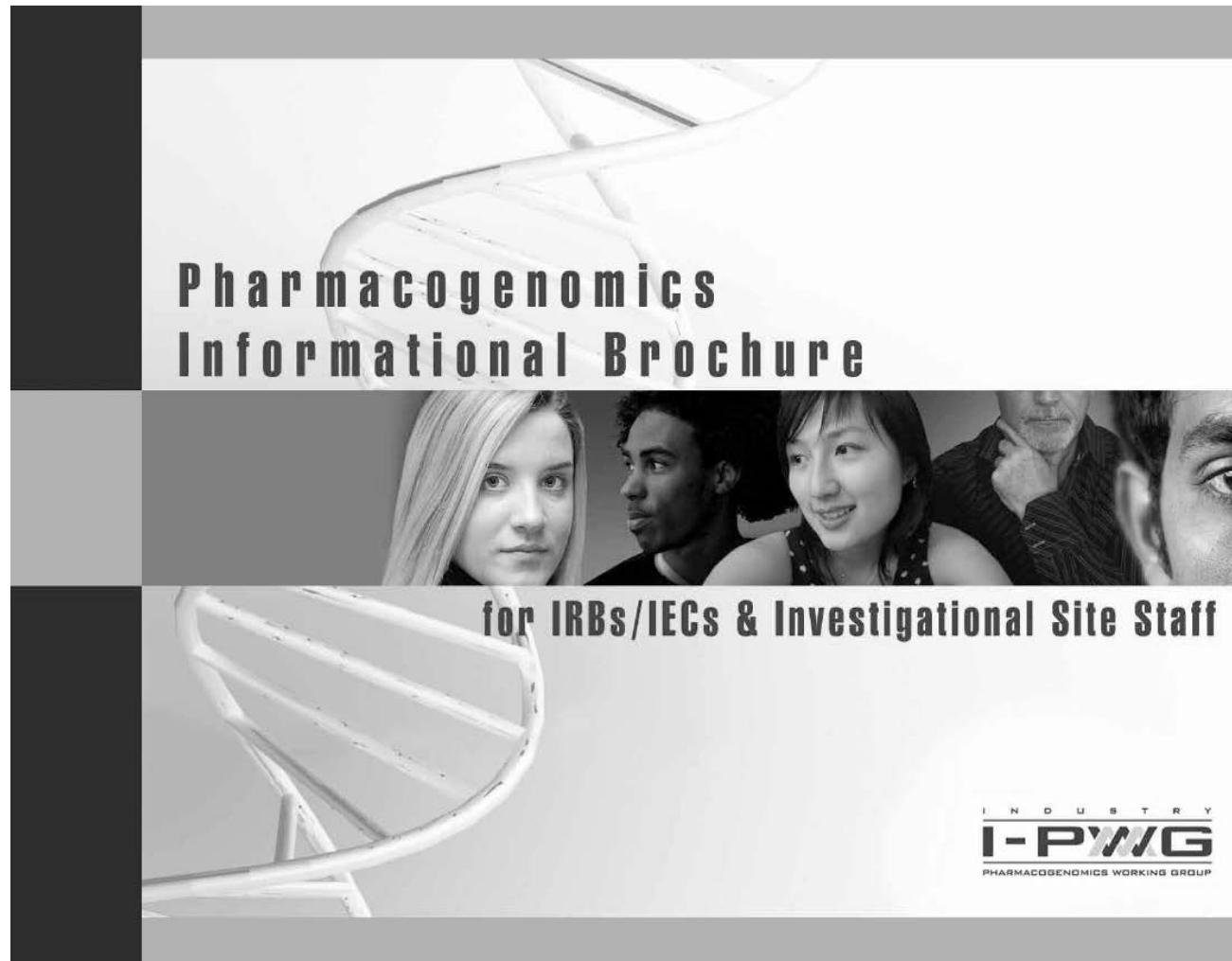




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## 12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



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

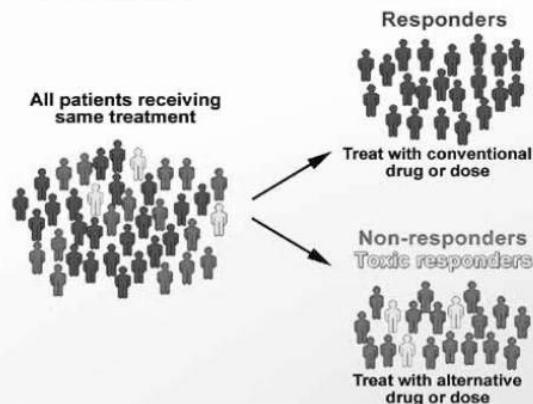
Developed by  
The Industry Pharmacogenomics Working Group (I-PWG)  
[www.i-pwg.org](http://www.i-pwg.org)

### What is DNA and What is Pharmacogenomics?

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

**Pharmacogenomics (PGx)** is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA<sup>1</sup>, and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the

purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



### Why is Pharmacogenomics Important?

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



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

### How is Pharmacogenomics Being Used in Drug Development?

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

PGx research is currently being used in drug development to:

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

2

### Pharmacogenomics Already a Reality in Drug Labels

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

- i) tests **required** for prescribing
- ii) tests **recommended** when prescribing
- iii) PGx information **for information only**.

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

[www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm](http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

### DNA Samples from Clinical Trials An Invaluable Resource

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



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Table adapted from ICH Guidance E15

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

**ii) Separation of Data and Restricted Access**

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

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data

usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form<sup>2</sup>.



### iii) Legislation on Genetic Discrimination

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

### Country-Specific Laws and Regulations on DNA Collection

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

### Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA),

EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued<sup>1,3,7-18</sup>, and are available through: <http://www.i-pwg.org>. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions<sup>19</sup>.

### Where to Get More Information

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

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

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



## Glossary

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

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

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

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

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

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

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*Created by the Industry Pharmacogenomics Working Group Education Task Force*

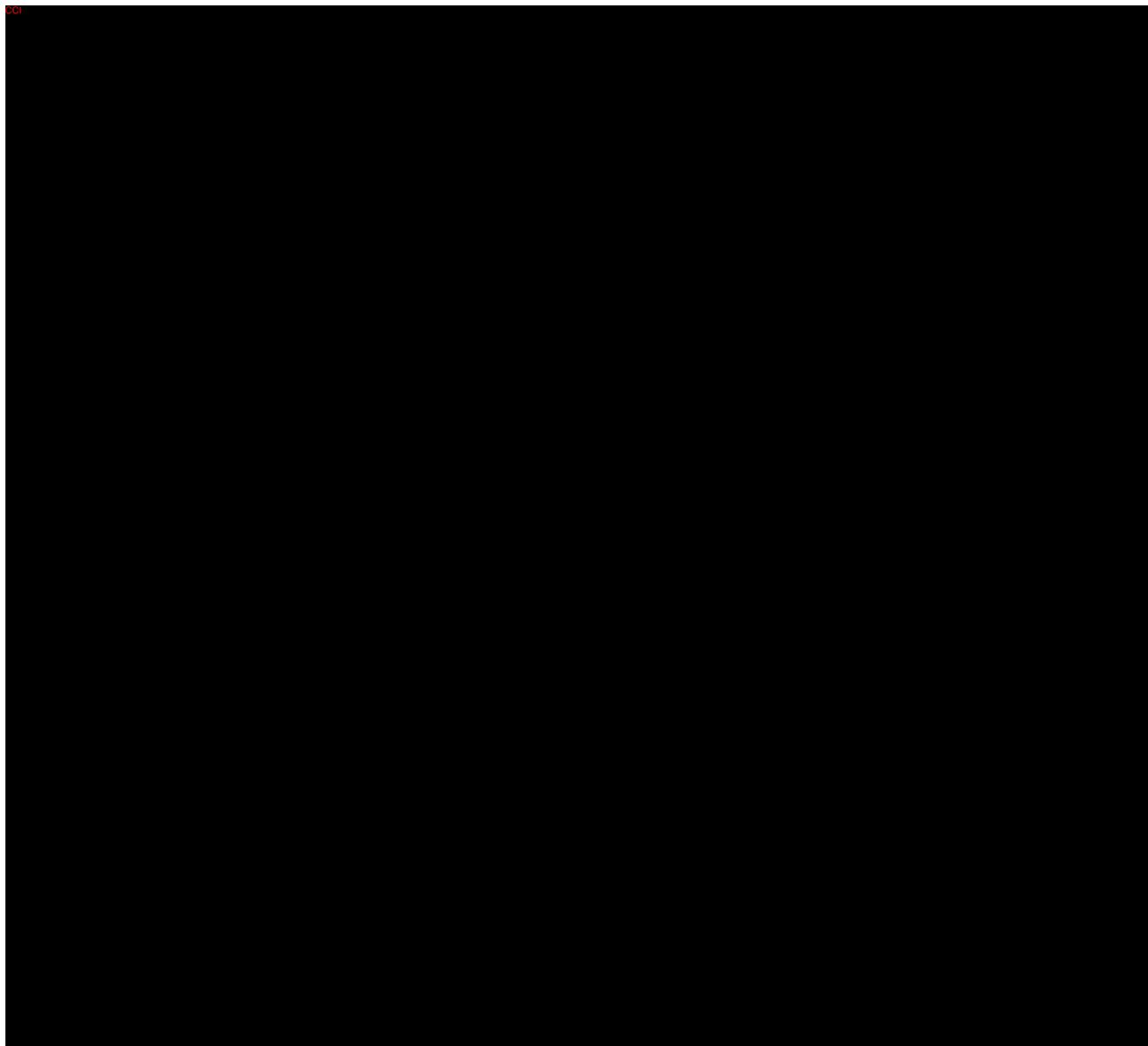
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<http://www.i-pwg.org>



## **12.5 Clinical Study Conduct System**

Clinical study conduct system is shown in attachment 1 and 2.

## **13.0 SIGNATURES**

### **13.1 Sponsor's Representative**

TYPED NAME

SIGNATURE

DATE

### **13.2 Investigator**

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

TYPED NAME

SIGNATURE

DATE