SCYNEXIS, Inc.

Clinical Trial Protocol

A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Coadministration of SCY-078 with Voriconazole in Patients with Invasive Pulmonary Aspergillosis (SCYNERGIA)

SCYNEXIS Protocol Number SCY-078-206

EUDRA CT Number 2018-002565-18

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1.0 Contact Information

Contract Research Organization (Europe Only)

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Safety Contact

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2.0 Protocol Approvals

PROTOCOL ID: SCY-078-206

A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Coadministration of SCY-078 with Voriconazole in Patients with Invasive Pulmonary Aspergillosis (SCYNERGIA)

SCYNEXIS, Inc. Approval:

[redacted]

Date

Investigator Agreement Statement

PROTOCOL ID: SCY-078-206

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I understand that all documentation provided to me by SCYNEXIS, Inc. or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's Brochure, case report forms, and other scientific data. This study will not commence without the prior written approval of a properly constituted Institutional Review Board or Ethics Committee. No changes will be made to the study protocol without the prior written approval of SCYNEXIS, Inc. and the Institutional Review Board/Ethics Committee, except where necessary to eliminate an immediate hazard to the patient. All patients will provide a written informed consent prior to participation.
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I have read, understood and agree to abide by all the conditions and instructions contained in this protocol, and in compliance with International Conference on Harmonization (ICH) guidelines, Good Clinical Practices (GCP), Safety Reporting obligations and any applicable local requirements.

Principal Investigator's Signature	Date

Principal Investigator's Name (Printed)

3.0 Table of Contents

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4.0 Revision History

Revisions to Protocol dated 01 August 2019 (Protocol Version 5.0) **Current Version and Date: Protocol Amendment 5 (Protocol Version 6.0) dated XX September 2020**	
Protocol Section	**Change and Rationale**
Section 1.0 Contact Information	Deleted [redacted] as the CRO and added [redacted] as the CRO for Europe.
Synopsis Study Design	Amended the following paragraphs to delete the ~~strikethrough~~ text and include the **bolded** text: This is a multicenter, randomized, double-blind, two-arm study to evaluate the safety, tolerability, efficacy and PK of the coadministration of SCY-078 plus voriconazole compared to the coadministration of SCY-078 placebo plus voriconazole in male and female subjects 18 years of age and older with a ~~possible~~, probable or proven IPA. ~~based on EORTC-MSG criteria. In addition, all subjects must be positive (≥0.5) for serum GMI (serum or BAL).~~ Being this a Phase 2 study, multiple secondary and exploratory endpoints are planned, which will be evaluated as data allow considering the limitation of the planned sample size. Subjects must meet all study criteria to be eligible for inclusion. Subjects with a probable or proven IPA **as defined in Section 22.3** ~~AND at least one positive serum or BAL GMI sample collected within 96 hours before enrollment (Baseline/Treatment Day 1)~~ who meet all other inclusion and exclusion criteria will enter the Treatment Period and will be randomized to one of the two study treatment groups. The Screening **Visit** ~~Period~~ and Baseline visit (Treatment Day 1) may occur simultaneously for subjects who have **met the criteria for a** ~~positive serum or BAL GMI test (Serum ≥ 0.5 or BAL ≥1)~~ **probable or proven** ~~at the time of~~ IPA **at screening** ~~diagnosis~~, if all other criteria are met Subjects with possible IPA may enter the Screening Period of the study. During the Screening Period, subjects will receive voriconazole or any other mold-active agent (e.g., echinocandin, amphotericin B, or other azoles for mold infections) as per label instructions and local standard practice, and samples for serum determination of GMI will be collected on a daily basis. **Other samples (e.g., bronchioalveolar lavage, cytology or histopathology) may**

	be collected as clinically indicated to confirm the IPA diagnosis. ~~For subjects that only have BAL GMI, subsequent BAL, if done, should be sent for GMI measurements.~~ Subjects may remain in the Screening Period (i.e. Screening Days -4 to -1) until ~~one positive serum or BAL GMI test is reported~~ **the criteria of probable or proven IPA is met (Section 22.3)**, but in no case for more than 4 days of mold-active antifungal treatment unless approved by the medical monitor, as explained below. This 4-day mold-active antifungal treatment limit prior to randomization is inclusive of any days of mold-active antifungal that the subject may have received prior to Screening. **Once the criteria for a probable or proven IPA is met** ~~a positive serum or BAL GMI test is reported~~ and, if all other inclusion and exclusion criteria are met, the subject will enter the Treatment Period and will be randomized to one of the two study treatment groups. Subjects **meeting criteria for probable or proven IPA** ~~with positive serum or BAL GMI results available~~ shortly after the subject has reached the 4-day mold-active antifungal treatment limit allowance (i.e., after 4 days but no more than 7 days of mold-active antifungal treatment) may be randomized into the study with the approval of the medical monitor, who will take into consideration the total number of days of mold-active agent administration up to that point as well as the subject´s response to therapy. If ~~serum or BAL GMI~~ **the criteria for probable or proven IPA is not met within 7 days after initiation of mold-active antifungal treatment for the IPA episode** ~~results are negative~~, the subject will not be randomized and will be discontinued from the study. Only limited information will be collected for screened subjects who do not qualify for enrollment. This study is intended for subjects with an IPA episode that, in the investigator´s judgement, requires antifungal therapy and is reasonable to expect that be adequately treated with voriconazole. ~~(i.e., the IPA is not due to a voriconazole-resistant isolate or a breakthrough infection while receiving a mold-active azole antifungal [voriconazole, posaconazole, isavuconazole or itraconazole] that requires therapy with a non-azole antifungal agent).~~ Subjects with breakthrough IPA while receiving ~~a mold-active azole~~ antifungal prophylaxis may be considered for enrollment **if, in the investigator´s judgement, the IPA episode is expected to be adequately treated with voriconazole.** ~~in circumstances in which the antifungal prophylaxis is considered not~~

	~~optimally administered (e.g. only few doses were given, frequent interruptions, subject not achieving adequate plasma exposures) and/or if the Aspergillus spp. isolate (when available) is known or expected to be susceptible to voriconazole.~~
Synopsis Target Population	Male or female subjects 18 years of age and older with a ~~possible,~~ probable or proven IPA ~~based on EORTC MSG criteria plus at least one positive serum GMI test.~~
Synopsis KEY Inclusion Criteria **AND** Section 12.1 Inclusion Criteria	Amended Inclusion #2 to delete the ~~strikethrough~~ text and include the **bolded** text: 2. Subject has a ~~possible,~~ probable or proven IPA based on **the protocol-specified criteria** ~~EORTC MSG~~ **(Section 22.3) that requires antifungal treatment**. **a. Note: Subjects with possible IPA may enter the Screening Phase of the study but will only be randomized after meeting criteria for probable or proven IPA.** The Inclusion Criteria was updated to clarify the IPA treatment requirement.
Synopsis KEY Inclusion Criteria **AND** Section 12.1 Inclusion Criteria	Remove Inclusion #3 in entirety: **3.** ~~Subject has a result of a serum GMI ≥0.5 OR a result from a BAL sample GMI ≥1. Either result should be from a sample obtained within the 96 hours preceding enrollment into the study (Baseline/Treatment Day 1).~~
Synopsis KEY Inclusion Criteria **AND** Section 12.1 Inclusion Criteria	Simplified Inclusion #6 to read as follows: 6. For subjects who are receiving antifungal prophylaxis, ~~the Subject has an~~ IPA episode **would**, in the investigator´s judgement, ~~requires antifungal therapy and may~~ be adequately treated with voriconazole. ~~(i.e., the IPA is not a breakthrough infection while receiving a mold-active azole antifungal [voriconazole, posaconazole, isavuconazole or itraconazole] that requires therapy with a non-azole antifungal agent).~~ **The Inclusion Criteria was updated to clarify the IPA treatment requirement.**
Synopsis Study Evaluations	Amended the following sentence with the **bolded** text: Efficacy Evaluations: Efficacy will be assessed primarily in terms of Global Response, ACM and GMI decrease **(GMI**

	decrease will only be assessed for subjects with a serum GMI above 0 at Baseline). Text added to clarify the efficacy evaluation
Section 8.1 Background Information	Exposure information was updated
Section 11.1 Overall Description of the Study	Amended the following paragraphs to delete the ~~strikethrough~~ text and include the **bolded** text: This is a multicenter, randomized, double-blind, two-arm study to evaluate the safety, tolerability, efficacy and PK of the coadministration of SCY-078 plus voriconazole compared to coadministration of SCY-078 placebo plus voriconazole in male and female subjects 18 years of age and older with ~~possible,~~ probable or proven IPA **as defined in** ~~based on EORTC-MSG criteria (see~~ Section ~~12.1~~22.3 (adapted EORTC-MSG criteria)). ~~In addition, all subjects must be positive (≥0.5) for serum GMI (serum or BAL).~~ The primary objective of the study is to evaluate the safety and tolerability of the coadministration of SCY-078 plus voriconazole compared to the coadministration of SCY-078 placebo plus voriconazole in the treatment of IPA. Secondary objectives include efficacy assessments based on Global Response, ACM and GMI decrease **(GMI decrease will only be assessed for subjects with a Serum GMI above 0 at Baseline)**, and PK. Being this a Phase 2 study, multiple **secondary and** exploratory endpoints are planned, which will be evaluated as data allow considering the limitations of the planned sample size. This study is intended for subjects with an IPA episode that, in the investigator´s judgement, requires antifungal therapy and is reasonable to expect that be adequately treated with voriconazole. ~~(i.e., the IPA is not due to a voriconazole-resistant isolate or a breakthrough infection while receiving a mold-active azole antifungal [voriconazole, posaconazole, isavuconazole or itraconazole] that requires therapy with a non-azole antifungal agent).~~ Subjects with breakthrough IPA while receiving ~~a mold-active azole~~ antifungal **prophylaxis** may be considered for enrollment **if, in the investigator´s judgement, the IPA episode is expected to be adequately treated with voriconazole.** ~~in circumstances in which the antifungal prophylaxis is considered nt optimally administered (e.g. only few doses were given, frequent interruptions, subject not achieving adequate~~

	~~plasma exposures) and/or if the Aspergillus spp. isolate (when available) is known or expected to be susceptible to voriconazole.~~ The addition of the BAL GMI was made to include all EORTC/MSG IPA diagnostic criteria. BAL GMI is not required throughout the study and is thus not included in the secondary objective measurement of efficacy.
Section 11.1.1.1 Screening Period (Days -4 to -1)	Amended the follow paragraphs to delete the ~~strikethrough~~ text and include the **bolded** text: Subjects with Probable or Proven IPA ~~Subjects with a probable or proven IPA AND at least one positive serum or BAL GMI sample collected within 96 hours before enrollment (Baseline/Treatment Day 1) who meet all other inclusion and exclusion criteria will enter the Treatment Period and will be randomized to one of the two study treatment groups.~~ ~~The Screening Period and Baseline visit (Treatment Day 1) may occur simultaneously. for subjects who have a positive serum or BAL GMI test (≥ 0.5 or 1 respectively) at the time of IPA diagnosis, if all other criteria are met.~~ **Subjects with a probable or proven IPA, as defined in Section 22.3 and who meet all other inclusion and exclusion criteria will enter the Treatment Period and will be randomized to one of the two study treatment groups.** **The Screening Visit and Baseline visit (Treatment Day 1) may occur simultaneously for subjects who have met the criteria for probable or proven IPA at screening, if all other criteria are met.** Subjects with Possible IPA ~~Subjects with possible IPA may enter the Screening Period of the study. During the Screening Period, subjects will receive voriconazole or any other mold-active agent (e.g., echinocandin, amphotericin B, or other azoles for mold infections) as per label instructions and local standard practice, and samples for serum determination of GMI will be collected on a daily basis. For subjects that only have BAL GMI, subsequent BAL, if done, should be sent for GMI measurements. Subjects may remain in the Screening Period (i.e., Screening Days -4 to -1) until one positive serum or BAL GMI test is reported, but in no case for more than 4 days of mold-active antifungal treatment unless approved by the medical monitor, as explained below. Once~~

	~~a positive serum or BAL GMI test is reported and if all other inclusion and exclusion criteria are met, the subject will enter the Treatment Period and will be randomized to one of the two study treatment groups.~~ ~~Subjects with positive serum or BAL GMI results available shortly after the subject has reached the 4-day mold-active antifungal treatment limit allowance (i.e., after 4 days but no more than 7 days of mold-active antifungal treatment) may be randomized into the study with the approval of the medical monitor, who will take into consideration the total number of days of mold-active agent administration up to that point as well as the subject´s response to therapy. If serum or BAL GMI results are negative, the subject will not be randomized and will be discontinued from the study. Only limited information will be collected for screened subjects who do not qualify for enrollment~~ **Subjects with possible IPA may enter the Screening Period of the study. During the Screening Period, subjects will receive voriconazole or any other mold-active agent (e.g., echinocandin, amphotericin B, or other azoles for mold infections) as per label instructions and local standard practice, and samples for serum determination of GMI will be collected on a daily basis. Other samples (e.g., bronchioalveolar lavage, cytology or histopathology) may be collected as clinically indicated to confirm the IPA diagnosis. Subjects may remain in the Screening Period (i.e. Screening Days -4 to -1) until the criteria of probable or proven IPA is met (Section 22.3), but in no case for more than 4 days of mold-active antifungal treatment unless approved by the medical monitor, as explained below. This 4-day mold-active antifungal treatment limit prior to randomization is inclusive of any days of mold-active antifungal that the subject may have received prior to Screening. Once the criteria for a probable or proven IPA is met and, if all other inclusion and exclusion criteria are met, the subject will enter the Treatment Period and will be randomized to one of the two study treatment groups.** **Subjects meeting criteria for probable or proven IPA shortly after the subject has reached the 4-day mold-active antifungal treatment limit allowance (i.e., after 4 days but no more than 7 days of mold-active antifungal treatment) may be randomized into the study with the approval of the medical monitor, who will take into consideration the total number of days of mold-active**

	agent administration up to that point as well as the subject´s response to therapy. If the criteria for probable or proven IPA is not met within 7 days after initiation of mold-active antifungal treatment for the IPA episode, the subject will not be randomized and will be discontinued from the study. Only limited information will be collected for screened subjects who do not qualify for enrollment
Section 11.1.1.2 Baseline (Treatment Day 1)	For subjects who have a probable or proven IPA ~~AND a positive serum GMI test at the time of IPA diagnosis,~~ the Screening Period and Baseline visit may be combined. For subjects who have a possible IPA at **Screening Visit** AND **the criteria for upgrading the case to probable or proven IPA is gathered** ~~a positive serum GMI test (≥ 0.5)~~ during the Screening Period, the inclusion and exclusion criteria will be reviewed again at Baseline to confirm eligibility.
Section 11.1.2 Study Assessment – Efficacy Assessments	Removed the word serum and included the word PCR from the following bullet point: • mycological testing, including fungal cultures, **PCR,** histopathological or cytopathological analysis of relevant tissues or samples (e.g., lung biopsy sample, bronchoalveolar lavage [BAL] fluid), and serological testing (~~serum~~ GMI). To ensure the section was aligned with the addition of BAL GMI.
Section 13.1.2 Treatment Duration	The word serum was deleted from the following paragraph: Subjects who have received more than 4 days but no more than 7 days of voriconazole or other mold-active agent before inclusion criteria are met (i.e., positive ~~serum~~ GMI results become available) may be randomized into the study with the approval of the medical monitor, who will take into consideration the total number of days of mold-active agent administration up to that point as well as the subject´s response to therapy. To ensure the section was aligned with the addition of BAL GMI.
Section 15.15 Galactomannan Index Assessment	Amended the following paragraph with the ~~strikethrough and~~ **bolded text**: Serum ~~(or BAL, if used)~~ GMI will be determined at all study visits. At Screening, at least one positive ~~serum~~ sample collected within 96 hours before enrollment must be

	available for all subjects. For subjects with a possible IPA, serum samples will be collected daily for a maximum Screening Period of 4 days (Days -4 to -1) **or** until one positive GMI result (≥0.5) is reported. ~~For subjects that only have~~ **BAL samples, if collected per local practices, should be sent for GMI.~~**~~, subsequent BAL if done, should be sent for GMI measurements~~**. ~~If a positive serum GMI test is reported~~ **(≥ 0.5 for serum or ≥ 1 for BAL)** ~~after 4 days but no more than 7 of mold active antifungal treatment, the case will be discussed with the medical monitor to evaluate eligibility. If serum GMI results are negative, the subject will not be randomized and will be discontinued from the study.~~ ~~Serum~~ GMI samples during the Screening Period for evaluation of enrollment qualification will be processed locally (either the site laboratory or a designated regional laboratory). These results will be available in real time to make enrollment decisions. Results from GMI tests processed locally should be entered into the eCRF. AND An immunoenzymatic sandwich microplate assay method will be generally used to determine ~~serum~~ GMI. Other methods such as lateral flow devices, which have received CE mark and/or FDA approval for galactomannan determination in serum **and BAL**, may be used during the Screening Period for evaluation of enrollment qualification. In these cases, enrollment qualification will be based on the device label recommendation for considering a serum test as positive~~, which in general should correspond to GMI ≥ 0.5 in a immunoenzymatic sandwich microplate assay.~~ The addition of the BAL GMI was made to include all EORTC/MSG IPA diagnostic criteria.
Section 15.21 Assessment of Treatment Outcome	Included the **bolded** text in the following bullet point: o Other mycological tests, including fungal cultures, histopathological and cytological analyses, and other serological tests **(including BAL GMI)** (Section 15.14) To ensure the section was aligned with the addition of BAL GMI.
Section 16.0	The following Procedure was updated with the bolded text:

Study Schedule Procedure	All Mycological Testing[j] **including BAL GMI[l] (**other than serum GMI, serum β -D Glucan, and plasma *Aspergillus* PCR**)** To ensure the section was aligned with the addition of BAL GMI.
Section 16.0 Study Schedule Footnotes	Footnote l was updated with the bolded text: l. At Screening, at least one positive serum **or BAL** sample collected within 96 hours before enrollment must be available for all subjects. For subjects with a possible IPA, serum **or BAL** samples will be collected daily for a maximum Screening Period of 4 days (Days -4 to -1) until at least one positive GMI result (≥ 0.5 **for serum and 1 for BAL**) is reported. If a positive serum **or BAL** GMI test is reported after 4 days but no more than 7 days of mold-active antifungal treatment, the case will be discussed with the medical monitor to evaluate eligibility. If GMI results during the Screening period are negative, the subject will not be randomized and will be discontinued from the study. The addition of the BAL GMI was made to include all EORTC/MSG IPA diagnostic criteria.
Section 19.7.1 Efficacy Assessments	Amended the Section with the following **bolded** text: Efficacy will be assessed primarily in terms of Global Response, ACM and GMI decrease **(GMI decrease will only be assessed for subjects with a Serum GMI above 0 at Baseline)**. The DRC evaluation of Global Response is considered the key efficacy evaluation, considering the expert and independent nature of the DRC assessment. In addition to Global Response, clinical, mycological and radiological outcomes will also be assessed. Exploratory efficacy assessments include, among others, recurrence, performance indicators and other serological biomarkers (β-D-glucan and *Aspergillus* PCR). BAL GMI is not required throughout the study and is ths not included in the secondary objective measurement of efficacy.
Section 19.7.1.3	Amended the section with the following **bolded** text: GMI decrease will be assessed in terms of absolute and percentage reduction relative to Baseline, and in terms of time to achieve the GMI absolute and percentage reductions.

	GMI decrease will be assessed in subjects with Baseline serum GMI above 0, only. BAL GMI is not required throughout the study and is ths not included in the secondary objective measurement of efficacy.
Section 22.3 Appendix C: Definitions of Invasive Fungal Disease (IFD)	Amended the following section with the ~~strikethrough~~ and **bolded** text: Mycological Criteria **(all available GMI results from serum or BAL within 7 days prior to enrollment should be included in the CRF)** Serum galactomannan (GM) with at least one GMI value of ≥~~1~~ **0.5** ~~OR two consecutive samples with values of ≥0.5~~ are adequate mycological evidence for considering an IPA as probable in this study. **BAL galactomannan (GM) with at least one GMI value of ≥1** **Cytology, direct microscopy, culture or polymerase chain reaction (PCR) from bronchoalveolar lavage (BAL) fluid, bronchial brush, or other lung samples indicating presence of Aspergillus spp** ~~o Demonstration of additional positive mycological criteria such us BAL GM, cytology, direct microscopy, culture from non-sterile sites, antigen detection and polymerase chain reaction (PCR) may be used by the DRC to confirm probable or proven IPA during the analysis. However, for the purpose of enrollment into the study, a positive serum GM is required.~~

5.0 Abbreviations

ABBREVIATION	DEFINITION
ACM	all-cause mortality
AE	adverse event
ALT	alanine aminotransferase
AMB	amphotericin B
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve (0 to infinity)
$AUC_{0–24}$	area under the concentration-time curve (0 to 24 hours)
BAL	bronchoalveolar fluid
BID	twice daily
BUN	blood urea nitrogen
CD	compact disk
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	clearance/fraction
CLSI	Clinical and Laboratory Standards Institute
C_{max}	maximum concentration
CPK	creatine phosphokinase
CRO	contract research organization
CSP	caspofungin
CT	computed tomography
CYP	cytochrome P450
DRC	Data Review Committee
DVD	digital versatile disk
EC	Ethics Committee
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form

ABBREVIATION	DEFINITION
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EoT	end of treatment
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
GMI	galactomannan index
GSI	glucan synthase inhibitor
GvHD	graft-versus-host disease
HCT	hematopoietic stem cell transplant
HDPE	high density polyethylene
HM	hematologic malignancy
IB	Investigator´s Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
ID	identification
IFD	invasive fungal disease
IPA	invasive pulmonary aspergillosis
IRB	Institutional Review Board
ISA	isavuconazole
ITT	Intent-to-treat
IV	intravenous
IWRS	interactive web response system
LDH	lactate dehydrogenase

ABBREVIATION	DEFINITION
LFAB	lipid formulation of amphotericin B
LFT	liver function test
MEC	minimal effective concentration
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MSG	Mycoses Study Group
NG	nasogastric
OTC	over-the-counter
PBPK	Physiologically Based Pharmacokinetic
PD	pharmacodynamics
PEG	percutaneous endoscopic gastrostomy
PI	principal investigator
PK	pharmacokinetics
Pop PK	population pharmacokinetics
PP	per protocol
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTcF	QTc interval corrected for heart rate using Fridericia´s
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	standard of care
TDM	therapeutic drug monitoring
TEAE	treatment-emergent adverse event

ABBREVIATION	DEFINITION
ULN	upper limit of normal
US	United States
WBC	white blood cell
WT	wild type
β-hCG	β-human chorionic gonadotropin

6.0 Protocol Synopsis

Title: A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of the Coadministration of SCY-078 with Voriconazole in Patients with Invasive Pulmonary Aspergillosis (SCYNERGIA)

Primary Objective:

To evaluate the safety and tolerability of the coadministration of SCY-078 and voriconazole compared with the coadministration of SCY-078 placebo and voriconazole in the treatment of invasive pulmonary aspergillosis (IPA).

Secondary Objectives:

- To evaluate the efficacy of the coadministration of SCY-078 and voriconazole compared with that of SCY-078 placebo and voriconazole in the treatment of IPA
  - based on Global Response
    - as determined by the Data Review Committee (DRC)
    - as determined by the Principal Investigator
  - based on all-cause mortality (ACM)
  - based on serum galactomannan index (GMI) decrease
  - based on clinical response, mycological response and radiological response
    - as determined by the DRC
    - as determined by the Principal Investigator
- To evaluate the pharmacokinetics (PK) of SCY-078 and voriconazole

Exploratory Objectives:

- To evaluate the efficacy of the coadministration of SCY-078 and voriconazole compared with coadministration of SCY-078 placebo and voriconazole
  - based on other biomarkers of fungal infection (i.e., serum levels of β-D-glucan and plasma *Aspergillus* PCR)
  - based on change in the performance indicator (i.e., Karnofsky score)
  - based on the rate of recurrence of IPA at Week 6 after End of Treatment (EoT) as determined by the DRC
  - based on the need for additional systemic antifungal treatment (other than secondary prophylaxis) until week 6 after EoT
- To evaluate the relationship between selected endpoints to ACM at Days 42 and 84.
- To evaluate healthcare resources utilization for the patients receiving the coadministration of SCY-078 and voriconazole compared with coadministration of SCY-078 placebo and voriconazole based on overall hospital stay and intensive care unit (ICU) stay.
- To assess the effect of the coadministration of SCY-078 and voriconazole compared with coadministration of SCY-078 placebo and voriconazole on on-schedule administration of planned therapies for the underlying condition.

Primary Endpoint:

- Frequency of treatment-emergent adverse events (TEAEs), drug-related adverse events (AEs), discontinuations due to AEs and deaths.

Secondary Endpoints:

- Global Response as measured by:
  - Percentage of subjects with Complete Response or Partial Response at EoT (key secondary endpoint), Day 42 and Day 84, as determined by the DRC
  - Percentage of subjects with Complete Response or Partial Response at EoT, Day 42 and Day 84, as determined by the Principal Investigator
- Overall survival, defined as the time from randomization to time of death up to Day 84
- Percentage of subjects who died (any cause) at Days 42 and 84
- Absolute reduction and percent change in serum GMI from Baseline to Weeks 1, 2, 4 and 6
- Percentage of subjects with the following changes in serum GMI from Baseline:
  - Fifty percent reduction or greater at Weeks 1, 2, 4 and 6
  - Twenty-five percent reduction or greater at Weeks 1, 2, 4 and 6
  - Any percent reduction at Weeks 1, 2, 4 and 6
  - Reduction equal to or greater than 0.25 at Weeks 1, 2, 4 and 6
  - Reduction to < 0.5 at Weeks 1, 2, 4 and 6
- Time to achieve the following changes in serum GMI from Baseline:
  - Fifty percent reduction
  - Twenty-five percent reduction
  - Any percent reduction
  - Reduction equal to or greater than 0.25
  - Reduction to < 0.5 in 2 consecutive samples
- Percentage of subjects with:
  - Clinical Response at EoT, Day 42 and Day 84, as determined by the DRC
  - Mycological Response at EoT, Day 42 and Day 84, as determined by the DRC
  - Radiological Response at EoT, Day 42 and Day 84, as determined by the DRC
- Percentage of subjects with:
  - Clinical Response at EoT, Day 42 and Day 84, as determined by the Principal Investigator
  - Mycological Response at EoT, Day 42 and Day 84, as determined by the Principal Investigator
  - Radiological Response at EoT, Day 42 and Day 84, as determined by the Principal Investigator
- SCY-078 and voriconazole plasma concentrations population PK analysis

Exploratory Endpoints:

- Absolute and percentage changes in serum β-D-glucan from Baseline at Weeks 1, 2, 4 and 6
- Percentage of subjects with the following changes in serum β -D-glucan from Baseline (if positive):
  - Fifty percent reduction or greater at Weeks 1, 2, 4 and 6
  - Twenty-five percent reduction or greater at Weeks 1, 2, 4 and 6
  - Any percent reduction at Weeks 1, 2, 4 and 6
  - Negative serum β -D-glucan at Weeks 1, 2, 4 and 6
- Percentage of subjects that convert from positive plasma *Aspergillus* PCR at Baseline to

negative at Weeks 1, 2, 4 and 6
- Absolute change in Karnofsky score from Baseline to Days 42 and 84
- Time to achieve a 10-point improvement in Karnofsky score from Baseline
- Percentage of subjects with a recurrence of the baseline fungal infection within 42 days (Week 6) after EoT
- Relationship between GMI decrease and ACM at Days 42 and 84
- Days of hospital stay, and Days of ICU stay
- Percentage of subjects who are able to receive on-schedule administration of the planned therapies for their underlying condition

Study Design:
This is a multicenter, randomized, double-blind, two-arm study to evaluate the safety, tolerability, efficacy and PK of the coadministration of SCY-078 plus voriconazole compared to the coadministration of SCY-078 placebo plus voriconazole in male and female subjects 18 years of age and older with a probable or proven IPA.

The primary objective of the study is to evaluate the safety and tolerability of the coadministration of SCY-078 plus voriconazole compared to the coadministration of SCY-078 placebo plus voriconazole in the treatment of IPA. Secondary objectives include efficacy assessments based on Global Response, ACM and GMI decrease, and PK. Being this a Phase 2 study, multiple secondary and exploratory endpoints are planned, which will be evaluated as data allow considering the limitation of the planned sample size. Subjects must meet all study criteria to be eligible for inclusion.

The study will be conducted at approximately 30 sites globally. Approximately 90 subjects will be screened to randomize a total of approximately 60 subjects (30 subjects per group) into one of the two treatment groups of the study (SCY-078 plus voriconazole or SCY-078 placebo plus voriconazole).
Subjects will receive study treatment for the entire duration of the antifungal therapy (i.e., for a recommended minimum of 6 weeks and a maximum of 13 weeks).

The study will consist of a Screening Period (Days -4 to -1) to assess subject eligibility; a Baseline visit (also considered Treatment Day 1) to confirm subject eligibility and begin study treatment; additional scheduled treatment visits (Treatment Days 3, 7, 10, 14 and treatment visits every 14 days thereafter until the EoT) to perform safety, tolerability, efficacy and PK assessments, an EoT visit to assess efficacy outcomes, a Follow-up (FU) visit 6 weeks after EoT (6-Week FU) to assess recurrence and safety, and 2 survival visits/contacts to determine survival status and treatment outcome. The Screening Period and Baseline visit may be combined for certain subjects. Unscheduled visits may also be conducted as needed.

Subjects with a **probable or proven IPA** as defined in Section 22.3 who meet all other inclusion and exclusion criteria will enter the Treatment Period and will be randomized to one of the two study treatment groups.

The Screening Visit and Baseline visit (Treatment Day 1) may occur simultaneously for subjects

who have met the criteria for probable or proven IPA at screening, if all other criteria are met.

Subjects with **possible IPA** may enter the Screening Period of the study. During the Screening Period, subjects will receive voriconazole or any other mold-active agent (e.g., echinocandin, amphotericin B, or other azoles for mold infections) as per label instructions and local standard practice, and samples for serum determination of GMI will be collected on a daily basis. Other samples (e.g., bronchioalveolar lavage, cytology or histopathology) may be collected as clinically indicated to confirm the IPA diagnosis. Subjects may remain in the Screening Period (i.e. Screening Days -4 to -1) until the criteria of probable or proven IPA is met (Section 22.3), but in no case for more than 4 days of mold-active antifungal treatment unless approved by the medical monitor, as explained below. This 4-day mold-active antifungal treatment limit prior to randomization is inclusive of any days of mold-active antifungal that the subject may have received prior to Screening. Once the criteria for a probable or proven IPA is met and, if all other inclusion and exclusion criteria are met, the subject will enter the Treatment Period and will be randomized to one of the two study treatment groups.

Subjects meeting criteria for probable or proven IPA shortly after the subject has reached the 4-day mold-active antifungal treatment limit allowance (i.e., after 4 days but no more than 7 days of mold-active antifungal treatment) may be randomized into the study with the approval of the medical monitor, who will take into consideration the total number of days of mold-active agent administration up to that point as well as the subject´s response to therapy. If the criteria for probable or proven IPA is not met within 7 days after initiation of mold-active antifungal treatment for the IPA episode, the subject will not be randomized and will be discontinued from the study. Only limited information will be collected for screened subjects who do not qualify for enrollment.

This study is intended for subjects with an IPA episode that, in the investigator´s judgement, requires antifungal therapy and is reasonable to expect that be adequately treated with voriconazole. Subjects with breakthrough IPA while receiving antifungal prophylaxis may be considered for enrollment if, in the investigator´s judgement, the IPA episode is expected to be adequately treated with voriconazole.

Target Population: Male or female subjects 18 years of age and older with a probable or proven IPA.

KEY Inclusion Criteria

Subjects must fulfill all of the following **KEY** criteria to be eligible for study admission:

1. Subject is a male or female adult ≥18 years of age on the day the study informed consent form (ICF) is signed.
2. Subject has a probable or proven IPA based on the protocol-specified criteria (Section 22.3) that requires antifungal treatment.
    b. Note: Subjects with possible IPA may enter the Screening Phase of the study but will only be randomized after meeting criteria for probable or proven IPA.
3. Subject has one of the following:
    c. a diagnosis of a hematological malignancy or a myelodysplastic syndrome or aplastic anemia or has undergone hematopoietic cell transplantation, **OR**
    d. who either recently resolved or ongoing neutropenia (neutropenia defined as absolute neutrophil count < 0.5 x 10^9/L [< 500/mm3] for > 10 days),

temporally related to the onset of fungal disease **OR**

e. who received treatment with other recognized T-cell immunosuppressants (such as cyclosporine, tacrolimus, monoclonal antibodies or nucleoside analogs) during the past 90 days including solid organ transplant patients. **OR**

f. with inherited severe immunodeficiency (e.g. chronic granulomatous disease, severe combined immunodeficiency).

4. Subject has not received more than 4 days (96 hours) of prior mold-active antifungal therapy for the treatment of the IPA episode in the 7 days preceding enrollment into the study (Baseline/Treatment Day 1). However, subjects who have received more than 4 days but less than 7 days of prior mold-active antifungal therapy for the treatment of the IPA episode in the 7 days preceding enrollment into the study may be enrolled but will require approval from the study medical monitor, who will evaluate each subject on a case-by-case basis.
5. For subjects who are receiving antifungal prophylaxis the IPA episode would, in the investigator´s judgement, be adequately treated with voriconazole.

KEY Exclusion Criteria

A subject will be excluded from participation in the study if he or she meets any of the following **KEY** exclusion criteria:

1. Subject has a fungal disease with central nervous system involvement suspected at Screening.
2. Subject is receiving, has received or anticipates to be receiving concomitant medications that are listed in the prohibited medication list (Appendix A in full protocol) within the specified washout periods.
3. Subject has a Karnofsky score <20.
4. Subject is expected to die from a non-infectious cause within 30 days from the day the study ICF is signed.
5. Subject is under mechanical ventilation.
6. Subject has abnormal liver test parameters: AST or ALT ≥5 x ULN and/or total bilirubin >2.5 x ULN.
   Note: Subjects with unconjugated hyperbilirubinemia (< 7mg/dL) with a diagnosis of Gilbert's disease **are not excluded.**

Study Drugs: SCY-078 250 mg and SCY-078 250 mg matching placebo tablets will be provided by the Sponsor. It is expected that voriconazole (intravenous [IV] and oral) will be provided by the site's pharmacy. In extenuating circumstances, when the site's pharmacy is not able to provide the SOC voriconazole, the Sponsor will assist in obtaining it.
SCY 078 citrate drug product for oral administration will be supplied as a tablet containing 250 mg of SCY-078 active ingredient on a free-base basis. In addition to the active ingredient, the tablet formulation also contains silicified microcrystalline cellulose, crospovidone, mannitol, colloidal silicon dioxide, magnesium stearate (non-bovine) and butylated hydroxyanisole.
IV voriconazole will be supplied in a single-use vial as a sterile lyophilized powder equivalent to 200 mg of voriconazole. Oral voriconazole will be supplied as a 200-mg tablet.
SCY-078 drug supplies (SCY-078 citrate and matching placebo tablets) will be packaged in high density polyethylene (HDPE) bottles fitted with induction seals and child-resistant polypropylene plastic closures.

Study Treatment Groups: All eligible subjects will be randomized in a 1:1 ratio to one of the two study treatment groups and will receive treatment for a recommended minimum of 6 weeks and a maximum of 13 weeks.

Once randomized, subjects will receive either voriconazole plus SCY-078 or voriconazole plus matching SCY-078 placebo for the entire duration of the antifungal treatment, until they reach EoT or a discontinuation occurs.

Voriconazole + SCY-078

- Either IV **voriconazole** (loading dose of 6 mg/kg BID on Day 1 followed by maintenance dose of 4 mg/kg BID from Day 2 onwards) **OR** oral **voriconazole** (loading dose of 400 mg BID on Day 1 followed by maintenance dose of 200 mg BID from Day 2 onwards).

  PLUS
- Oral **SCY-078** (loading dose of 500 mg [2 tablets of 250 mg] BID on Days 1 and 2 followed by maintenance dose of 500 mg [2 tablets of 250 mg] QD from Day 3 onwards). After the first 10 randomized subjects have been treated with the SCY-078 and voriconazole for at least 7 days, an interim PK analysis will be conducted. Based on the data from this analysis, the oral **SCY-078** dose for subjects subsequently randomized may be increased up to a loading dose of 750 mg (3 tablets of 250 mg) BID on Days 1 and 2 followed by a maintenance dose of 750 mg (3 tablets of 250 mg) QD from Day 3 onwards.

Voriconazole + SCY-078 Placebo

- Either IV **voriconazole** (loading dose of 6 mg/kg BID on Day 1 followed by maintenance dose of 4 mg/kg BID from Day 2 onwards) **OR** oral voriconazole (loading dose of 400 mg BID on Day 1 followed by maintenance dose of 200 mg BID from Day 2 onwards).

  PLUS
- Placebo matching oral **SCY-078**.
  - Subjects prior to interim PK analysis: loading dose of 2 tablets given BID on Days 1 and 2 followed by maintenance dose of 2 tablets given QD from Day 3 onwards
  - Subjects subsequently randomized (depending on interim PK analysis): loading dose of up to 3 tablets given BID on Days 1 and 2 followed by a maintenance dose of up to 3 tablets given QD from Day 3 onwards

Subjects will receive the administration of voriconazole as per label instructions and local standard practice. The individual dose of voriconazole may be adjusted by the investigator according to results from standard of care voriconazole drug monitoring evaluations. Subjects should be instructed to take oral voriconazole 1 hour before or after a meal, every 12 hours. The dose of SCY-078 will not be adjusted for a particular subject. Subjects will be instructed to take the oral SCY-078 preferably with meal, twice a day (BID) approximately 12 hours apart the first 2 days (loading dose) and once daily (QD) subsequently (maintenance dose). The dose of SCY-078 may be adjusted for subjects randomized after the interim PK analysis. Until a decision to adjust the dose is made based on data from this analysis, subjects will continue receiving SCY-078 500 mg doses.

Study Blinding, Randomization and Stratification: This is a double-blind study. All site and sponsor personnel will be blinded to treatment assignment. Subject randomization will be performed using an Interactive Web Response System (IWRS). Eligible subjects will be stratified to one of these groups at randomization:

- Hematological malignancies and /or hematopoietic cell transplantation recipients
- Solid organ transplant recipients
- Other immunocompromising conditions

In the event that the web-based IWRS system is not available, emergency unblinding can occur by contacting the Endpoint help-desk as follows: http://www.endpointclinical.com/help-desk.

Study Evaluations

Safety Evaluations: Subjects will be evaluated for safety and tolerability throughout the study, including parameters such as physical exam including visual function assessment, vital signs, 12-lead electrocardiograms (ECGs), safety laboratory tests (hematology, blood chemistry and urinalysis), concomitant medications, AEs and treatment discontinuations. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.

AEs will be collected and evaluated from Baseline (Treatment Day 1)), after the first dose of SCY-078 and SOC voriconazole and through the end of the study. AEs will also be collected at any unscheduled visits. A general physical exam will be conducted at Screening and Baseline (Treatment Day 1), at EoT and at the 6-Week FU visit. The physical examination will include an abbreviated assessment of general appearance, skin, eyes, heart, chest and abdomen. An overall visual function assessment will also be conducted as part of the physical exam to investigate visual acuity, visual field and color perception at Screening or Baseline. This visual function assessment will be repeated at approximately Treatment Day 28 if voriconazole treatment continues beyond 28 days. Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at Screening and Baseline (Treatment Day 1), at EoT and at unscheduled visits, if applicable. Safety laboratory tests (hematology, blood chemistry and urinalysis) will be performed at Screening and Baseline (Treatment Day 1), and on Treatment Days 7 and 14, at EoT and 6-Week FU. In addition, serum transaminase levels, bilirubin levels, serum electrolytes (potassium, magnesium and calcium) and amylase and lipase should be monitored at initiation of voriconazole therapy (Day 1) and then weekly during the first month of treatment (Day 7, Day 14, around Day 21 and Day 28). Monitoring frequency of these laboratory parameters may be reduced to monthly intervals during continued use of voriconazole if no clinically significant changes are noted. All medications (including prescription and over the counter [OTC] medications, supplements, and herbal products) taken from 28 days before Screening through the EoT will be recorded on the eCRF. Only the use of antifungal medications, antibiotics for any reason or medications to treat an AE will be recorded after EoT and through the 6-Week FU visit.

Efficacy Evaluations: Efficacy will be assessed primarily in terms of Global Response, ACM and GMI decrease (GMI decrease will only be assessed for subjects with a positive serum GMI at Baseline). In addition to Global Response, clinical, mycological and radiological outcomes will also be assessed. Exploratory efficacy assessments include, among others, recurrence,

performance indicators and other serological biomarkers (β-D-glucan and *Aspergillus* PCR).

The following treatment outcome definitions will be used for the assessment of efficacy:
Global Response will be assessed based on the following definitions:

- Global Response
  - Complete Response: Survival and resolution of all attributable symptoms and signs of disease; plus, successful radiological outcome; plus, documented mycological eradication of infected sites that are accessible to repeated sampling or presumed eradication of sites that are not accessible to repeated sampling.
  - Partial Response: Survival and improvement of attributable symptoms and signs of disease; plus at least 25% reduction in diameter of radiological lesion(s); plus, documented mycological eradication of infected sites that are accessible to repeated sampling or presumed eradication of sites that are not accessible to repeated sampling. In cases of radiological stabilization (defined as 0%-25% reduction in the diameter of the lesion), resolution of attributable symptoms and signs of fungal disease can be equated with a partial response. In cases of radiological stabilization, biopsy of an infected site (e.g., lung biopsy) showing no evidence of hyphae and negative culture results can be equated with a partial response.
  - Stable response: Survival and no improvement in any attributable symptoms and signs of disease; plus, radiological stabilization (defined as a 0%-25% reduction in the diameter of the lesion); or persistent isolation of mold or histological presence of invasive hyphae in infected sites.
  - Progression of disease: Worsening clinical symptoms and signs of disease; plus, new sites of disease or radiological worsening of preexisting lesions; or persistent isolation of mold species from infected sites.
  - Death: Death during the prespecified period of evaluation regardless of attribution.

Clinical, mycological and radiological outcome will be assessed based on the following definitions:

- Clinical response
  - Success:
    - Resolution of all attributable clinical symptoms and physical findings
    - Partial resolution of attributable clinical symptoms and physical findings
  - Failure:
    - No resolution of any attributable clinical symptoms and physical findings and/or worsening
  - Not applicable:
    - No attributable signs and symptoms present at Baseline and no symptoms attributable to invasive fungal disease developed post Baseline

- Mycological response
  - Success:
    - Eradication
    - Presumed eradication
  - Failure:

- Persistence
- Presumed persistence

- Not applicable:
  - No mycological evidence available at Baseline

- Radiological response
  - Day 42:
    - Success (improvement of at least 25% from Baseline)
    - Failure
    - No post Baseline radiology available for patient with baseline evidence of radiological disease
    - Radiology not applicable at Baseline
  - Day 84:
    - Success (improvement of at least 50% from Baseline)
    - Failure
    - No post Baseline radiology available for patient with baseline evidence of radiological disease
    - Radiology not applicable at Baseline
  - EoT:
    - Success (improvement of at least 25% from Baseline if EoT occurs prior to Day 42; if EoT occurs after Day 42, at least 50% improvement from Baseline)
    - Failure
    - No post Baseline radiology available for patient with baseline evidence of radiological disease
    - Radiology not applicable at Baseline

Pharmacokinetic Evaluations: Voriconazole level determination as well as SCY-078 PK will be performed for all study subjects. Therapeutic drug monitoring (TDM) for voriconazole will be conducted as per local standard practice and samples for voriconazole TDM will be analyzed at the local laboratory. The target trough plasma concentration should be above 1.5 mg/L.

For the first 20 randomized subjects, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 2-4 hours and 6-8 hours after dosing for SCY-078 and voriconazole central lab PK testing. The PK data from the first 20 subjects will be assessed in an interim PK analysis that will keep the study team blinded.

For subsequent randomized subjects, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 4-8 hours after dosing for SCY-078 and voriconazole central lab PK testing. Results for plasma concentrations of SCY-078 and voriconazole analyzed by the central laboratory will not be available in real time.

Statistical Analyses:

All statistical processing will be performed using SAS® version 9.3 or later, unless otherwise stated. Descriptive statistics (i.e., number of subjects, mean, standard deviation, median, minimum, maximum) will be presented for all continuous variables; number and percentage of

subjects will be presented for categorical variables. For parameters measured over time, observed data and changes from baseline will be described for each time point. A Statistical Analysis Plan (SAP) describing all statistical analyses in detail will be provided as a separate document.

Sample Size Determination

This is an exploratory study with safety as a primary objective. As a result, no formal sample size calculations are defined and the data from this study will provide safety data for SCY-078 in patients along with a preliminary view of efficacy data, which can be used to design future studies.

Analysis Populations

The study populations used for the analyses are as follows:

Intent-to-Treat (ITT)/Safety Population: The ITT Population will include all randomized subjects who receive at least one dose of randomized study medication. The **Safety Population** will be the same as the ITT population.

Modified Intent-to-Treat (mITT) Population: The mITT population will be a subset of the ITT population that will include subjects who have a probable or proven IPA at baseline, per DRC, with at least one positive serum GMI at baseline.

Per-Protocol (PP) Population: The PP Population will be a subset of the ITT population and will include subjects who have a probable or proven IPA at baseline, per DRC, with at least one positive serum GMI at baseline, have completed at least 14 days of randomized study treatment and have at least one efficacy assessment post Baseline (Treatment Day 1) and no major protocol deviations.

PK Population: The PK Population will include all enrolled subjects who provide at least one PK sample.

Handling of Missing Data, Dose Adjustments and Early Withdrawals

For the efficacy analyses, subjects who do not have an EoT assessment will be assigned an indeterminate outcome, so will be classed as treatment failures for the corresponding efficacy analyses. For subjects who withdraw from the study early, every effort will be made to collect EoT visit information at the point of withdrawal.

Safety Analyses

All safety analyses will be conducted using the ITT/safety population; all safety variables will be listed.

The incidence and severity of TEAEs and serious adverse events (SAEs) and their relationship to treatment will be summarized. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or higher and presented by system organ class and preferred term.

Early discontinuation of study drug treatment will be presented and will include the reasons for and timing of such discontinuations.

Prior and concomitant medications will be summarized; medications will be classified based on the World Health Organization´s Drug Dictionary terminology.

Abnormal physical examinations will be listed. Laboratory evaluations will be summarized as observed values and changes from Baseline; shifts with respect to the laboratory reference range will be summarized. Events of clinical interest will be summarized.

Vital signs and ECG evaluations will be summarized as observed values and changes from

Baseline.

Efficacy Analyses

The secondary efficacy endpoint, the percentage of subjects with successful Global Response (Complete Response or Partial Response) at EoT, Day 42 and Day 84 as determined by the DRC and the Principal Investigator will be presented by treatment group along with an estimate of the difference between treatment groups. The response rate will be calculated for each treatment group as the number of successes divided by the total number of patients (success + failure + indeterminate). The difference in response rates between treatments will be presented along with a 95% confidence interval (CI), calculated using the method of Miettinen and Nurminen. The secondary analysis of ACM at Day 42 and Day 84 will be presented by treatment group along with an estimate of the difference between treatment groups. In addition, a Kaplan Meier plot will be produced to summarize overall survival over time.
The remaining secondary and exploratory endpoints will be summarized by treatment group.

Provided sufficient data are available to allow meaningful presentation, results of the key efficacy parameters will also be presented by oral SCY-078 dose level; by baseline *Aspergillus* species; by baseline minimum inhibitory concentration (MIC) and minimal effective concentration (MEC) for voriconazole and SCY-078, respectively; and by baseline neutropenia and persistent neutropenia at Week 2.

Considering the exploratory nature of this study, further analysis may be defined in the statistical analysis plan, as deemed appropriate. For example, if the data are heterogeneous within this randomized study, attempts may be made to match patients across the treatment groups on key disease criteria, provided sufficient data are available, to better understand the comparability of the randomized groups.

Pharmacokinetic Analyses

The sparse samples collected in this study will be analyzed using Population PK (Pop PK) analysis methods to estimate PK parameters (C_{max}, AUC, clearance/fraction absorbed [CL/F]) as applicable. Key collection and analysis timepoints include Day 1, Day 7 (i.e., steady state) and Day 14.
After the first 20 subjects have been treated for at least 7 days, an interim PK evaluation will be conducted to ensure that there are no clinically relevant effects of the co-administration of SCY-078 and voriconazole on the PK exposure (predicted AUC and C_{max} based on updated population PK model) of both drugs. The data from this analysis will inform, and if necessary adjust, the doses of the study drug for subjects subsequently randomized. The overall goal, considering that IPA is a life-threatening condition, is to ensure that >80% of subjects achieve an exposure that is at least equal to that reported as efficacious in the mice models of invasive aspergillosis (15.6 µg•mL/hr).
The results from the PK analyses will be presented in a separate report.

7.0 Schematic of Study Design

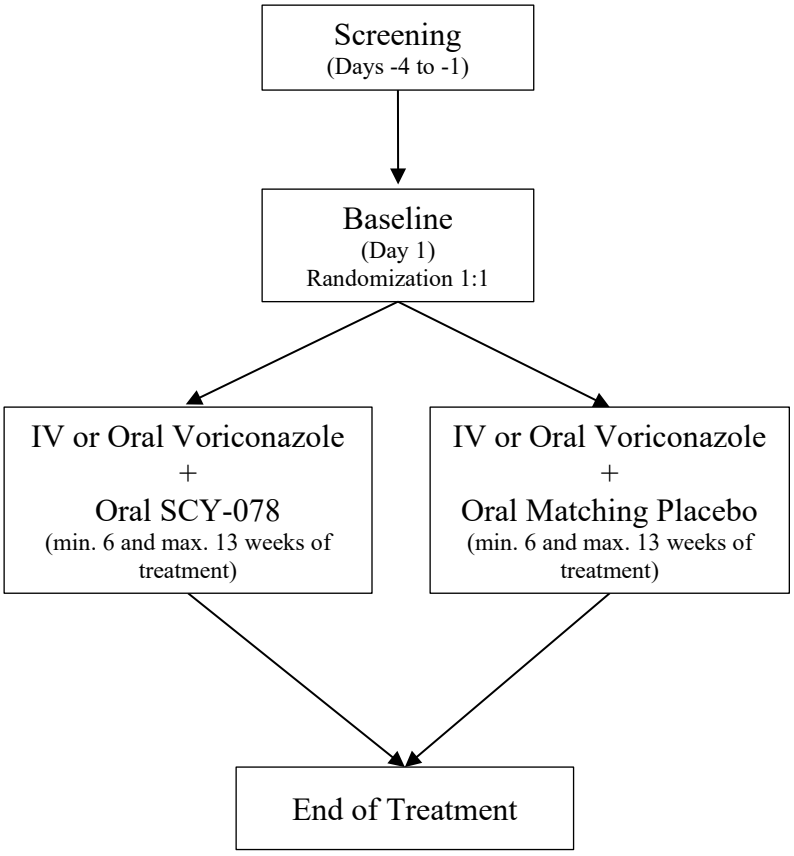


Figure 1 Schematic of Study Design

8.0 Background Information and Scientific Rationale

8.1 Background Information

Introduction and rationale

SCY-078 represents the first compound of the triterpene class of β-(1,3)-D-glucan synthesis inhibitors in development for the treatment of fungal infections. It is structurally distinct and retains activity *in vitro* against both azole-resistant and, importantly, the majority of clinical *Candida* isolates containing FKS gene mutations, which confer echinocandin resistance. Unlike echinocandins, SCY-078 is orally bioavailable, with *in vitro* and *in vivo* activity against *Candida* and *Aspergillus* species and, as such, it would represent the first oral non-azole treatment alternative for these infections.

Aspergillus species are ubiquitous in nature, and inhalation of infectious conidia from the environment is a frequent event. Tissue invasion is uncommon and invasive pulmonary aspergillosis (IPA) occurs most frequently in the setting of neutropenia and immunosuppression associated with therapy for hematologic malignancies, hematopoietic cell transplantation, or solid organ transplantation.

Histopathologically, invasive aspergillosis is characterized by progression of the infection across tissue planes. One hallmark of infection is vascular invasion with subsequent infarction and tissue necrosis. Most invasive infections are caused by members of the *A. fumigatus* species complex followed by *A. flavus*, *A. niger*, and *A. terreus*.

Treatment options for Invasive Aspergillosis

Voriconazole and isavuconazole are recommended for first-line (or "primary") therapy for IPA and lipid formulations of amphotericin B (LFABs) as well as echinocandins are alternative treatments.[1,2] However, diagnosis and treatment are still sub-optimal, and outcomes remain poor, especially in hematopoietic stem cell transplant (HSCT) recipients, with studies demonstrating unfavorable responses in >40% of such patients.[3] This is reflected by increased efforts in prophylactic and diagnostic strategies to either prevent the disease or start treatment as early as possible. Polyenes, azoles and SCY-078 target different cellular sites, impacting the fungal cell membrane and the cell wall, respectively. Voriconazole and isavuconazole are azole drugs that block the synthesis of ergosterol. The mechanism of action of polyenes, such as amphotericin B (AMB), has been proposed to be an interaction with cell membrane sterol resulting in the production of aqueous pores. Echinocandins such as caspofungin block the synthesis of (1-3)-β-D glucan, an essential component of the fungal cell.

Development of resistance of *Aspergillus* spp. against currently used antifungal agents has been reported and is particularly concerning for azoles. The widespread use of triazole antifungals in agricultural industry is suspected as the cause for the increasing numbers of "azole-resistant invasive aspergillosis". Lipid formulations of amphotericin B are often the recommended alternative treatment for invasive aspergillosis in patients who fail or have infections that are

resistant to mold-active azoles.[2,4] However, their use is often constrained by renal toxicity. Caspofungin is also approved for therapy in patients with invasive aspergillosis who experience failure with other antifungal drugs (i.e., approved for "salvage" therapy). It should be noted that neither echinocandins nor amphotericin B formulations are available for oral administration, posing a considerable limitation in terms of optimal patient care for fungal infections, which typically require several weeks of therapy.

Combination therapy

Although monotherapy with a single antifungal agent is in general recommended for most cases of IPA, combination therapy with 2 agents with different mechanisms of action has been explored in multiple trials and is recommended in some circumstances in recognized guidelines, particularly when there is a high risk of azole resistance.[2,5,6]

The largest randomized controlled study evaluating antifungal combination therapy for patients with IPA was reported by Marr K et al. in 2015.[7] This study assessed the safety and efficacy of voriconazole and anidulafungin compared with voriconazole monotherapy for the treatment of IPA. The study included 454 patients with hematological malignancies or hematopoietic stem cell transplantation and suspected or documented IPA and the primary analysis was done in 277 patients with documented IPA. Although the study failed to demonstrate statistically significant improvement in all-cause mortality with the combination therapy when compared with monotherapy, there was a clear trend towards improved survival in the group receiving combination therapy. Overall mortality rates at 6 weeks were 19.3% (26 of 135) for combination therapy and 27.5% (39 of 142) for monotherapy (difference, - 8.2 percentage points [95% CI, -19.0 to 1.5]; P = 0.087).

Most patients (218 of 277 [78.7%]) had a diagnosis of IPA established by radiographic findings and mycological evidence in the form of galactomannan positivity. In a post hoc analysis of this dominant subgroup, 6-week mortality was lower in combination therapy than in monotherapy (15.7% [17 of 108] vs. 27.3% [30 of 110]; difference, -11.5 percentage points [CI, -22.7 to -0.4]; P= 0.037). A limitation of this study was that anidulafungin is only available intravenously (IV), thus limiting its use for long-term administration as often needed in IPA patients, resulting in a median duration of the combination therapy of 14 days.

SCY-078 antifungal activity

The spectrum and potency of activity of SCY-078 has been evaluated by numerous independent laboratories against an extensive panel of clinically relevant yeast and mold isolates using the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) methods. Overall, the epidemiological studies have demonstrated that SCY-078 has potent, broad-spectrum activity against the majority of the clinical isolates tested. These studies have laid the foundation in support of the use of SCY-078 for the treatment of invasive fungal infections.

***In vitro* activity against *Candida* spp.**

SCY-078 has been evaluated against >2000 *Candida* isolates, including all clinically relevant species, more than 400 *C. glabrata* isolates and >100 *C. auris* isolates. These *in vitro* studies have demonstrated the broad range of anti-*Candida* spectrum of activity of SCY-078. Additionally, SCY-078 demonstrated *in vitro* activity against pre-formed biofilms, which is a relevant feature when addressing catheter-related *Candida* infections. Studies conducted with azole- and echinocandin-resistant strains have shown that SCY-078 retains activity (i.e., no significant change in minimum inhibitory concentration when compared to wild type) against >90% of azole-resistant strains and >70% of *Candida* strains with FKS mutations commonly associated with echinocandin resistance. Interestingly, although SCY-078 and the echinocandins share a similar mechanism of action (β-[1,3]-D-glucan synthesis inhibition), their clearly different molecular structure provides them with some differentiating characteristics in terms of microbiological activity.

***In vitro* activity against *Aspergillus* spp.**

The *in vitro* activity of SCY-078 has been evaluated against >450 clinical *Aspergillus* isolates, including most clinically relevant species and azole-resistant strains, both with mutational resistance as well as a wide range of so-called cryptic *Aspergillus* species with reduced antifungal susceptibility.

A recent study including more than 300 clinical *Aspergillus* spp. isolates illustrates the potent activity of SCY-078 against *Aspergillus* species.[8]

Table 1 *In vitro* Activity of SCY-078 against *Aspergillus* species

	MEC (µg/ml)		
Species	**Range**	**50%**	**90%**
A. flavus (n=54)	<0.06 to 0.25	<0.06	<0.06
A. fumigatus (n=134)	<0.06 to 4	<0.06	0.125
A. niger (n=27)	<0.06 to 0.5	<0.06	<0.06
A. terreus (n=72)	<0.06 to 0.125	<0.06	0.125
Other *Aspergillus* spp (n=24)	<0.06 to 0.25	<0.06	<0.06
A. glaucus (n=5)	<0.06 to 0.125	ND[a]	ND
A. nidulans (n=9)	<0.06 to 0.125	ND	ND
A. ustus (n=1)	<0.06	ND	ND
A. versicolor (n=8)	<0.06 to 0.25	ND	ND
A. westerdijkiae (n=1)	<0.06	ND	ND
All isolates (n=311)	<0.06 to 4	<0.06	0.125

a: ND, not determined (MEC_{50}[s] and MEC_{90}[s] were not determined to the low number of isolates.

***In vitro* synergistic activity of SCY-078 with other antifungals against *Aspergillus* spp.**
The combination of SCY-078 with azoles and polyenes has demonstrated synergistic or additive anti-fungal activity *in vitro*. This is consistent with findings for combinations with established glucan-synthase inhibitors (GSIs). No antagonistic effects were observed.

As illustrated in the table below, combination testing of SCY-078 with isavuconazole, voriconazole or amphotericin B demonstrated synergistic activity against most of the strains tested.[8]

Table 2 *In vitro* activity of SCY-078 plus VOR in combination against *A. fumigatus* strains (each test performed in duplicate)

	MIC (µg/ml)					
	Drug tested alone		Drug in combination			
Aspergillus fumigatus MRL strain	SCY-078	VOR	SCY-078	VOR	FICI	Interpretation[a]
20438	8	1	0.125	0.25	0.27	S
	4	1	0.25	0.25	0.31	S
28378	8	0.5	0.5	0.125	0.31	S
	4	0.25	0.5	0.016	0.19	S
28382	8	0.5	0.5	0.125	0.31	S
	8	0.5	0.016	0.25	0.5	S
28401	8	2	0.25	0.5	0.28	S
	8	2	0.125	0.5	0.27	S
28383[b]	8	>16	0.031	>16	1	NI
	8	>16	0.031	>16	1	NI
28500[b]	4	>16	1	>16	1.25	NI
	8	>16	1	>16	1.13	NI

Abbreviations: FICI = fractional inhibitory concentration index?

a: S, synergistic interaction (FICI ≤ 0.5); NI, no interaction (0.5 < FICI ≤ 4.0).

b: Azole-resistant strains.

Efficacy in animal models

The antifungal efficacy of SCY-078 has been evaluated in several murine models of disseminated candidiasis and aspergillosis. In a disseminated candidiasis murine model, the most relevant pharmacokinetic/pharmacodynamics (PK/PD) parameter associated with efficacy was AUC/MIC and SCY-078 area under the curve (AUC) in plasma necessary to achieve target efficacy in these models was estimated to be 11.2 µg•mL•hr. This exposure target has guided subsequent steps of the development.[9]

The *in vivo* activity of SCY-078 was assessed against wild type (WT) and azole-resistant (TR34, L98H) *A. fumigatus* strains in neutropenic ICR mice. Mice were infected IV into the lateral tail

vein and SCY-078 was administered orally as a loading dose followed by twice daily (BID) maintenance doses. Intraperitoneal caspofungin (CSP) and AMB were used as comparator.

Oral SCY-078 was well tolerated at all doses. Treatment with SCY-078 at 7.5 mg/kg/day or 10 mg/kg/day BID significantly increased mean survival in all strains ($P \leq 0.003$). SCY-078 exposure resulting in significant reductions in fungal kidney burden ($p<0.05$) and serum GM levels ($p<0.005$) in all *Aspergillus* strains was 15.6 μg•mL/hr.

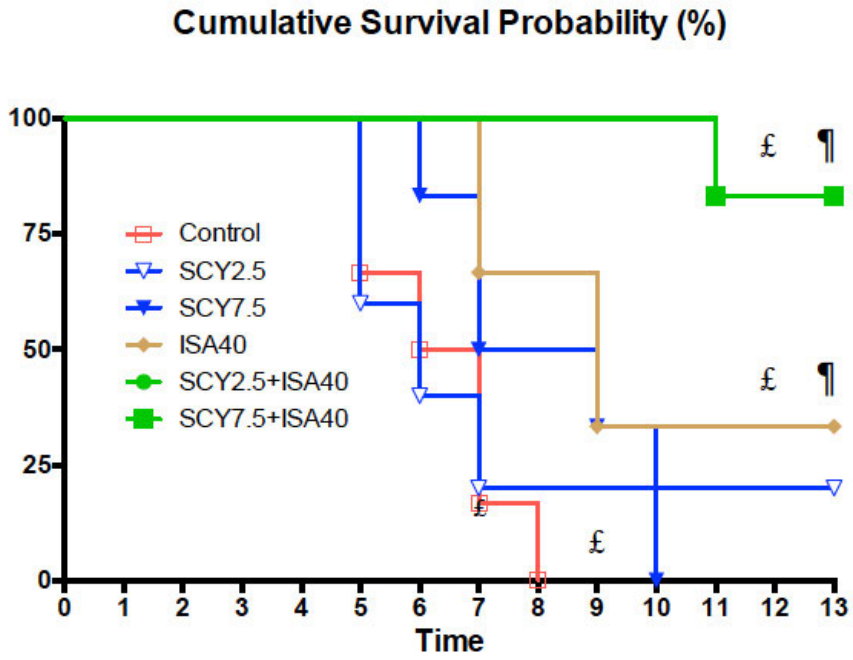
Evidence for efficacy of combination treatment from animal models

Combinations, in particular of azoles and echinocandins have been reported in several animal models, consistently showing evidence of improved outcomes when azoles and echinocandins are given in combination when compared with agent alone.[10,11,12]

The combination of SCY-078 with isavuconazole (ISA) was investigated for the pharmacokinetics, pharmacodynamics, and antifungal efficacy against experimental pulmonary aspergillosis in a neutropenic rabbit model. Galactomannan antigen expression (GMI) and (1→3)-β-D-glucan concentrations in serum were incorporated as surrogate molecular and biochemical markers of invasive aspergillosis.

The combination of SCY-078 and isavuconazole at the selected doses was more active than either agent alone, as measured by increased survival, reduced organism-mediated pulmonary injury, as well as decreased serum galactomannan and (1→3)-β-D-glucan levels in treatment of experimental IPA in persistently neutropenic rabbits.

Figure 2 Cumulative survival probability in neutropenic rabbit model of experimental pulmonary aspergillosis (n=6 each group)

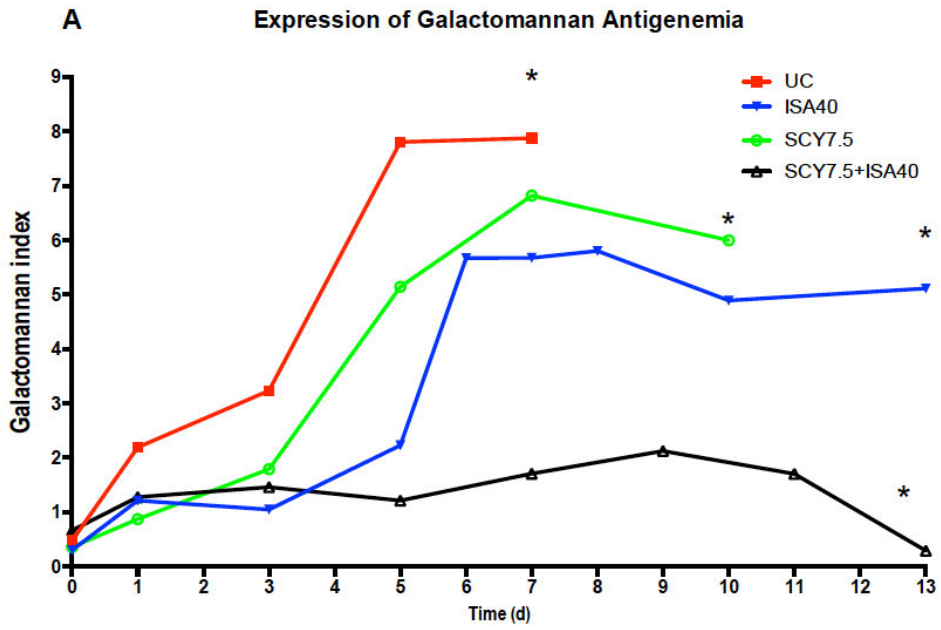


¶, p<0.05, prolonged survival in SCY2.5+ISA40 and SCY7.5+ISA40 -treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and ISA40

£, p<0.01, prolonged survival of rabbits treated with SCY2.5+ISA40, SCY7.5+ISA40, ISA40 alone in comparison to that of UC

The significantly greater survival was likely related to the synergistic antifungal activity and reduction of organism-mediated pulmonary injury, as reflected by lung weights and pulmonary hemorrhage score. This reduction was also paralleled by similar declines in serum galactomannan and (1→3)-β-D-glucan.

Figure 3 Galactomannan antigenemia in neutropenic rabbit model of experimental pulmonary aspergillosis (n=6 each group)



*p < 0.05; lower GMI in rabbits treated with combination therapy in comparison to that of single drug therapy.

The usefulness of serial GMI sampling in reflecting the therapeutic response was confirmed in this study and also in clinical practice as outlined in our study rationale further below.

Clinical experience

As of April 2020, approximately 1244 (376 healthy subjects and 868 patients) have been exposed to SCY-078 in 29 clinical trials.

In Phase 1 studies, oral SCY-078 has been generally safe and well tolerated following single oral doses of up to 1600 mg and multiple oral doses of up to 800 mg for 28 consecutive days. In Phase 2 and 3 studies, SCY-078 was also generally safe and well tolerated. The dose regimens have included a loading dose of up to 1500 mg (750 mg BID) on Days 1 and 2 followed by maintenance doses of 750 mg once daily (QD) for up to 90 days in patients with refractory fungal infections.

Adverse events (AEs) with oral SCY-078 were generally transient and mild to moderate in intensity. The most frequently reported treatment-related AEs were mild to moderate

gastrointestinal (GI) events (diarrhea, nausea, abdominal pain, and vomiting). There appears to be a dose relationship with the frequency and severity of GI AEs. With the exception of transient increases in liver function tests (LFTs) in a few subjects (not clinically significant but notable), no clinically important abnormalities have been noted in routine blood and urine chemistry panels, electrocardiograms (ECGs), and physical examinations including vital signs.

Peak plasma concentrations after oral administration of SCY-078 occur within approximately 4 to 6 hours post-dose. Plasma concentrations decline from C_{max} in an approximately monophasic decline, with a harmonic mean terminal half-life of ~20 hours. Dosing with a high-fat meal increased AUC and C_{max} by ~60%, within the intersubject variability. The mean $AUC_{0-\infty}$ and C_{max} appeared, in general, to be dose proportional for doses from 10 mg to 1600 mg. Plasma exposures of SCY-078 were not altered in subjects who were older than 65 years compared to younger subjects or in healthy female subjects compared to healthy male subjects after single oral dose administration.

Additional pre-clinical and clinical information can be found in the Investigator's Brochure (IB).

Drug-Drug Interactions Potential

In vitro evaluation of the potential of SCY-078 to cause drug-drug interactions indicated that SCY-078 was a potential reversible inhibitor of CYP2C8 (IC50, 1.5 μM), a moderate reversible inhibitor of CYP3A4/5 (IC50, 7.2 μM), but not an inhibitor of other enzymes investigated (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, IC50 all >10 μM). The potential of SCY-078 to induce human CYP3A4/5 at clinically efficacious concentrations based on *in vitro* evaluations is low. SCY-078 metabolism was predominantly oxidative, with cytochrome P450 (CYP) 3A being the primary enzyme involved in its oxidative metabolism and strong inhibitors of CYP3A would be expected to increase plasma levels of SCY-078.

Multiple doses of ketoconazole, a potent CYP3A4 inhibitor, increased SCY-078 area under the concentration-time curve (0 to infinity) ($AUC_{0-\infty}$) by approximately 5.8-fold. Multiple doses of diltiazem, a moderate CYP3A4 inhibitor, increased SCY-078 area under the concentration-time curve (0 to 24 hours) (AUC_{0-24}) by 2.5-fold. The coadministration of SCY-078 with multiple doses of a proton-pump inhibitor (pantoprazole) decreased SCY-078 $AUC_{0-\infty}$ by ~30%.

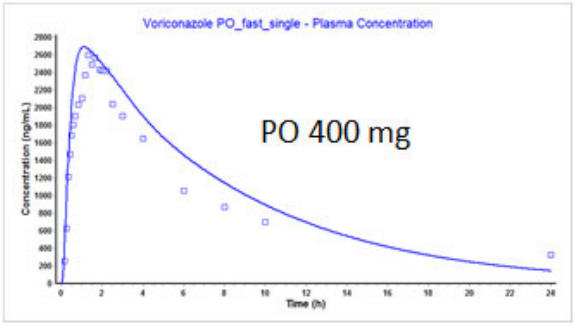
In a subsequent clinical trial, SCY-078 showed not to be a CYP2C8 inhibitor at clinically relevant plasma concentrations, based on the absence of effect of the coadministration of SCY-078 with rosiglitazone.[13] SCY-078 showed only mild potential for interaction with tacrolimus, as the relative tacrolimus exposure ($AUC_{0-\infty}$) was 1.42-fold greater when SCY-078 was coadministered with tacrolimus.[14]

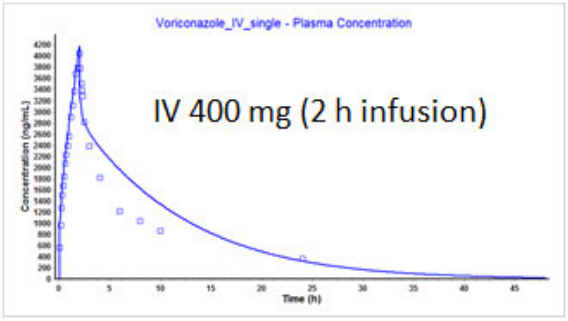
To further evaluate the potential for drug-drug interaction of SCY-078 with mold-active azoles (voriconazole), a Physiologically Based Pharmacokinetic (PBPK) model was developed.

This PBPK model was developed using GastroPlus® software (v9.0, Simulations Plus, Inc.). The model parameters for SCY-078 and voriconazole were obtained from previously conducted

experiments and/or collected from the literature. ADMET Predictor was used to supplement physiochemical parameters as necessary.

The results indicated that SCY-078 would not be expected to have any clinically meaningful effect on the PK profile of voriconazole, as illustrated below in the graph showing observed voriconazole levels (dots) and simulated voriconazole levels with the addition of SCY-078 (solid line). Physicians will be advised to follow voriconazole label guidelines and local clinical practice for therapeutic drug monitoring.





The impact of the co-administration of voriconazole on SCY-078 was also evaluated in this model using the proposed dosing regimen of each drug for this indication. The results indicate that co-administration of SCY-078 with voriconazole may result in an increase of SCY-078 exposure (both AUC and C_{max}) in the range of 20%-30%. The estimated overall exposure with the dosing regimen currently being used in other invasive fungal disease studies where SCY-078 is administered as monotherapy (i.e., Study SCY-078-301 dose regimen of 750 mg BID for 2 days followed by 750 mg QD), after considering a potential 30% increase, is within the safe exposure range established to date for SCY-078. As a precautionary measure, the SCY-078 dose administered in this study where SCY-078 is co-administered with voriconazole, will be reduced by 30% until the results of the model are confirmed in an interim PK analysis that will include the first 20 randomized subjects.

Additionally, as further expanded in the IB, the results of the non-clinical toxicology studies conducted with SCY-078 thus far do not suggest overlapping toxicities with voriconazole. Most commonly reported toxicology findings for SCY-078 have been limited to phospholipidosis, which is regarded as an adaptive response and of no consequence to human safety, and mucosal degeneration of the glandular stomach, observed primarily in rats, and regarded to be irrelevant for human risk assessment.

Conclusion

Co-administration of SCY-078 with a mold-active azole such as voriconazole has the potential to improve clinical outcomes in patients with life-threatening IPA.

Non-clinical data do not indicate a potential for antagonistic antifungal activity when SCY-078 is combined with other mold-active agents and actually strongly suggest the potential for synergistic effect.
The risk for overlapping toxicities or clinically meaningful drug-drug interaction when SCY-078 is co-administered with voriconazole is low.
All patients in the proposed study will receive an effective approved therapy (i.e., voriconazole) with the potential advantage of receiving a combination regimen that may result in improved outcomes.
For additional information on SCY-078, please refer to the IB.

8.2 Rationale for the Study

Despite the introduction of new antifungal agents, the morbidity and mortality associated with invasive aspergillosis is very high; therefore, the evaluation of novel treatment strategies such as combination therapy, which may improve the outcomes for this condition, is warranted.
Combination therapy studies typically evaluate the combination regimen with each one of its individual components and with placebo, if feasible. In the case of IPA, considering the high mortality associated with this disease, placebo-controlled trials are not ethical. The two components of the combination therapy proposed in this protocol are voriconazole, an approved mold-active azole coadministered with SCY-078, an investigational GSI. GSIs have activity against *Aspergillus* and studies have been conducted administering echinocandins as monotherapy to IPA patients. However, GSI as monotherapy is only approved for salvage therapy and not as first-line therapy, whereas mold-active azoles are recommended as first-line therapy in most treatment guidelines. In line with these guidelines, the only monotherapy arm in this study is with a mold-active azole (voriconazole) taken with placebo, and monotherapy with SCY-078 is not included in this design. Regardless of this limitation in the design, the study as planned should be able to provide information towards defining the potential improvement in efficacy by adding SCY-078 to a voriconazole regimen for the treatment of IPA.
Voriconazole was selected as the mold-active azole to use in this combination taking the following elements into consideration:

- it is the first recommended choice is most treatment guidelines,
- there is substantial information regarding its safety and efficacy for this indication and voriconazole has been used as comparator in most registration trials,
- it can be administered both orally and intravenously allowing for initiation with IV and step-down to oral when appropriate,
- it is widely available in the intended countries and institutions,
- the investigators responsible for treating the intended population for this study are familiar with its use, and
- there has not been any new antifungal that has demonstrated better efficacy.

Rationale for the objectives of the study

This study will evaluate the safety of SCY-078 when coadministered with voriconazole to the intended population. This Phase 2 study also aims to investigate the effect of the coadministration of SCY-078 with voriconazole on multiple outcome endpoints including ACM and global response (typical endpoints for this indication) but also investigates other biological markers of therapeutic response such as serum galactomannan index. The information from this study is expected to guide the selection of clinically relevant endpoints to evaluate subsequently in a larger Phase 3 study.

Rationale for proposed doses

Voriconazole

The subjects in the study will receive either intravenous or oral formulation of voriconazole, as indicated and per investigator's discretion. Typical regimen for IPA includes start of therapy with the IV formulation of voriconazole with subsequent step-down to oral formulation. The doses of voriconazole will be as recommended in the label. The drug-drug interaction simulation PBPK-based model does not indicate any need for a modification to the approved dose of voriconazole when coadministered with SCY-078. Therapeutic drug monitoring will follow label recommendation and also local practices. Modifications to voriconazole dose will be allowed aiming to maintain recommended serum concentration target ranges above 1.5 mg/L and to avoid potential toxicities associated with high exposure (i.e., > 6mg/L).

SCY-078

The oral formulation of SCY-078 will be administered in this study. The oral formulation allows for a combination strategy for the entire duration of the antifungal treatment. At the time of initiation of this study, an intravenous formulation of SCY-078 is not available. The dose selected for study SCY-078-206 took into consideration the data from the study in invasive candidiasis patients (SCY-078-202) as well as the PK data available from other Phase 1 studies with the oral formulation of SCY-078.

In summary:

<u>Population Pharmacokinetic Modeling and Simulation</u>

A population PK model to describe the SCY-078 concentration-time profile in healthy subjects and patients treated for fungal infections was developed in order to provide predictions of the percentage of patients that achieve daily AUC values above the efficacy target for invasive fungal infection (11.2 µg•mL•hr for invasive candidiasis models and 15.6 µg•mL•hr for invasive aspergillosis models). The population PK model for SCY-078 was based on pooled data from nine Phase 1 studies and two Phase 2 studies. The overall dataset consisted of a total of more than 5000 measurable plasma drug concentrations of SCY-078 collected from nearly 200 healthy subjects and over 30 patients treated for fungal infections. A simulation was performed based on

the oral dosing regimen for the treatment of IPA, which consists of a two-day loading dose regimen of 750 mg BID administered on Days 1 and 2 followed by an oral maintenance dose of 750 mg QD starting on Day 3. Based on this simulation, it is predicted that greater than about 90% of patients will reach target exposure by Day 2, which is in line with antifungal agents that require loading doses. The target exposure is maintained during treatment. This dosing regimen is currently being used in other invasive fungal disease studies (SCY-078-301).

The impact of the co-administration of voriconazole on SCY-078 was evaluated in a PBPK model. The results indicate that co-administration of SCY-078 with voriconazole may result in an increase of SCY-078 exposure (both AUC and C_{max}) in the range of 20%-30%. The estimated overall exposure with the dosing regimen currently being used in other invasive fungal disease studies (750 mg BID for 2 days followed by 750 mg QD), after considering a potential 30% increase, is within the safe exposure range established to date for SCY-078. As a precautionary measure, the SCY-078 dose administered in this study will be reduced by 30% until the results of the model are confirmed in an interim PK analysis that will include the first 20 randomized subjects. Specifically, the first 10 subjects assigned to SCY-078 and voriconazole therapy will receive an oral SCY-078 loading dose of 500 mg BID on Days 1 and 2 followed by a maintenance dose of 500 mg QD from Day 3 onwards. Based on the data from this analysis, the oral SCY-078 dose may be increased up to a loading dose of 750 mg BID on Days 1 and 2 followed by a maintenance dose of 750 mg QD from Day 3 onwards.

9.0 Study Objectives

9.1 Primary Objectives

- To evaluate the safety and tolerability of the coadministration of SCY-078 and voriconazole compared with coadministration of SCY-078 placebo and voriconazole in the treatment of invasive pulmonary aspergillosis (IPA).

9.2 Secondary Objectives

- To evaluate the efficacy of the coadministration of SCY-078 and voriconazole compared with that of SCY-078 placebo and voriconazole in the treatment of IPA.
    - based on Global Response
        - as determined by the DRC
        - as determined by the Principal Investigator
    - based on all-cause mortality (ACM)
    - based on serum galactomannan index (GMI) decrease
    - based on clinical response, mycological response and radiological response
        - as determined by the DRC
        - as determined by the Principal Investigator

- To evaluate the pharmacokinetics (PK) of SCY-078 and voriconazole.

9.3 Exploratory Objectives

The exploratory objectives will be evaluated as data allow and include:

- To evaluate the efficacy of the coadministration compared with coadministration of SCY-078 placebo and voriconazole
    - based on other biomarkers of fungal infection (i.e., serum levels of β-D-glucan and plasma *Aspergillus* PCR)
    - based on change in the performance indicator (i.e., Karnofsky score)
    - based on the rate of recurrence of IPA at Week 6 after end of treatment (EoT) as determined by the DRC
    - based on the need for additional systemic antifungal treatment (other than secondary prophylaxis) until Week 6 after EoT
- To evaluate the relationship between selected endpoints to ACM at Days 42 and 84.
- To evaluate healthcare resources utilization for the patients receiving the coadministration of SCY-078 and voriconazole compared with coadministration of SCY-078 placebo and voriconazole based on overall hospital stay and intensive care unit stay.
- To assess the effect of the coadministration of SCY-078 and voriconazole compared with coadministration of SCY-078 placebo and voriconazole on on-schedule administration of planned therapies for the underlying condition.

10.0 Study Endpoints

10.1 Primary Endpoints

- Frequency of treatment-emergent adverse events (TEAEs), drug-related adverse events (AEs), discontinuations due to AEs and deaths.

10.2 Secondary Endpoints

Efficacy as measured by:

- Global Response as measured by:
    - Percentage of subjects with Complete Response or Partial Response at EoT (key secondary endpoint), Day 42 and Day 84, as determined by the DRC
    - Percentage of subjects with Complete Response or Partial Response at EoT, Day 42 and Day 84, as determined by the Principal Investigator
- Overall survival, defined as the time from randomization to time of death up to Day 84
- Percentage of subjects who died (any cause) at Days 42 and 84

- Absolute reduction and percent change in serum GMI from Baseline to Weeks 1, 2, 4 and 6
- Percentage of subjects with the following changes in serum GMI from Baseline:
    - Fifty percent reduction or greater at Weeks 1, 2, 4 and 6
    - Twenty-five percent reduction or greater at Weeks 1, 2, 4 and 6
    - Any percent reduction at Weeks 1, 2, 4 and 6
    - Reduction equal to or greater than 0.25 at Weeks 1, 2, 4 and 6
    - Reduction to < 0.5 at Weeks 1, 2, 4 and 6
- Time to achieve the following changes in serum GMI from Baseline:
    - Fifty percent reduction
    - Twenty-five percent reduction
    - Any percent reduction
    - Reduction equal to or greater than 0.25
    - Reduction to < 0.5 in 2 consecutive samples
- Percentage of subjects with:
    - Clinical Response at EoT, Day 42 and Day 84, as determined by the DRC
    - Mycological Response at EoT, Day 42 and Day 84, as determined by the DRC
    - Radiological Response at EoT, Day 42 and Day 84, as determined by the DRC
- Percentage of subjects with:
    - Clinical Response at EoT, Day 42 and Day 84, as determined by the Principal Investigator
    - Mycological Response at EoT, Day 42 and Day 84, as determined by the Principal Investigator
    - Radiological Response at EoT, Day 42 and Day 84, as determined by the Principal Investigator

PK as measured by:

- SCY-078 and voriconazole plasma concentrations population PK analysis

10.3 Exploratory Endpoints

Efficacy as measured by:

- Absolute and percentage changes in serum β-D-glucan from Baseline at Weeks 1, 2, 4 and 6
- Percentage of subjects with the following changes in serum β-D-glucan from Baseline (if positive):
    - Fifty percent reduction or greater at Weeks 1, 2, 4 and 6
    - Twenty-five percent reduction or greater at Weeks 1, 2, 4 and 6
    - Any percent reduction at Weeks 1, 2, 4 and 6
    - Negative serum β-D-glucan at Weeks 1, 2, 4 and 6

- Percentage of subjects that convert from positive plasma *Aspergillus* PCR at Baseline to negative at Weeks 1, 2, 4 and 6
- Absolute change in Karnofsky score (unit change = 10) from Baseline to Days 42 and 84
- Time to achieve a 10-point improvement in Karnofsky score from Baseline
- Percentage of subjects with a recurrence of the baseline fungal infection within 42 days (Week 6) after EoT
- Relationship between GMI decrease and ACM at Days 42 and 84
- Days of hospital stay, and days of ICU stay
- Percentage of subjects who are able to receive on schedule administration of the planned therapies for their underlying condition

11.0 Study Design

11.1 Overall Description of the Study

This is a multicenter, randomized, double-blind, two-arm study to evaluate the safety, tolerability, efficacy and PK of the coadministration of SCY-078 plus voriconazole compared to coadministration of SCY-078 placebo plus voriconazole in male and female subjects 18 years of age and older with probable or proven IPA as defined in Section 22.3 (adapted EORTC-MSG criteria).

The primary objective of the study is to evaluate the safety and tolerability of the coadministration of SCY-078 plus voriconazole compared to the coadministration of SCY-078 placebo plus voriconazole in the treatment of IPA. Secondary objectives include efficacy assessments based on Global Response, ACM and GMI decrease (GMI decrease will only be assessed for subjects with a serum GMI above 0 at Baseline) , and PK. Being this a Phase 2 study, multiple secondary and exploratory endpoints are planned, which will be evaluated as data allow considering the limitations of the planned sample size.

Subjects must meet all study criteria to be eligible for inclusion.

This study is intended for subjects with an IPA episode that, in the investigator´s judgement, requires antifungal therapy and is reasonable to expect that be adequately treated with voriconazole. Subjects with breakthrough IPA while receiving antifungal prophylaxis may be considered for enrollment if, in the investigator´s judgement, the IPA episode is expected to be adequately treated with voriconazole.

The study will be conducted at approximately 30 sites globally. Approximately 90 subjects will be screened to randomize a total of approximately 60 subjects (30 subjects per group) into one of the two treatment groups of the study (SCY-078 plus voriconazole or SCY-078 placebo plus voriconazole).

Subjects will receive study treatment for the entire duration of the antifungal therapy (i.e., for a recommended minimum of 6 weeks and a maximum of 13 weeks).

The study will consist of a Screening Period (Days -4 to -1) to assess subject eligibility; a

Baseline visit (also considered Treatment Day 1) to confirm subject eligibility and begin study treatment; additional scheduled treatment visits (Treatment Days 3, 7, 10, 14 and treatment visits every 14 days thereafter until the EoT) to perform safety, tolerability, efficacy and PK assessments, an EoT visit to assess efficacy outcomes, a Follow-up (FU) visit 6 weeks after EoT (6-Week FU) to assess recurrence and safety, and 2 survival visits/contacts to determine survival status and treatment outcome. The Screening Period and Baseline visit may be combined for certain subjects. Unscheduled visits may also be conducted as needed.
A summary description of the study visits, treatment groups and assessments is provided below. A schematic of the study design is available in Section 7.0. Detailed descriptions of study treatments are provided in Section 13.0. A full description of each study procedure is available in Section 15.0 and a detailed schedule of procedures by study visit is available in Section 16.0.

11.1.1 Study Visits

11.1.1.1 Screening Period (Days -4 to -1)

At Screening, subjects will be assessed to determine eligibility. All subjects must have a diagnosis of possible, probable or proven IPA. Subjects must have a current IPA episode that, in the Investigator´s judgement, requires antifungal therapy and may be adequately treated with voriconazole, and must be able to tolerate medication orally or through a nasogastric (NG) tube or percutaneous endoscopic gastrostomy (PEG) tube to be able to participate in the study.

Subjects with Probable or Proven IPA

Subjects with a **probable or proven IPA,** as defined in Section 22.3 and who meet all other inclusion and exclusion criteria will enter the Treatment Period and will be randomized to one of the two study treatment groups.

The Screening Visit and Baseline visit (Treatment Day 1) may occur simultaneously for subjects who have met the criteria for probable or proven IPA at screening, if all other criteria are met.

Subjects with Possible IPA

Subjects with **possible IPA** may enter the Screening Period of the study. During the Screening Period, subjects will receive voriconazole or any other mold-active agent (e.g., echinocandin, amphotericin B, or other azoles for mold infections) as per label instructions and local standard practice, and samples for serum determination of GMI will be collected on a daily basis. Other samples (e.g., bronchioalveolar lavage, cytology or histopathology) may be collected as clinically indicated to confirm the IPA diagnosis. Subjects may remain in the Screening Period (i.e. Screening Days -4 to -1) until the criteria of probable or proven IPA is met (Section 22.3), but in no case for more than 4 days of mold-active antifungal treatment unless approved by the medical monitor, as explained below. This 4-day mold-active antifungal treatment limit prior to randomization is inclusive of any days of mold-active antifungal that the subject may have received prior to Screening. Once the criteria for a probable or proven IPA is met and, if all other inclusion

and exclusion criteria are met, the subject will enter the Treatment Period and will be randomized to one of the two study treatment groups.

Subjects meeting criteria for probable or proven IPA shortly after the subject has reached the 4-day mold-active antifungal treatment limit allowance (i.e., after 4 days but no more than 7 days of mold-active antifungal treatment) may be randomized into the study with the approval of the medical monitor, who will take into consideration the total number of days of mold-active agent administration up to that point as well as the subject´s response to therapy. If the criteria for probable or proven IPA is not met within 7 days after initiation of mold-active antifungal treatment for the IPA episode, the subject will not be randomized and will be discontinued from the study. Only limited information will be collected for screened subjects who do not qualify for enrollment

11.1.1.2 Baseline (Treatment Day 1)

For subjects who have a **probable or proven IPA** the Screening Period and Baseline visit may be combined. For subjects who have a **possible IPA** at Screening Visit AND the criteria for upgrading the case to probable or proven IPA is gathered during the Screening Period, the inclusion and exclusion criteria will be reviewed again at Baseline to confirm eligibility. Eligible subjects will be enrolled in the study and randomized in a 1:1 ratio to one of the two study treatment groups: (IV or oral voriconazole + oral SCY-078) or IV or oral voriconazole + matching oral SCY-078 placebo.
Subjects will begin randomized study treatment and clinical, radiological, mycological, PK and safety procedures will be performed.

11.1.1.3 Treatment Days 3, 5, 7, 10, 14, and every 14 days thereafter

Subjects will continue on their randomized study treatment and will undergo clinical, radiological and mycological procedures for the assessment of efficacy. They will also have blood samples drawn for PK assessment and clinical laboratory tests and AE collection for safety monitoring.
Subjects will receive study treatment for a recommended minimum of 6 weeks and a maximum of 13 weeks.

11.1.1.4 End of Treatment (EoT)

Subjects will receive study treatment for a maximum duration of 13 weeks. At EoT, subjects will undergo safety procedures and clinical, radiological and mycological assessments for the determination of efficacy outcomes. EoT procedures should also be performed for subjects who discontinued from study treatment before the EoT visit.

11.1.1.5 6-Week Follow-Up (6 Weeks After EoT)

A FU visit will be conducted 6 weeks after the EoT visit to assess recurrence and to conduct a final safety assessment.

11.1.1.6 Visits on Treatment Days 42 and 84

Visits will be conducted on Days 42 and 84 to assess clinical, mycological and radiological outcomes as determined by an independent DRC. In addition, patient-reported outcomes (Karnofsky scale) will be scored.

Survival will also be assessed at these visits. These can be conducted as in-person visits or phone contacts and will document subject status (alive or deceased) and relationship to the IPA. If subject is deceased, the date of death and the investigator´s assessed relationship to the fungal infection will also be recorded. If an autopsy is conducted, key findings should be collected in the eCRF.

11.1.2 Study Assessments

The study will include safety, tolerability, efficacy and PK assessments.

Safety and Tolerability

Subjects will be evaluated for safety and tolerability throughout the study, including parameters such as physical exam including visual function assessment, vital signs, 12-lead ECGs, safety laboratory tests (hematology, blood chemistry and urinalysis), concomitant medications, AEs and treatment discontinuations. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.

Efficacy Assessments

Efficacy will be assessed primarily in terms of Global Response (a composite assessment that includes clinical, radiological and mycological evaluations) at EoT, Day 42 and Day 84 as assessed by an independent DRC and the Principal Investigator; ACM at Days 42 and 84; and GMI decrease at Weeks 1, 2, 4 and 6. Clinical, mycological and radiological outcomes at EoT, Day 42 and Day 84 as determined by an independent DRC and by the Principal Investigator will also be assessed.

The following study procedures will be performed to assess treatment outcome:

- clinical signs and symptoms of IPA
- radiological assessments, including chest computed tomography (CT) scans and other imaging procedures (e.g., X-ray, ultrasound, CT and magnetic resonance imaging [MRI])
- mycological testing, including fungal cultures, PCR, histopathological or cytopathological analysis of relevant tissues or samples (e.g., lung biopsy sample, bronchoalveolar lavage [BAL] fluid), and serological testing (GMI).

Exploratory efficacy assessments include, among others, recurrence, Karnofsky Performance Status outcomes and other serological biomarkers (β-D-glucan and *Aspergillus* PCR).

Pharmacokinetics

Voriconazole level determination as well as SCY-078 PK will be performed for all study subjects.

Therapeutic drug monitoring (TDM) for voriconazole will be conducted as per local standard practice and samples for voriconazole TDM will be analyzed at the local laboratory. The target trough plasma concentration should be above 1.5 mg/L.

For the first 20 randomized subjects, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 2-4 hours and 6-8 hours after dosing for SCY-078 and voriconazole central lab PK testing. Results for plasma concentrations of SCY-078 and voriconazole analyzed by the central laboratory will not be available in real time. The PK data from the first 20 subjects will be assessed in an interim PK analysis that will keep the study team blinded.
For subsequent randomized subjects, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 4-8 hours after dosing for SCY-078 and voriconazole central lab PK testing. Results for plasma concentrations of SCY-078 and voriconazole analyzed by the central laboratory will not be available in real time.

11.2 Blinding, Randomization and Stratification

This is a double-blind study. All site and sponsor personnel will be blinded to treatment assignment. Subject randomization will be performed using an Interactive Web Response System (IWRS).
Approximately 60 eligible subjects (30 subjects per treatment arm) will be randomized in a 1:1 ratio to one of the two study treatment arms: voriconazole and SCY-078 or voriconazole and SCY-078 placebo. For the purpose of maintaining treatment blinding, all randomized subjects will receive SCY-078 or SCY-078 matching placebo. Subjects will be randomized at Baseline, after all baseline evaluations have been completed. Only one randomization number and study treatment arm will be assigned to each eligible subject.
Eligible subjects will be stratified to one of these groups at randomization:

- Hematological malignancies and /or hematopoietic cell transplantation recipients
- Solid organ transplant recipients
- Other immunocompromising conditions

11.3 Study Duration/End of Study

Each subject is expected to complete the study, including all FU and Survival visits, within approximately 132 days. The end of study is when the last visit of the last subject occurs.

11.4 Number of Subjects and Centers

The study will be conducted at approximately 30 sites globally. Approximately 90 subjects are planned to be screened to randomize a total of approximately 60 subjects (30 subjects per group)

into one of the two treatment groups of the study (voriconazole and SCY-078 or voriconazole and SCY-078 placebo).

12.0 Study Population

12.1 Inclusion Criteria

Subjects must fulfill all of the following criteria to be eligible for study admission:

1. Subject is a male or female adult ≥18 years of age on the day the study informed consent form (ICF) is signed.
2. Subject has a probable or proven IPA based on the protocol-specified criteria (Section 22.3) that requires antifungal treatment.

   Note: Subjects with possible IPA may enter the screening phase of the study but will only be randomized after meeting criteria for probable or proven IPA
3. Subject has a result of a serum GMI from a sample obtained within the 96 hours preceding enrollment into the study (Baseline/Treatment Day 1).
4. Subject has one of the following:
   a. has a diagnosis of a hematological malignancy or a myelodysplastic syndrome or aplastic anemia or has undergone a hematopoietic cell transplantation **OR**
   b. who either recently resolved or ongoing neutropenia (neutropenia defined as absolute neutrophil count < 0.5 x 10^9/L [< 500/mm3] for > 10 days), temporally related to the onset of fungal disease **OR**
   c. who received treatment with other recognized T-cell immunosuppressants (such as cyclosporine, tacrolimus, monoclonal antibodies or nucleoside analogs) during the past 90 days including solid organ transplant patients **OR**
   d. with inherited severe immunodeficiency (e.g. chronic granulomatous disease, severe combined immunodeficiency).
5. Subject has not received more than 4 days (96 hours) of prior mold-active antifungal therapy for the treatment of the IPA episode in the 7 days preceding enrollment into the study (Baseline/Treatment Day 1). However, subjects who have received more than 4 days but less than 7 days of prior mold-active antifungal therapy for the treatment of the IPA episode in the 7 days preceding enrollment into the study may be enrolled but will require approval from the study medical monitor, who will evaluate each subject on a case-by-case basis.
6. For subjects who were receiving antifungal prophylaxis, the IPA episode would, in the investigator´s judgement, be adequately treated with voriconazole .
7. Subject is able to tolerate medication orally or through a nasogastric (NG) tube or percutaneous endoscopic gastrostomy (PEG) tube.
8. Subject is not pregnant and is highly unlikely to become pregnant or to impregnate a partner since he/she meets at least one of the following criteria:

a. Subject is a female subject who is not of reproductive potential and is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as one who: (1) has reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels in the postmenopausal range as determined by the local laboratory, or 12 months of spontaneous amenorrhea); (2) is 6 weeks´ post-surgical bilateral oophorectomy or hysterectomy; or (3) has undergone bilateral tubal ligation. Spontaneous amenorrhea does not include cases for which there is an underlying disease that causes amenorrhea (i.e., anorexia nervosa).
b. Subject is a male subject who is not of reproductive potential and is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as one whom has undergone a successful vasectomy. A successful vasectomy is defined as (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.
c. Subject is a male or female subject who is of reproductive potential, is not pregnant or nursing, and agrees to remain abstinent or use (or have his/her partner use) 2 acceptable methods of contraception starting from the time of consent through 28 days after the completion of study therapy. Acceptable methods of birth control are intrauterine device, condom and highly effective hormonal contraceptives.

Note: Participating females of childbearing potential must have a negative urine or serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at Screening and prior to enrollment (Baseline/Treatment Day 1) (performed by the site's local laboratory).

9. Subject and/or legal representative is/are able to understand and sign a written ICF, which must be obtained prior to treatment and any study-related procedures.
10. Subject and/or legal representative is able to understand and sign a consent or authorization form, which shall permit the use, disclosure and transfer of the subject's personal health information (e.g., in the US, a Health Information Portability and Accountability Act Authorization form).
11. Subject and/or legal representative is able to understand and follow all study-related procedures including study drug administration.
12. Subject is willing and able to comply with the study restrictions and participate for the full length of the study.

12.2 Exclusion Criteria

A subject will be excluded from participation in the study if he or she meets any of the following exclusion criteria:

1. Subject has a fungal disease with central nervous system involvement suspected at Screening.

2. Subject is receiving, has received or anticipates to be receiving concomitant medications that are listed in the prohibited medication list (Section 22.1) within the specified washout periods.
3. Subject has a Karnofsky score <20.
4. Subject is expected to die from a non-infectious cause within 30 days from the day the study ICF is signed.
5. Subject is under mechanical ventilation.
6. Subject has abnormal liver test parameters: AST or ALT ≥5 x ULN and/or total bilirubin >2.5 x ULN.
   Note: Subjects with unconjugated hyperbilirubinemia (< 7mg/dL) with a diagnosis of Gilbert's disease **are not excluded.**
7. Subject has a grade II-IV acute or extensive chronic graft-versus-host disease (GvHD).
8. Subject has renal failure requiring dialysis.
9. Subject has a prolonged QTcF interval (Fridericia's correction: $QTc= QT/(RR)^{0.33}$) >480 ms for females and prolonged QTcF interval (Fridericia's correction: $QTc= QT/(RR)^{0.33}$) >450 ms for males, on the baseline ECG or other abnormalities deemed clinically significant by the investigator that would put the subject at unacceptable risk for participation in the study.
10. Subject has any other condition including history of conditions or medications that may increase the risk for QTc prolongation, or laboratory abnormality that, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study or may interfere with the assessments included in the study.
11. Subject has a known hypersensitivity to SCY-078 and/or voriconazole or any of the components of the formulations.
12. Subject has participated in any other investigational study (except open-label studies including approved chemotherapy agents) within at least 28 days or 5.5 half-lives of the investigational product (whichever is longer) before signing the ICF.
13. Subject has received prior treatment with SCY-078 in a previous trial.
14. Subject is an employee of SCYNEXIS, Inc., the investigator or the Contract Research Organization (CRO) involved in the study, or is an immediate family member (partner, offspring, parent, sibling, or sibling's offspring) of an employee involved in the study.
15. Subject is unlikely to comply with protocol requirements.

12.3 Discontinuation Criteria

A subject may be discontinued from the study or study drug for any of the following reasons:

- Withdrawal of consent;
- Investigator or Sponsor decision that withdrawal is in the subject's best interest;
- Lack of efficacy, defined as deterioration of the clinical condition or delayed response requiring, in the opinion of the investigator, alternative antifungal therapy;

- Occurrence of an AE that, in the opinion of the investigator, warrants discontinuation of the subject from the study drug;
- Pregnancy;
- Lost to follow up (every attempt should be made to contact the subject).

The reason for a subject's discontinuation of treatment or withdrawal from the study will be clearly documented in the source documents and on the electronic case report form (eCRF). All EoT procedures should be performed for subjects who discontinue from study treatment before the EoT visit.

12.4 Replacement of Dropouts

Subjects who discontinue early from treatment will not be replaced.

13.0 Study Treatments

13.1 Study Treatment Groups

13.1.1 Description of Study Groups

All eligible subjects will be randomized in a 1:1 ratio to one of the two study treatment groups and will receive treatment for a recommended minimum of 6 weeks and a maximum of 13 weeks.

Once randomized, the subjects will receive either voriconazole plus SCY-078 or voriconazole plus matching SCY-078 placebo for the entire duration of the antifungal treatment, until they reach EoT or a discontinuation occurs.

Voriconazole + SCY-078

- Either IV **voriconazole** (loading dose of 6 mg/kg BID on Day 1 followed by maintenance dose of 4 mg/kg BID from Day 2 onwards) **OR** oral **voriconazole** (loading dose of 400 mg BID on Day 1 followed by maintenance dose of 200 mg BID from Day 2 onwards). For subjects weighing <40 kg, the loading and maintenance dose of oral voriconazole will be determined per label instructions.
  PLUS
- Oral **SCY-078** (loading dose of 500 mg [2 tablets of 250 mg] BID on Days 1 and 2 followed by maintenance dose of 500 mg [2 tablets of 250 mg] QD from Day 3 onwards). After the first 10 randomized subjects have been treated with the coadministration therapy for at least 7 days, an interim PK analysis will be conducted. Based on the data from this analysis, the oral **SCY-078** dose for subjects subsequently randomized may be increased up to a loading dose of 750 mg (3 tablets of 250 mg) BID on Days 1 and 2

followed by a maintenance dose of 750 mg (3 tablets of 250 mg]) QD from Day 3 onwards.

Voriconazole + SCY-078 Placebo

- Either IV **voriconazole** (loading dose of 6 mg/kg BID on Day 1 followed by maintenance dose of 4 mg/kg BID from Day 2 onwards) **OR** oral voriconazole (loading dose of 400 mg BID on Day 1 followed by maintenance dose of 200 mg BID from Day 2 onwards). For subjects weighing <40 kg, the loading and maintenance dose of oral voriconazole will be determined per label instructions.
  PLUS
- Placebo matching oral **SCY-078**
  - Subjects randomized prior to the interim PK analysis: loading dose of 2 tablets given BID on Days 1 and 2 followed by maintenance dose of 2 tablets given QD from Day 3 onwards.
  - Subjects subsequently randomized (depending on interim PK analysis): loading dose of up to 3 tablets given BID on Days 1 and 2 followed by maintenance dose of up to 3 tablets given QD from Day 3 onwards

Subjects will receive the administration of voriconazole as per label instructions and local standard practice. The individual dose of voriconazole may be adjusted by the investigator according to results from standard-of-care voriconazole drug monitoring evaluations. Subjects should be instructed to take oral voriconazole 1 hour before or after a meal, every 12 hours. The dose of SCY-078 will not be adjusted for a particular subject. Subjects will be instructed to take the oral SCY-078 preferably with meal, twice a day (BID) approximately 12 hours apart the first 2 days (loading dose) and once daily (QD) subsequently (maintenance dose). The dose of SCY-078 may be adjusted for subjects who are randomized after the interim PK analysis. Until a decision to adjust the dose is made based on data from this analysis, subjects will continue receiving SCY-078 500 mg doses.
See Section 13.1.4 for voriconazole dosing recommendations. For additional information on voriconazole, please refer to Section 22.2 (Appendix B: Voriconazole Label).
A summary of the study treatment groups is provided in Table 3.

Table 3 Study Treatment Groups **First 20 Randomized Subjects**[a]

Drugs	Voriconazole +		SCY-078	Voriconazole +		SCY-078 matching placebo
Route	**IV**[b]	**Oral**	**Oral**	**IV**[b]	**Oral**	**Oral**
Loading dose	6 mg/kg BID (Day 1)	400 mg[c] BID (Day 1)	500 mg BID (Days 1 & 2)	6 mg/kg BID (Day 1)	400 mg[c] BID (Day 1)	Placebo BID (Days 1 & 2)
Maintenance	4 mg/kg	200 mg[d]	500 mg	4 mg/kg	200 mg[d]	Placebo

dose	BID (Day 2 onwards)	BID (Day 2 onwards)	QD (Day 3 onwards)	BID (Day 2 onwards)	BID (Day 2 onwards)	QD (Day 3 onwards)
Subsequent Subjects (depending on interim pharmacokinetic analysis)						
Drugs	Voriconazole +		SCY-078	Voriconazole +		SCY-078 matching placebo
Route	**IV[b]**	**Oral**	**Oral**	**IV[b]**	**Oral**	**Oral**
Loading dose	6 mg/kg BID (Day 1)	400 mg[c] BID (Day 1)	750 mg BID (Days 1 & 2)	6 mg/kg BID (Day 1)	400 mg[c] BID (Day 1)	Placebo BID (Days 1 & 2)
Maintenance dose	4 mg/kg BID (Day 2 onwards)	200 mg[d] BID (Day 2 onwards)	750 mg QD (Day 3 onwards)	4 mg/kg BID (Day 2 onwards)	200 mg[d] BID (Day 2 onwards)	Placebo QD (Day 3 onwards)

Abbreviations: BID: twice a day; IV: intravenous

a: The 500 mg dose will be administered to the first 20 randomized subjects. An interim pharmacokinetic analysis will be conducted and, based on data from this analysis, the SCY-078 dose may be increased up to the 750 mg dose for subjects subsequently randomized.

b: IV voriconazole should be infused over 1 to 2 hours (rate not to exceed 3 mg/kg/h). It should not be administered as an IV bolus injection.

c: Administering an oral voriconazole loading dose is only recommended in subjects who cannot tolerate IV voriconazole due to potential renal adverse effects.

d: For subjects who take oral voriconazole and weigh <40 kg, the loading and maintenance dose will be per label instructions.

13.1.2 Treatment Duration

Subjects may receive voriconazole or other mold-active agent starting before or during the Screening Period for a maximum of 4 days prior to randomization.

Subjects who have received more than 4 days but no more than 7 days of voriconazole or other mold-active agent before inclusion criteria are met (i.e., positive GMI results become available) may be randomized into the study with the approval of the medical monitor, who will take into consideration the total number of days of mold-active agent administration up to that point as well as the subject´s response to therapy.

Once randomized, the duration of the study treatment will be based on clinical improvement, degree of immunosuppression and response on imaging. In this study, in line with IDSA guidelines, the recommended study treatment duration is for a minimum of 6 weeks. The maximum treatment duration in this study will be 13 weeks. Subjects will receive study treatment (i.e., voriconazole plus oral SCY-078 or voriconazole plus oral SCY-078 matching placebo) for the entire duration of the antifungal therapy up to EoT. The first oral dose of SCY-078 or SCY-078 matching placebo will be administered after randomization.

13.1.3 Renal Insufficiency

In patients with moderate or severe renal insufficiency (creatinine clearance <50 mL/min), accumulation of the IV voriconazole vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk balance for the patient justifies the use of IV voriconazole. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral voriconazole therapy.

13.1.4 Voriconazole Dosing and Dose Adjustment

Voriconazole will be administered as per voriconazole label instructions.

Important recommendations for voriconazole treatment

- Voriconazole therapy should be initiated using the IV formulation administered for at least 3 days unless there is a contraindication or lack of vascular access. The IV formulation should be followed by maintenance oral voriconazole.
- Initiation of voriconazole therapy (i.e., loading dose) with an oral formulation rather than an IV is recommended in subjects who cannot tolerate IV voriconazole (see Section 13.1.3 [Renal Insufficiency]).
- IV voriconazole should be infused over 1 to 2 hours (rate is not to exceed 3 mg/kg/h). IV voriconazole should not be administered as an IV bolus injection.
- Oral treatment may be given on an inpatient or outpatient basis, as needed.
- The loading dose of voriconazole should be administered only once, at the beginning of voriconazole therapy.

Dose adjustment

Adjustment of voriconazole doses will be allowed, at the investigator's discretion and per local standard practice, with the objective of maintaining voriconazole trough levels above 1.5 mg/L and to avoid potential toxicities associated with high exposure (i.e., > 6 mg/L).

13.1.5 Oral Treatment via NG or PEG Tube

For subjects who are unable to take oral tablets but are able to tolerate medications through an NG or PEG tube, SCY-078 (or matching placebo) tablets may be crushed and administered with approximately 8 oz./240 mL of water via an NG or PEG tube. The tube should be flushed with water before and after drug administration.

13.2 Dietary Requirements

Oral SCY-078 should be taken with meals or immediately after a meal and with approximately 8 oz./240 mL of water. Oral voriconazole should be administered 1 hour before or 1 hour after a meal.

13.3 Study Drug

Study drug, SCY-078 250-mg and SCY-078 250-mg matching placebo tablets will be provided by the Sponsor. Standard of care (SOC) voriconazole (IV and oral) will be provided by the study site's pharmacy. In extenuating circumstances when the site's pharmacy is not able to provide the SOC voriconazole, the Sponsor will assist in obtaining it.

13.3.1 SCY-078 Description

Study Drug Identifier: SCY-078
Empirical Formula: $C_{50}H_{75}N_5O_{11}$ (citrate salt)
Molecular Weight: 922.18 (citrate salt)
Physical Description: White to off-white solid
Chemical Name: (1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-15-[[(2R)-2-amino-2,3,3-trimethylbutyl]oxy]-8-[(1R)-1,2-dimethylpropyl]-14-[5-(4-pyridinyl)-1H-1,2,4-triazol-1-yl]-1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-1,6a,8,10a-tetramethyl-4H-1,4a-propano-2H-phenanthro[1,2-c]pyran-7-carboxylic acid, citrate salt]

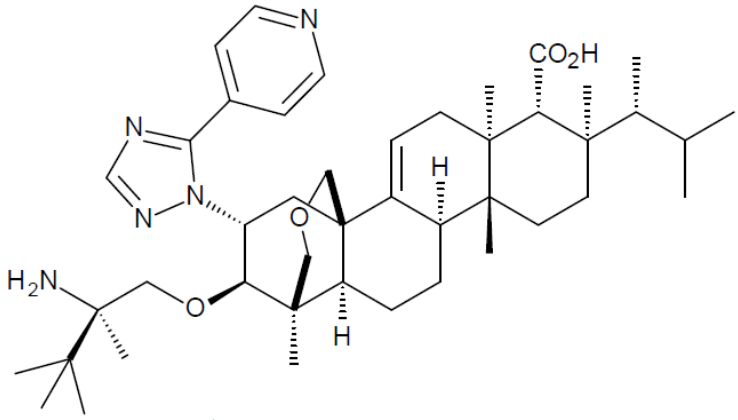


Figure 4 Chemical Structure of SCY-078 Citrate

13.3.2 Formulation, Packaging and Labelling

SCY-078 citrate drug product for oral administration will be supplied as a tablet containing 250 mg of SCY-078 active ingredient on a free-base basis. In addition to the active ingredient, the tablet formulation also contains silicified microcrystalline cellulose, crospovidone, mannitol, colloidal silicon dioxide, magnesium stearate (non-bovine) and butylated hydroxyanisole.
IV voriconazole will be supplied in a single-use vial as a sterile lyophilized powder equivalent to 200 mg of voriconazole. Oral voriconazole will be supplied as a 200-mg tablet.
SCY-078 drug supplies (SCY-078 citrate and matching placebo tablets) will be packaged in high density polyethylene (HDPE) bottles fitted with induction seals and child-resistant polypropylene plastic closures.

Labels on the bottles containing SCY-078 and matching placebo tablets will include the following information and any other information required by applicable regulations:

- Sponsor information
- Protocol number
- Protocol visit number
- Place to write the subject number
- Route of administration
- Lot number
- Product name and potency
- Contents, e.g. number of tablet count per bottle
- Storage conditions
- Name of manufacturer and date of manufacture
- Caution statement: "Caution: New Drug – Limited by Federal (United States) Law to Investigational Use Only"

13.3.3 Storage and Stability

The pharmacist or appropriate designee at each clinical research site will be responsible for the study drug. For long-term storage at the site, SCY-078 drug supplies (SCY-078 citrate and matching placebo tablets) provided in bottles must be kept in a secure area (e.g., locked cabinet) and stored at room temperature, between 15°C and 30°C.

IV and oral voriconazole supplies should be stored following voriconazole prescribing information.

The site will be required to keep a temperature log to establish a record of compliance with these storage conditions. All study drugs will be kept in a secure cabinet or room with access restricted to necessary clinic personnel.

13.4 Drug Accountability

The investigator or designee will inventory and acknowledge receipt of all shipments of the study drug. Drug accountability logs will be used to maintain accurate records of receipt, dispensing, administration to each subject and return of drug. A study monitor will periodically check the supplies of investigational products held by the site to verify accountability of all study drugs. At the conclusion of the study, after final drug accountability has been completed by the monitor, all unused study drug and all medication containers will be returned to the Sponsor or destroyed on-site if the site has procedures in place for study drug destruction.

Drug supplies will be maintained in a secure, limited-access storage area under the recommended storage conditions (see Section 13.3.3).

The study drug supplied for this study is only for use in subjects properly consented and enrolled under this protocol.
This is a double-blind study. A study site designee (e.g. pharmacist, study nurse/coordinator) will:

- Record the treatment in the appropriate drug accountability log
- Count the number of tablets per bottle before dispensing to the subject
- Report and document any study medication issues such as crushed or broken tablets
    - All product quality complaints should be reported to the Sponsor
- Collect and count the number of tablets remaining at the EoT visit
- Review subject diary and tablet count, record any unused or remaining drug in the drug accountability log and eCRF, and note any discrepancies and reason for discrepancies

13.5 Subject Compliance with Study Drug Dosing

Subjects who are not hospitalized and subjects who are discharged from the hospital will be instructed to have the study medication (including empty bottles/units) with them at each visit. Compliance will be assessed based on remaining study drug as compared to what should have been taken and the subject diary where the subject will enter the details of dosing. Details of treatment including any missing dose will be recorded in the eCRF. Sites are encouraged to contact the medical monitor or Sponsor for concerns of compliance with the treatment regimen, especially for subjects who miss doses due to problems with tolerability.

14.0 Non-Study Treatments

14.1 Prior and Concomitant Medications

All medications (including prescription and OTC medications, supplements, and herbal products) taken from 28 days before Screening through the EoT will be recorded on the eCRF. Only the use of antifungal medications, antibiotics for any reason or medications to treat an AE will be recorded after EoT and through the 6-Week FU visit. Start and stop times of concomitant medications taken during antifungal therapy will be recorded on the eCRF. Subjects will also record any new concomitant medications taken between visits in the subject diary.
Certain concomitant medications must be administered with caution or close monitoring as described in Section 14.2 and Section 14.3.

14.2 Prohibited Medications

Medications specifically not permitted prior to the study and during treatment or through the 6-Week FU visit include the following:

- Other investigational drug(s).
- Other antifungals except randomized study drug.

- Mold-active antifungal therapy for the treatment of the IPA episode for more than 4 days (96 hours) in the 7 days preceding enrollment into the study (Baseline/Treatment Day 1), except for those subjects who have received more than 4 days but less than 7 days of prior mold-active antifungal therapy for the treatment of the IPA episode in the 7 days preceding enrollment into the study and were granted approval for randomization by the medical monitor.
- Select strong CYP3A4/5 inhibitors, CYP3A4/5 inducers, and select P-gp substrates.

A detailed list of prohibited medications and timeframes is provided in Section 22.1 (Appendix A).

14.3 Medications to be Administered with Caution and Monitored as Appropriate

The following medications must be administered with caution and must be monitored as appropriate:

- Select CYP3A4 substrates, including but not limited to sirolimus, tacrolimus, warfarin, cyclosporine and amiodarone
- Organic anion-transporting polypeptide 1B3 (OATP1B3) substrates

A detailed list of medications to be administered with caution is provided in Section 22.1 (Appendix A).

14.4 Voriconazole Drug Interactions

The systemic exposure to voriconazole is expected to be reduced by the concomitant administration of the following agents and their use is **contraindicated**:

- *Rifampin* **(potent CYP450 inducer)**
- *Rifabutin* **(potent CYP450 inducer)**
- *Ritonavir* **(potent CYP450 inducer)**
- *St. John's Wort* **(CYP450 inducer; P-gp inducer)**
- *Carbamazepine and long-acting barbiturates* **(potent CYP450 inducers)**

The systemic exposure of the following drugs is expected to be significantly increased by coadministration of voriconazole and their use is **contraindicated**:

- *Sirolimus* **(CYP3A4 substrate)**
- *Terfenadine, astemizole, cisapride, pimozide and quinidine* **(CYP3A4 substrates)**
- *Ergot alkaloids*

Coadministration of voriconazole with the following agents could result in significant drug

interactions that may require dosage adjustment, frequent monitoring of drug levels and/or frequent monitoring of drug-related adverse events/toxicity:

- *Alfentanil (***CYP3A4 substrate***)*
- *Fentanyl* **(CYP3A4 substrate)**
- *Oxycodone* **(CYP3A4 substrate)**
- *Cyclosporine* **(CYP3A4 substrate)**
- *Methadone* **(CYP3A4, CYP2C19, CYP2C9 substrate)**
- *Tacrolimus* **(CYP3A4 substrate)**
- *Warfarin* **(CYP2C9 substrate)**
- *Oral Coumarin Anticoagulants* **(CYP2C9, CYP3A4 substrates)**
- *Statins* **(CYP3A4 substrates)**
- *Benzodiazepines* **(CYP3A4 substrates)**
- *Calcium Channel Blockers* **(CYP3A4 substrates)**
- *Sulfonylureas* **(CYP2C9 substrates)**
- *Vinca Alkaloids* **(CYP3A4 substrates)**
- *Non-Steroidal Anti-Inflammatory Drugs* **(NSAIDs; CYP2C9 substrates)**
- *Efavirenz,* **a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate)**
- *Phenytoin* **(CYP2C9 substrate and potent CYP450 inducer)**
- *Omeprazole* **(CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate)**
- *Oral Contraceptives* **(CYP3A4 substrate; CYP2C19 inhibitor)**
- *Other HIV Protease Inhibitors* **(CYP3A4 substrates and inhibitors)**
- *Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)* **(CYP3A4 substrates, inhibitors or CYP450 inducers)**

Additional information regarding medications that are contraindicated or require specific precautions when coadministered with voriconazole can be found in Section 22.2 (Appendix B: Voriconazole Label).

14.5 Study Restrictions

There are no additional study restrictions other than those described in Sections 12.2 (Exclusion Criteria), Section 13.2 (Dietary Requirements) and Section 14.2 (Prohibited Medications).

15.0 Study Procedures

The following sections provide a description of the individual study procedures to be performed during the conduct of the study. Detailed schedules of study assessments are provided in the Schedule of Visits and Procedures in Table 4.

15.1 Informed Consent

Every study subject (or the subject´s legal representative) must provide written informed consent at Screening, prior to participating in any screening evaluations or any other study activities (see Section 20.3).

15.2 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed at Screening and at Baseline (Treatment Day 1) prior to randomization to study drug treatment to ensure that the subject qualifies for the trial.

15.3 Subject Enrollment and Assignment of Subject Number

At Baseline/Treatment Day 1, all subjects who have signed an ICF will receive an 8-digit subject identification (ID) number that will be composed of a 3-digit study number (206) and a 2-digit site number followed by a 3-digit sequentially assigned subject number starting at 001. Subject numbers will be sequentially assigned by the database upon entry by the site. For instance, if site 01 enters the first subject in the database, the subject ID will be 206-01-001. The second subject entered in the database will get the subject number 002 as entered by any site, so that if site 02 enters the second subject, the subject ID will be 206-02-002. This number will be unique to each subject and will be used to identify the subject throughout the study.

Subjects who are screen failures or who are not eligible for enrolment will be recorded as such in the subject screening log. The subject numbers assigned to eligible subjects will be recorded in the eCRF. Only one subject number will be assigned to each eligible subject.

For subjects who signed an ICF (i.e., are assigned a subject number) but were NOT randomized because they did not meet all of the inclusion/exclusion criteria or other reason, selected Screening visit pages of the eCRF will be completed. The criteria that were not met for enrolment will also be documented in the eCRF.

All eligible subjects must be approved by the Sponsor for enrollment. When available, the antifungal therapy administered and Survival status at Days 42 and 84 will be collected for subjects who signed the ICF but were NOT randomized.

15.4 Randomization

At Baseline (Treatment Day 1), subjects who meet all of the inclusion and none of the exclusion criteria will be randomized to one of the two study treatment groups. Subject randomization will be performed using an IWRS, which will assign a unique randomization number for each

randomized subject corresponding to a study treatment. Only one randomization number and study drug treatment will be assigned to each eligible subject.

15.5 Medical History and Demographics

At Screening, a complete medical history for the prior 5 years will be recorded for each subject. The medical history will include previous and current medical diagnoses, as well as major surgical procedures. Subject demographics such as age, sex, race and ethnicity will also be collected.

15.6 General Physical Examination, Including Visual Function Assessment

A general physical exam will be conducted at Screening and Baseline (Treatment Day 1), at EoT and at the 6-Week FU visit. The physical examination will include an abbreviated assessment of general appearance, skin, eyes, heart, chest and abdomen.

An overall assessment and questions to investigate visual acuity, visual field and color perception should be conducted by the Principal Investigator or designee during Screening or at Baseline and again at approximately Treatment Day 28 (if voriconazole treatment continues beyond 28 days). An ophthalmologist exam is recommended if there are clinically significant visual function abnormalities identified during the general physical exams at or after Baseline. An ophthalmologist exam is not required for the enrollment of patients into the study but should be conducted as early as possible, if clinically significant visual function abnormalities are identified. Additional evaluations of visual function may be conducted as needed, at the investigator's discretion. Any visual disturbance identified should be documented either as part of the subject's medical history and/or as an AE, accordingly.

15.7 Vital Signs

Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at Screening and Baseline (Treatment Day 1), at EoT and at unscheduled visits, if applicable.

15.8 Twelve-Lead Electrocardiogram

A 12-lead ECG will be obtained and evaluated locally by a physician for the presence of abnormalities at Screening and Baseline (Treatment Day 1), once between days 7 and 21, at EoT and at unscheduled visits, if applicable.

Heart rate, PR interval, QRS, QT and QTcF values will be recorded in the eCRF. Any clinically relevant abnormality will be recorded as AE accordingly and will be followed up to resolution/satisfaction.

15.9 Pregnancy Test

A urine or serum pregnancy test will be performed at Screening, Baseline (Treatment Day 1), and at EoT, as well as once a month while on study treatment, by the local laboratory for all female subjects of childbearing potential.

15.10 Karnofsky Performance Status Scale

Karnofsky scores will be determined using the Karnofsky Performance at Screening and Baseline (Treatment Day 1), every 14 days during treatment up to EoT, at EoT, and on Day 42 and Day 84 (42 and 84 days after Baseline [Treatment Day 1] [first dose of study drug]).

15.11 Targeted Physical Examination, Including Clinical Evaluation of Signs and Symptoms of Infection

A targeted examination of the fungal infection site, including the signs and symptoms of the fungal disease, will be conducted at Screening and Baseline (Treatment Day 1), on Treatment Days 3, 5, 7 and 14, and then every 14 days up to EoT, at EoT and at the 6-Week FU visit.
The signs and symptoms of the fungal disease include, but are not limited to, the following:

- Fever, defined as oral temperature ≥38.3°C (≥101°F) on one occasion or >37.8°C (>100°F) on two measurements at least 4 hours apart
- Hypothermia <36°C (<96.8°F)
- Hypertension
- Tachycardia
- Hemoptysis
- Cough
- Respiratory distress
- Thoracic pain
- Pleural rub

Subjects who are not hospitalized or who are discharged from the hospital during study treatment will record selected signs and symptoms on subject diaries and the signs and symptoms will also be assessed by the site staff at the study visits. The site will assess whether the signs and symptoms recorded on the subject diary are related to the *Aspergillus* infection.

15.12 Chest CT Scan

A chest CT scan obtained within 5 days prior to enrollment must be available at Baseline (Treatment Day 1). In line with current aspergillosis treatment guidelines, follow-up chest CT scans will be performed to evaluate response to treatment, ideally within 3 days prior to or after EoT. Additional chest CT scans may be performed at other visits including the 6-Week FU visit, if applicable.
The results of all chest CT scans should be documented on the eCRF. A digital copy of the CT scan images will be uploaded to a designated central imaging system.

Special attention should be given to evaluate, and document radiological signs often associated with invasive pulmonary aspergillosis:

i. Dense well-circumscribed lesion(s) (nodules) with or without halo sign
ii. Hypodense sign
iii. Air crescent sign
iv. Cavity

A detailed description of EORTC/MSG criteria is available in Section 22.3 (Appendix C).

15.13 Other Imaging

If images other than the chest CT scan are available at Baseline (Treatment Day 1) to support the diagnosis of IPA (e.g., X-ray, ultrasound, magnetic resonance imaging), these other images will be collected, if available, to evaluate response.

The results of these studies should be documented on the eCRF.

15.14 Mycological Testing Other than Serum GMI, Serum β-D Glucan and Plasma *Aspergillus* PCR

Other mycological tests include fungal cultures (e.g., BAL culture, culture from biopsy), histopathological or cytopathological analysis of relevant tissues or samples (e.g., lung biopsy sample, BAL fluid.), and other tests (BAL GMI). Primary testing of these samples, including culture, histopathology and cytopathology, should be conducted at the site. All available results from these tests must be collected in the eCRF, including those available at Screening and those collected subsequently, until the FU visit.

BAL and relevant tissue samples should be submitted to the central laboratory for additional diagnostic tests including histopathology and *Aspergillus* PCR, if sufficient material is available. The site's local microbiology laboratory will be primarily responsible for the fungal cultures of relevant clinical samples and should perform species identification as per local standards. A sample of all mold isolates, including *Aspergillus,* should be sent to the central laboratory for species identification confirmation and antifungal susceptibility testing that will include voriconazole and SCY-078, at a minimum. The central laboratory will process these samples in batches and the results will not be available in real time to the sites.

Details for the procedures to collect, store and ship biological samples and mold isolates, including *Aspergillus,* will be described in the laboratory manual.

15.15 Galactomannan Index Assessment

Serum GMI will be determined at all study visits. At Screening, at least one sample collected within 96 hours before enrollment must be available for all subjects. For subjects with a possible IPA, serum samples will be collected daily for a maximum Screening Period of 4 days (Days -4 to -1) or until one positive GMI result (≥ 0.5) is reported. BAL samples, if collected per local practices, should be sent for GMI determination.

GMI samples during the Screening Period for evaluation of enrollment qualification will be processed locally (either the site laboratory or a designated regional laboratory). These results will be available in real time to make enrollment decisions. Results from GMI tests processed locally should be entered into the eCRF.

At Baseline, a serum sample will be collected for all randomized subjects within 2 hours before the first dose of SCY-078 or matching placebo for the determination of GMI. Serum GMI will also be assessed at all subsequent study visits, including all treatment visits, EoT, 6-Week FU visit and unscheduled visits. For randomized subjects, serum GMI samples collected after randomization will be analyzed at a central laboratory and results will not be available in real-time. If, at investigator's discretion, serum GMI results are needed during the study for adequate subject's care, additional GMI samples should be processed locally, and results should also be entered in the eCRF.

An immunoenzymatic sandwich microplate assay method will be generally used to determine serum GMI. Other methods such as lateral flow devices, which have received CE mark and/or FDA approval for galactomannan determination in serum and BAL, may be used during the Screening Period for evaluation of enrollment qualification. In these cases, enrollment qualification will be based on the device label recommendation for considering a serum test as positive.

15.16 Serum β-D-Glucan and Plasma *Aspergillus* PCR Test

Blood samples will be collected to perform serum β-D-glucan and plasma *Aspergillus* PCR testing throughout the study at all scheduled visits. Testing may also be conducted at unscheduled visits, if applicable. Serum β-D-Glucan and plasma *Aspergillus* PCR tests will be processed by a central laboratory. Procedures for collecting, storing, and shipping samples to the central laboratory are described in the study laboratory manual. It is anticipated that some sites may not have the central laboratory data on time, therefore if the sites happen to perform these tests locally, the results from the local laboratory should be recorded in the eCRF.

15.17 Safety Laboratory Tests

Safety laboratory tests (hematology, blood chemistry and urinalysis) will be performed at Screening and Baseline (Treatment Day 1), and on Treatment Days 7 and 14, at EoT and 6-Week FU. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy. If clinically indicated, safety tests will be repeated every 14 days following Treatment Day 14 up to EoT, and at unscheduled visits. These may also be done more frequently as follow-up to a laboratory abnormality. If the subject is still receiving study drug by Day 42 (i.e., EoT has not occurred), a safety lab assessment should be conducted on Day 42 or on Day 56.

Safety laboratory tests will be processed at a central laboratory. Procedures for collecting, storing, and shipping samples to the central laboratory are described in the study laboratory manual.

Results from safety laboratory test by the central lab will be made available to the sites on an ongoing basis; however, the site should not relay on timely availability of these result to make medical decisions for subjects' care.

Additional laboratory tests should be collected and analyzed by the local laboratory, as needed, to make real-time medical decisions. Specifically, in line with voriconazole label recommendations, serum transaminase levels, bilirubin levels, serum electrolytes (potassium, magnesium and calcium) and amylase and lipase should be monitored at initiation of voriconazole therapy (Day 1) and then weekly during the first month of treatment (Day 7, Day 14, Day 21 and Day 28). Monitoring frequency of these laboratory parameters may be reduced to monthly intervals during continued use of voriconazole if no clinically significant changes are noted.

The following laboratory parameters will be determined for all samples sent to the central laboratory:

Hematology

- White blood cell (WBC) count
- Red blood cell (RBC) count
- Platelet count
- Hemoglobin
- Hematocrit
- Differential WBC count will include percentages for segmented neutrophils, lymphocytes, monocytes, eosinophils and basophils, and absolute counts for neutrophils, lymphocytes, atypical lymphocytes, monocytes, eosinophils and basophils.

Blood Chemistry

- Sodium
- Potassium
- Magnesium
- Calcium
- Alkaline Phosphatase
- Chloride
- Blood urea nitrogen (BUN)
- Creatinine
- Total creatine phosphokinase (CPK)
- Aspartate aminotransferase (AST/SGOT)
- Alanine aminotransferase (ALT/SGPT)
- Gamma glutamyl transferase (GGT)
- Lactate dehydrogenase (LDH)
- Bilirubin (total, direct)
- Total protein
- Glucose
- Albumin
- Amylase
- Lipase

Urinalysis

- Appearance (clarity, color)
- Specific gravity
- pH
- Blood
- Bilirubin
- Glucose
- Ketones
- Protein
- Leukocytes
- Urobilinogen

15.18 Voriconazole Therapeutic Drug Monitoring

TDM for voriconazole will be conducted as per local standard practice. Samples for voriconazole TDM will be processed at a local laboratory. All results available from locally conducted tests of voriconazole plasma concentrations, including those prior to randomization, will be documented on the eCRF. The target trough plasma concentration should be above 1.5 mg/ L.

15.19 Voriconazole Level Determination

Voriconazole plasma level determinations will be conducted for all subjects at a central laboratory. For the first 20 randomized subjects, blood samples for the determination of voriconazole levels will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 2-4 hours and 6-8 hours after dosing. The PK data from the first 20 subjects will be assessed in an interim PK analysis. For subjects subsequently randomized, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 4-8 hours after dosing. The time of dosing and sample collection must be recorded in the eCRF. Procedures for collecting, storing, and shipping samples to the central laboratory are described in the study laboratory manual.

The results from voriconazole plasma concentration analyses performed at the central laboratory will not be available for making real-time decisions for voriconazole TDM. Voriconazole TDM will be conducted as per local standard practice and samples for voriconazole TDM will be processed at a local laboratory, as indicated in Section 15.17, Voriconazole Therapeutic Drug Monitoring.

15.20 SCY-078 Pharmacokinetic Sample Collection

PK testing for the determination of SCY-078 will be conducted for all subjects by a central laboratory. For the first 20 randomized subjects, blood samples for SCY-078 PK testing will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 2-4 hours and 6-8 hours after dosing. The PK data from the first 20 subjects will be assessed in an interim PK analysis. For subjects subsequently randomized, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14 approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 4-8 hours after dosing.

On PK sampling days, the investigator must record the dosing times and sample collection times in the eCRF and on the subject's medical record. Results for plasma concentrations of SCY-078 analyzed by the central laboratory will not be available in real time
Procedures for collecting, storing, and shipping plasma samples to the central laboratory for PK are described in the study PK Manual.
In addition to blood, other biological samples such as pleural effusion and tissue biopsies may also analyzed for SCY-078 PK determination, when available.

15.21 Assessment of Treatment Outcome

Efficacy will be assessed primarily in terms of Global Response (a composite assessment that includes clinical, radiological and mycological evaluations) as determined by an independent DRC and the Principal Investigator at EoT, Day 42 and Day 84, ACM at Days 42 and 84, as well as by GMI decrease from Baseline. Clinical, mycological and radiological outcomes at EoT, Day 42 and Day 84 as determined by the DRC and by the Principal Investigator will also be assessed.
The following study procedures will be performed to assess treatment outcome:

- Clinical signs and symptoms of IPA (Section 15.11)
- Radiological assessments
  - Chest CT scans (Section 15.12)
  - Other imaging procedures, as applicable (e.g., X-ray, ultrasound, CT and MRI) (Section 15.13).
- Mycological testing
  - Serum GMI (Section 15.15)
  - Serum β-D glucan and plasma *Aspergillus* PCR (Section 15.16)
  - Other mycological tests, including fungal cultures, histopathological and cytological analyses, and other serological tests (including BAL GMI) (Section 15.14)

15.22 Recurrence

Recurrence (after EoT) will be assessed by measuring recurrence of the baseline fungal infection within 42 days after EoT (6-Week FU). The DRC will be responsible for determining recurrence.

15.23 Survival

Survival will be determined on Day 42 and Day 84 (42 and 84 days after Baseline [Treatment Day 1] [first dose of study drug] for randomized subjects and 42 and 84 days after the ICF is signed for screen failures). This can be an in-person visit or a phone contact, and will document subject status (alive or deceased). If subject is deceased, the date of death and the investigator's assessed relationship to the fungal infection will also be recorded. If autopsy is conducted, key findings should be collected in the eCRF.
See Section 19.7 for a detailed description of efficacy outcomes.

15.24 Study Drug Dispensing

The study drug will be dispensed at Baseline (Treatment Day 1), and approximately every 14 days thereafter until EoT. Subjects who are hospitalized and are later discharged from hospital will be dispensed their study drug at the time they are discharged.
See Section 13.3.2 for information on study drug supplies.

15.25 Study Drug Dosing

Study drug doses (oral SCY-078 or oral SCY-078 matching placebo) will be administered daily to subjects from Baseline (Treatment Day 1) through EoT. The study drugs will be administered in a blinded fashion. Treatment may be given on an inpatient or outpatient basis, as needed, and for as long as is clinically indicated, at the investigator´s discretion, but in no event for more than a total of 13 weeks (i.e. 91 days) of study drug treatment.
For subjects who are unable to take oral medications, SCY-078 tablets may be crushed and administered with approximately 8 oz./240 mL of water via an NG or PEG tube. The tube should be flushed with water before and after drug administration.
Oral SCY-078 will be administered preferably with meal.
Loading dose:

- The first 4 doses of oral SCY-078 500 mg will be administered BID, approximately every 12 hr (total dose of 1000 mg per day for 2 days)

Maintenance dose:

- Starting with the 5th dose of oral SCY-078 500 mg the subsequent doses will be administered QD (total dose of 500 mg per day). The 5th dose may be administered within 12 to 24 hrs of the 4th dose, to allow for adjustment to a QD dose regimen that is the most convenient for the patient (either AM or PM). Subsequent doses should be administered approximately 24 hr apart.

The dose of SCY-078 may be adjusted for subjects who are randomized after the interim PK analysis. Until a decision to adjust the dose is made based on data from this analysis, subjects will continue receiving SCY-078 500 mg doses as described above.
If after interim PK analysis the daily dose is changed from 500 mg to 750 mg the dosing instructions will be the same but 500mg dose will be substituted by 750 mg dose. Specifically, the loading dose will be oral SCY-078 750 mg BID for 4 doses, followed by maintenance dose of 750 mg QD subsequently.
For subjects who are intolerant of SCY-078 due to gastrointestinal (GI) related conditions such as clinically significant nausea or diarrhea, the following dose administration adjustments are allowed:

- Each tablet of SCY-078 may be administered every 10-20 min rather than all at once.
- The daily dose during the maintaining phase (after the first 4 loading doses) can be changed from QD to BID, administering 250 mg of SCY-078 (one tablet) approximately every 12 hr, preferably with a meal (total dose of 500 mg per day).

  - If, after the interim PK analysis the daily dose is increased to 750 mg of SCY078 per day, the daily dose during the maintaining phase (after 2 days of loading dose) can be changed from QD to BID, administering 375 mg of SCY-078 (one tablet and ½) approximately every 12 hr, preferably with a meal (total dose of 750 mg per day).
- Interruption of administration of SCY-078 tablets for up to 2 days (after loading dose has been completed) is also allowed, if GI side effects are persistent.
- At the investigator's discretion, concomitant medication(s) to potentially decrease GI events may be given to the subject.

Further details of the study treatment and dietary requirements for treatment administration are provided in Section 13.1 and Section 13.2, respectively.

15.26 Study Drug Collection and Treatment Compliance Evaluation

Study drug use will be recorded for treatment compliance evaluation daily from Baseline (Treatment Day 1) through EoT (see Section 13.5 for further details).

15.27 Subject Diary Dispensing, Collection and Review

Non-hospitalized subjects will complete a subject diary up to their EoT visit. The subjects will record the date/time of study medication dosing, selected signs and symptoms, medical concerns or complaints and concomitant medications.

Subject diaries will be dispensed at Screening and will be reviewed at clinic visits after Treatment Day 14 up to EoT. Subject diaries will be collected at EoT.

15.28 Prior and Concomitant Medication Review

All medications (including prescription and OTC medications, supplements, and herbal products) taken from 28 days before Screening through the EoT will be recorded on the eCRF. Only the use of antifungal medications, antibiotics for any reason or medications to treat an AE will be recorded after EoT and through the 6-Week FU visit. Prior and concomitant medications will also be reviewed at unscheduled visits. See Section 22.1 (Appendix A) for prohibited medications, medications to be administered with caution and further details for non-study treatments.

15.29 Adverse Event Monitoring

AEs will be collected and evaluated from Baseline (Treatment Day 1), after the first dose of study drug SCY-078, and SOC voriconazole and through the end of the study. AEs will also be collected at any unscheduled visits.

The effect of voriconazole on visual function is not known if treatment continues beyond 28 days. There have been post-marketing reports of prolonged visual adverse events, including optic neuritis and papilledema. If voriconazole treatment continues beyond 28 days, as recommended in the label as part of standard of care, visual function including visual acuity, visual field and

color perception should be monitored to identify potential visual disturbances. Any visual disturbance identified should be reported as an adverse event.
See Section 17.0 for details regarding safety assessment and monitoring.

16.0 Study Schedule

Detailed schedules of all study visits and procedures are presented in the Schedules of Visits and Procedures (Table 4 and Table 5).

Table 4 Schedule of Treatment Visits and Procedures (Study SCY-078-206)

Visit	Screening Period	Baseline (Treatment Day 1)	Treatment Day 3	Treatment Day 5	Treatment Day 7	Treatment Day 10	Treatment Day 14	Every 14 days during treatment[a]	EoT[b]	6-Week FU (6 weeks after EoT)	Unscheduled Visits
Days (allowable window)	Day -4 to Day -1[c]	0	+ 1	+1	+1	+1	+1	± 2 days	± 1 day	± 2 days	
Procedure											
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Subject Enrollment and ID Assignment		X									
Randomization		X									
Medical History and Demographics	X										
General Physical exam, including Visual Function Assessment[d]	X	X						X (VFA only, TD28)	X	X	
Vital Signs	X	X							X		If applic.
12-Lead ECG	X	X				X[e]			X		If applic.
Pregnancy Test[f]	X	X							X		
Karnofsky Score	X	X					X	X	X		
Targeted Physical Exam including Clinical Evaluation of Signs and Symptoms of Infection	X	X	X	X	X		X	X	X	X	
Chest CT scan		X[g]	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	X[h]	If applic.	If applic.
Other Imaging		X[i]	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.
All Mycological Testing[j] including BAL GMI[l] (other than	X[k]	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.

Visit	Screening Period	Baseline (Treatment Day 1)	Treatment Day 3	Treatment Day 5	Treatment Day 7	Treatment Day 10	Treatment Day 14	Every 14 days during treatment[a]	EoT[b]	6-Week FU (6 weeks after EoT)	Unscheduled Visits
Days (allowable window)	Day -4 to Day -1[c]	0	+ 1	+1	+1	+1	+1	± 2 days	± 1 day	± 2 days	
Procedure											
serum GMI, serum β -D Glucan, and plasma *Aspergillus* PCR)											
Serum GMI	X[l]	X[m]	X	X	X	X	X	X	X	X	X
Serum β -D Glucan and plasma *Aspergillus* PCR	X	X	X	X	X	X	X	X	X	X	If applic.
Safety Laboratory Assessments[n]	X	X			X		X	If applic.[o]	X	X	If applic.
Voriconazole TDM[p]	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.
Voriconazole level determination[q]		X	X		X	If applic.[r]	X	If applic.[r]			If applic.
SCY-078 Plasma PK[s]		X	X		X		X				
Assessment of treatment outcome									X	X	
Assessment of Recurrence										X	
Study Drug Dispensing		X						X			
Study Drug Dosing[t]		X----------X									
Study Drug Collection and Compliance Evaluation		X----------X									
Subject Diary Dispensing, Collection and Review[u]	X							X	X		
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; applic.= applicable; BAL = bronchoalveolar lavage; BID = twice daily; ECG=electrocardiogram; eCRF = electronic case report form; EoT=end of treatment; GM = galactomannan; PK = pharmacokinetic(s), QD = once daily; TD = Treatment Day; TDM = therapeutic drug monitoring; VFA = visual function assessment.

Visit	Screening Period	Baseline (Treatment Day 1)	Treatment Day 3	Treatment Day 5	Treatment Day 7	Treatment Day 10	Treatment Day 14	Every 14 days during treatment[a]	EoT[b]	6-Week FU (6 weeks after EoT)	Unscheduled Visits
Days (allowable window)	Day -4 to Day -1[c]	0	+ 1	+1	+1	+1	+1	± 2 days	± 1 day	± 2 days	
Procedure											

a. Antifungal treatment duration will be for a recommended minimum of 6 weeks and a maximum of 13 weeks.
b. All EoT procedures should be performed for subjects who discontinue from study treatment before the EoT visit.
c. The Screening Period and Baseline/Treatment Day 1 visits may be combined.
d. An overall assessment and questions to investigate visual acuity, visual field and color perception should be conducted by the Principal Investigator or designee during Screening or at Baseline and again at approximately Treatment Day 28 (if voriconazole treatment continues beyond 28 days). An ophthalmologist exam is recommended if there are clinically significant visual function abnormalities identified during the general physical exams at or after Baseline. An ophthalmologist exam is not required for the enrollment of patients into the study but should be conducted as early as possible, if clinically significant visual function abnormalities are identified. Additional evaluations of visual function may be conducted as needed, at the investigator's discretion. Any visual disturbance identified should be documented either as part of the subject's medical history and/or as an AE, accordingly.
e. A 12-lead ECG will also be performed once between Days 7 and 21.
f. Pregnancy test should be done, locally, once a month, while subject is on study treatment.
g. A chest CT scan obtained within 5 days prior to enrollment must be available at Baseline (Treatment Day 1).
h. Follow-up chest CT scans will be performed to evaluate response to treatment, ideally within 3 days prior to or after EoT.
i. If images other than the chest CT scan are available at Baseline (Treatment Day 1) to support the diagnosis of IPA, subsequent comparative imaging studies will be collected, if available, to evaluate response.
j. Mycological testing other than serum GMI, serum β-D glucan and plasma *Aspergillus* PCR tests will include fungal cultures (e.g. BAL culture, culture from biopsy), histopathological or cytopathological analysis of relevant tissues or samples (e.g., lung biopsy sample, BAL fluid.), and other tests (BAL GMI).
k. These procedures will be repeated only if clinically indicated.
l. At Screening, at least one positive serum or BAL sample collected within 96 hours before enrollment must be available for all subjects. For subjects with a possible IPA, serum or BAL samples will be collected daily for a maximum Screening Period of 4 days (Days -4 to -1) until at least one positive GMI result (≥ 0.5 for serum and ≥ 1 for BAL) is reported. If a positive serum or BAL GMI test is reported after 4 days but no more than 7 days of mold-active antifungal treatment, the case will be discussed with the medical monitor to evaluate eligibility. If GMI results during the Screening period are negative, the subject will not be randomized and will be discontinued from the study.
m. Samples for serum GMI assessments will be obtained within 2 hours before first dose of randomized treatment.
n. Clinical safety laboratory assessments by the central laboratory will include hematology, blood chemistry and urinalysis. Additional laboratory tests should be collected and analyzed by the local laboratory, as needed, to make real-time medical decisions. Specifically, in line with voriconazole label recommendations, serum transaminase levels, bilirubin levels, serum electrolytes (potassium, magnesium and calcium) and amylase and lipase should be monitored at initiation of voriconazole therapy (Day 1) and then weekly during the first month of treatment (Day 7, Day 14 and Day 21, Day 28). Monitoring frequency of these laboratory parameters may be reduced to monthly intervals during continued use of voriconazole if no clinically significant changes are noted.
o. If the subject is receiving study drug by Day 42 (i.e., EOT has not occurred), a safety lab assessment should be conducted on Day 42 or on Day 56.
p. Voriconazole TDM will be conducted as per local standard practice and samples will be processed locally. All results available from locally conducted tests of voriconazole plasma concentrations, including those prior to Randomization, will be documented in the eCRF.
q. Blood samples for voriconazole level determination will be performed for all study subjects at a central laboratory. For the first 20 randomized subjects, blood PK samples

Visit	Screening Period	Baseline (Treatment Day 1)	Treatment Day 3	Treatment Day 5	Treatment Day 7	Treatment Day 10	Treatment Day 14	Every 14 days during treatment[a]	EoT[b]	6-Week FU (6 weeks after EoT)	Unscheduled Visits
Days (allowable window)	Day -4 to Day -1[c]	0	+ 1	+1	+1	+1	+1	± 2 days	± 1 day	± 2 days	
Procedure											

will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing and at 2-4 hours and 6-8 hours after dosing on Treatment Days 1, 7 and 14. The PK data from the first 20 subjects will be assessed in an interim PK analysis. For subjects subsequently randomized, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 4-8 hours after dosing. The time of dosing and sample collection must be recorded in the eCRF.

r. Blood samples for voriconazole level determination to be collected as needed (e.g., within 7 days after making any dose adjustment or evidence of toxicity) and sent to the central lab.

s. Samples for SCY-078 PK will be collected from all subjects. For the first 20 randomized subjects, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and at 2-4 hours and 6-8 hours after dosing on Treatment Days 1, 7 and 14. The PK data from the first 20 subjects will be assessed in an interim PK analysis. For subjects subsequently randomized, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and at 4-8 hours after dosing on Treatment Days 1, 7 and 14. The time of dosing and sample collection must be recorded in the eCRF and on the subject´s medical record.

t. All randomized subjects will receive either SCY-078 + voriconazole or SCY-078 placebo + voriconazole.

u. For non-hospitalized patients only.

Table 5 Schedule of Treatment Visits and Procedures for Days 42 and 84 (Study SCY-078-206)

PROCEDURE Visit	Visit/contact **Survival Day 42**	Visit/contact **Survival Day 84**
Days (allowable window)	± 2	± 4
Assessment of treatment outcome	X	X
Subject Status (alive/ deceased)	X	X
Karnofsky Score	X	X

17.0 Safety Assessments and Monitoring

17.1 Definition of an Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a study drug/study intervention, whether or not related to the study drug/study intervention.

Any laboratory abnormality that is deemed to be clinically significant in the opinion of the investigator will be considered an AE and should be recorded in the eCRF, whether or not it is related to the study drug.

Stable chronic conditions that are present prior to clinical trial enrollment and do not worsen are not considered AEs and will be accounted for in the subject's medical history.

The following can be considered AEs:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after the initiation of treatment with study medication, even though it may have been present prior to the start of the study
- Continuous persistent disease or symptoms present at Baseline that worsen after signing the informed consent or following the initiation of treatment with study medication

The following are **not** considered AEs:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction or transfusion); the condition that leads to the procedure is an AE
- Pre-existing disease or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic surgery or elective surgery or social/convenience admissions)
- The disease being studied, or signs or symptoms associated with the disease, unless more severe than expected for the subject's condition or a worsening of the disease being studied

17.2 Definition of a Serious Adverse Event

A SAE is defined as an AE meeting one of the following outcomes:

- Death
- Life-threatening event

- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Any other important medical event that may not result in one of the above outcomes may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

A life-threatening AE is any AE that places the subject, in the view of the investigator, at immediate risk of death from the AE as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.

17.3 Events of Clinical Interest

The following are considered events of clinical interest (ECIs), and must be recorded as such on the AE eCRF when the PI becomes aware of the ECI:

- QTc >500 ms or a >60-ms change from Baseline, confirmed by repeat testing
- ALT or AST >8 x ULN, if new compared to Baseline, confirmed by repeat testing
- ALT or AST >5 x ULN for more than 2 weeks and if new compared to Baseline, confirmed by repeat testing
- ALT or AST >3 x ULN and either total bilirubin >2 x ULN or INR >1.5 and if new compared to Baseline, confirmed by repeat testing
- ALT or AST >3 x ULN, confirmed by repeat testing, with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)]

17.4 Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information.

An overdose can occur if a subject has taken, accidentally or intentionally, a drug administered in a dose exceeding the protocol-specified dose. An overdose must be reported within 24 hours of the site becoming aware of the overdose if such overdose occurs with an associated SAE. If an overdose occurs without an associated SAE, the overdose must be reported within 5 working days and documented in the subject medical record.

17.5 Pregnancy

Female subjects who become pregnant should be immediately discontinued from the study and followed up to determine the outcome of the pregnancy. The pregnancy must be reported to the Sponsor within 24 hours of the site becoming aware of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

17.6 Unexpected Adverse Event

An AE is considered “unexpected” if it is not listed in the IB or is of greater specificity or severity than those that have been observed with the particular study drug being tested. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

17.7 Grading of Adverse Events

The severity (or intensity) of an AE refers to the extent to which it affects the subject’s daily activities and will be classified by the investigator as mild, moderate or severe using the following criteria:

- Mild: Awareness of sign or symptom, but easily tolerated. Not likely to require medical attention.
- Moderate: Discomfort enough to cause some interference with daily activity. May require medical intervention.
- Severe: Intense enough to disrupt daily activities. Likely requires medical intervention.

Clarification of the difference in meaning between “severe” and “serious”

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

17.8 Causality Assessment

The investigator will assess causality (i.e., whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Related: The temporal relationship of the AE with the study drug makes causality possible and cannot be due to another cause such as other drugs, a surgical intervention or an underlying disease.
- Not related: The temporal relationship of the AE with the study drug makes causality improbable and can be due to another cause such as other drugs, a surgical intervention or an underlying disease.

17.9 Adverse Event Collection Timeframe

AEs will be collected and evaluated from Baseline (Treatment Day 1), after the first dose of SCY-078 study drug, and SOC voriconazole and through the end of the study.
All AEs reported by the subject or observed by members of the clinical staff will be evaluated by the principal investigator (PI) or qualified designee. The PI will attempt, if possible, to establish a diagnosis based on presenting signs and symptoms. The nature of the AE, time of onset relative to study drug administration, duration, severity, and relationship to treatment should be determined. Details of any corrective treatment must be recorded in the eCRF. The PI will determine whether any changes have occurred in baseline signs and symptoms. All AEs and SAEs will be collected in the eCRF.

17.10 Serious Adverse Event Reporting Requirements

All SAEs must be reported within 24 hours of the site becoming aware of the SAE. Any event that is serious, study drug-related, and unexpected as assessed by the medical monitor or the Sponsor will be submitted to the regulatory authorities in accordance with national regulatory laws and regulations. The PI will be responsible for reporting all SAEs that require reporting to the local Institutional Review Board/Ethics Committee (IRB/EC) in accordance with its regulations and guidelines.

17.11 Adverse Event and Serious Adverse Event Follow-up

All AEs and SAEs will be followed up to resolution (the subject's health has returned to her baseline status or all variables have returned to normal) or until an outcome is reached, stabilization occurs (the investigator does not expect any further improvement or worsening of the event) or the event is otherwise explained, regardless of whether the subject is still participating in the study. All appropriate therapeutic measures should be undertaken and recorded. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

17.12 Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports and Follow-Up SAE Reports:

To report an SAE, the SAE eCRF form within the Electronic Data Capture (EDC) system must be completed. All SAEs, whether or not deemed drug-related or expected, must be reported by the investigator or qualified designee within 24 hours of first becoming aware of the event. The investigator/qualified designee will enter the required information regarding the SAE into the appropriate form, which will automatically result in distribution of the information to the appropriate Sponsor contact.

17.13 Procedures for Emergency Unblinding

This is a double-blind study. The investigator should only be unblinded if this information is necessary to determine treatment of an emergency. The Interactive Web Response Systems (IWRS) can provide the information necessary to unblind the investigator, in case of an emergency. In the event that the web-based IWRS system is not available, emergency unblinding can occur by contacting the [redacted] help-desk as follows: [redacted] If the investigator is unblinded, the reason for unblinding should be documented in the comment page of the eCRF.

18.0 Data Collection, Study Monitoring and Record Management

18.1 Data Collection and Reporting

Data for this study will be collected using eCRFs. The investigator and study site staff will receive training regarding the completion of the eCRF. Visit-specific data should be entered into the eCRF and be ready for review as soon as possible, but no later than 5 days after each visit/time point.

All protocol-required information collected during the study must be entered by the investigator or designated representative in the source documents and eCRF. All data entry, modification or deletion will be recorded indicating the individual subject, original value, the new value, the reason for change, who made the change, and when the change was made. All data changes will be clearly indicated with a means to locate prior values. The investigator will maintain a list of individuals who are authorized to enter or correct data on the eCRFs.

The investigator or designated sub-investigator, following review of the data in the eCRF, will confirm the validity of each subject's data by signing the eCRF.

18.2 Study Monitoring

Study progress will be monitored by the Sponsor or its representative as frequently as necessary to ensure adequate and accurate data collection, protocol compliance, and

study conduct in accordance with accepted regulatory requirements. The PI must make all the subject data available to the monitor for review during the planned site monitoring visits. Arrangements for monitoring visits will be made in advance, except in emergency cases.

18.3 Investigator Study Files

The PI is responsible for maintaining all study-related documents in study files. The Sponsor will notify the PI when retention of study files is no longer necessary. The following documents will be kept in the study files or be readily accessible:

- original protocol and all amendments;
- signed agreement or protocol;
- signed and dated study staff roles and responsibilities log;
- copy of the current *curriculum vitae* of the PI and of all sub-investigators;
- IRB/EC membership list and all IRB/EC approvals for the protocol and amendments, informed consent documentation and all updates, advertisements, and written information provided to subjects; all IRB/EC correspondence; documentation that the IB and subsequent revisions have been submitted to the IRB/EC; documentation that all SAEs and any periodic safety reports have been submitted to the IRB/EC; and annual IRB/EC renewals (as required);
- updated laboratory certification and the laboratory's normal values (covering the entire time interval of the study for all laboratory tests conducted during the study);
- all confirmations of investigational drug receipt, drug accountability logs and drug return records;
- a CD or DVD containing final subject eCRF data;
- all correspondence to or from the Sponsor or its designees;
- blank informed consent form;
- Investigator's Brochure;
- subject screening log;
- subject list (contains subject initials and/or protocol-specific subject number);
- all subjects' original signed informed consents; and,
- monitoring visit log.

18.4 Retention of Records

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Sponsor will inform the PI/institution in writing of the need for record retention and will notify the PI/institution in writing when the trial-related records are no longer needed.

An investigator who withdraws from the responsibility of maintaining study records or wishes to move them to a new location has the obligation to place them in safekeeping and to inform the Sponsor of their location.

19.0 Analytical Plan

All statistical processing will be performed using SAS® version 9.3 or later, unless otherwise stated.

Descriptive statistics (i.e., number of subjects, mean, standard deviation, median, minimum, maximum) will be presented for all continuous variables; number and percentage of subjects will be presented for categorical variables. For parameters measured over time, observed data and changes from baseline will be described for each time point.

When feasible, based on adequate sample size sub-group analyses including by gender and by underlying condition will be conducted.

A Statistical Analysis Plan (SAP) describing all statistical analyses in detail will be provided as a separate document.

19.1 Sample Size Determination

This is an exploratory study with safety as a primary objective. As a result, no formal sample size calculations are defined and the data from this study will provide safety data for SCY-078 in patients along with a preliminary view of efficacy data, which can be used to design future studies. Given that this is early Phase 2 trial, it would be difficult to try to estimate a sample size that would be required to achieve some evidence of statistical superiority of the efficacy endpoints being evaluated. The sample size needed to achieve statistical superiority on all-cause mortality is much larger than is feasible for this early stage study. In addition there is insufficient information on effect size for the other endpoints such as global response and kinetics of galactomannan as a marker of efficacy. The main goal of this study is to obtain preliminary estimates of the effect size expected for all of the efficacy endpoints.

19.2 Analysis Populations

The study populations used for the analyses are as follows:

Intent-to-Treat (ITT)/Safety Population: The ITT Population will include all randomized subjects who receive at least one dose of randomized study medication. The **Safety Population** will be the same as the ITT population.

Modified Intent-to-Treat (mITT): The mITT population will be a subset of the ITT population that will include subjects who have a probable or proven IPA at baseline, per DRC, with at least one positive serum GMI at baseline.
Per-Protocol (PP) Population: The PP Population will be a subset of the ITT population and will include subjects who have a probable or proven IPA at baseline, per DRC, with at least one positive serum GMI at baseline, have completed at least 14 days of randomized study treatment and have at least one efficacy assessment post Baseline (Treatment Day 1) and no major protocol deviations.
PK Population: The PK Population will include all enrolled subjects who provide at least one PK sample.

19.3 Subject Disposition, Discontinuation, and Baseline Data

Subject disposition in terms of the number and percentage of subjects enrolled by site will be tabulated. The number of subjects enrolled, number completing the study and reasons for discontinuation will be summarized. Subject demographics and baseline characteristics such as age, race, ethnicity, sex, weight, height, body mass index, country and other relevant parameters will be tabulated.
Baseline is defined as the last non-missing assessment prior to the date (and time if appropriate) of the first dose of study drug. Change from baseline is defined as: post-baseline value – baseline value.

19.4 Handling of Missing Data, Dose Adjustments, and Early Withdrawals

For the efficacy analyses, subjects who do not have an EoT assessment will be assigned an indeterminate outcome, so will be classed as treatment failures for the corresponding efficacy analyses. For subjects who withdraw from the study early, every effort will be made to collect EoT visit information at the point of withdrawal.

19.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary terminology. The number and percentage of subjects taking each medication before and after the first dose of study drug will be tabulated. Medications taken and stopped prior to the first dose of study drug will be considered prior medications. Medications started on or before the FU visit date with missing stop dates or stop dates after the first dose of study drug will be considered concomitant medications.

19.6 Safety

19.6.1 Safety Assessments

Subjects will be evaluated for safety and tolerability throughout the study, including parameters such as physical exam including visual function assessment, vital signs, 12-lead ECGs, safety laboratory tests (hematology, blood chemistry and urinalysis), concomitant medications, AEs and treatment discontinuations. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.
Safety procedures are described in **Section 15.0** and safety assessments are described in **Section 17.0**.

19.6.2 Safety Analyses

All safety analyses will be conducted using the ITT/safety population; all safety variables will be listed.
The incidence and severity of TEAEs and SAEs and their relationship to treatment will be summarized. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or higher and presented by system organ class and preferred term.
Early discontinuation of study drug treatment will be presented and will include the reasons for and timing of such discontinuations.
Prior and concomitant medications will be summarized; medications will be classified based on the World Health Organization´s Drug Dictionary terminology.
Abnormal physical examinations will be listed. Laboratory evaluations will be summarized as observed values and changes from Baseline; shifts with respect to the laboratory reference range will be summarized. Events of clinical interest will be summarized.
Vital signs and ECG evaluations will be summarized as observed values and changes from Baseline.

19.7 Efficacy

19.7.1 Efficacy Assessments

Efficacy will be assessed primarily in terms of Global Response, ACM and GMI decrease (GMI decrease will only be assessed for subjects with a Serum GMI above 0 at Baseline). The DRC evaluation of Global Response is considered the key efficacy evaluation, considering the expert and independent nature of the DRC assessment. In addition to Global Response, clinical, mycological and radiological outcomes will also be assessed. Exploratory efficacy assessments include, among others, recurrence, performance indicators and other serological biomarkers (β-D-glucan and *Aspergillus* PCR).

19.7.1.1 Treatment Outcome

Global Response will be assessed based on the following definitions:

- Global Response
  - Complete Response: Survival and resolution of all attributable symptoms and signs of disease; plus, successful radiological outcome; plus, documented mycological eradication of infected sites that are accessible to repeated sampling or presumed eradication of sites that are not accessible to repeated sampling.

  - Partial Response: Survival and improvement of attributable symptoms and signs of disease; plus at least 25% reduction in diameter of radiological lesion(s); plus, documented mycological eradication of infected sites that are accessible to repeated sampling or presumed eradication of sites that are not accessible to repeated sampling. In cases of radiological stabilization (defined as 0%-25% reduction in the diameter of the lesion), resolution of attributable symptoms and signs of fungal disease can be equated with a partial response. In cases of radiological stabilization, biopsy of an infected site (e.g., lung biopsy) showing no evidence of hyphae and negative culture results can be equated with a partial response.

  - Stable response: Survival and no improvement in any attributable symptoms and signs of disease; plus, radiological stabilization (defined as a 0%-25% reduction in the diameter of the lesion); or persistent isolation of mold or histological presence of invasive hyphae in infected sites.

  - Progression of disease: Worsening clinical symptoms and signs of disease; plus, new sites of disease or radiological worsening of preexisting lesions; or persistent isolation of mold species from infected sites.

  - Death: Death during the prespecified period of evaluation regardless of attribution.

Clinical, mycological and radiological outcome will be assessed based on the following definitions:

- Clinical response
  - Success:
    - Resolution of all attributable clinical symptoms and physical findings
    - Partial resolution of attributable clinical symptoms and physical findings
  - Failure:

        - No resolution of any attributable clinical symptoms and physical findings and/or worsening
    - Not applicable:
        - No attributable signs and symptoms present at Baseline and no symptoms attributable to invasive fungal disease developed post Baseline

- Mycological response
    - Success:
        - Eradication
        - Presumed eradication
    - Failure:
        - Persistence
        - Presumed persistence
    - Not applicable:
        - No mycological evidence available at Baseline

- Radiological response
    - Day 42:
        - Success (improvement of at least 25% from Baseline)
        - Failure
        - No post Baseline radiology available for patient with baseline evidence of radiological disease
        - Radiology not applicable at Baseline

    - Day 84:
        - Success (improvement of at least 50% from Baseline)
        - Failure
        - No post Baseline radiology available for patient with baseline evidence of radiological disease
        - Radiology not applicable at Baseline

    - EoT:
        - Success (improvement of at least 25% from Baseline if EoT occurs prior to Day 42; if EoT occurs after Day 42, at least 50% improvement from Baseline)
        - Failure
        - No post Baseline radiology available for patient with baseline evidence of radiological disease
        - Radiology not applicable at Baseline

19.7.1.2 All-Cause Mortality

All-cause mortality will be defined as death during the prespecified period of evaluation, regardless of attribution. Survival will be determined via an in-person visit or a phone contact, and will document subject status (alive or deceased) as well as date of death. If subject is deceased, the investigator´s assessed relationship to the fungal infection will also be recorded. If autopsy is conducted, key findings should be collected in the eCRF.

19.7.1.3 GMI Decrease

GMI decrease will be assessed in terms of absolute and percentage reduction relative to Baseline, and in terms of time to achieve the GMI absolute and percentage reductions. GMI decrease will be assessed in subjects with Baseline serum GMI above 0, only.

19.7.1.4 Recurrence

Recurrence is defined as a diagnosis of probable or proven IPA based on EORTC after EoT in patients who have previously achieved complete response. Re-emergence of the *Aspergillus* infection is required to be with the same species (if *Aspergillus* isolates are available for both the baseline and the recurrent episode) and involving the same site that was initially identified at Screening. The DRC will be responsible for determining recurrence.

19.7.2 Efficacy Analyses

The secondary efficacy endpoint, the percentage of subjects with successful Global Response (Complete Response or Partial Response) at EoT, Day 42 and Day 84 as determined by the DRC and the Principal Investigator will be presented by treatment group along with an estimate of the difference between treatment groups. The response rate will be calculated for each treatment group as the number of successes divided by the total number of patients (success + failure + indeterminate). The difference in response rates between treatments will be presented along with a 95% confidence interval (CI), calculated using the method of Miettinen and Nurminen. The secondary analysis of ACM at Day 42 and Day 84 will be presented by treatment group along with an estimate of the difference between treatment groups. In addition, a Kaplan Meier plot will be produced to summarize overall survival over time.

The remaining secondary and exploratory endpoints will be summarized by treatment group.

Provided sufficient data are available to allow meaningful presentation, results of the key efficacy parameters will also be presented by baseline *Aspergillus* species; by baseline minimum inhibitory concentration (MIC) and minimal effective concentration (MEC) for voriconazole and SCY-078, respectively; and by baseline neutropenia and persistent neutropenia at Week 2.

Considering the exploratory nature of this study, further analysis may be defined in the statistical analysis plan, as deemed appropriate. For example, if the data are heterogeneous within this randomized study, attempts may be made to match patients across the treatment groups on key disease criteria, if sufficient data are available, to better understand the comparability of the randomized groups.

19.8 Pharmacokinetics

19.8.1 Pharmacokinetic Assessments

PK testing for the determination of SCY-078 will be conducted for all subjects. For the first 20 randomized subjects, blood samples for SCY-078 PK testing will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 2-4 hours and at 6-8 hours after dosing.
Voriconazole level determination will also be performed for all study subjects predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 2-4 hours and at 6-8 hours after dosing.
The PK data from the first 20 subjects will be assessed in an interim PK analysis that will keep the study team blinded.
For subsequent randomized subjects, blood PK samples will be collected predose on Treatment Days 1, 3, 7 and 14, approximately within 1 hour before dosing, and on Treatment Days 1, 7 and 14 at 4-8 hours after dosing for SCY-078 and voriconazole central lab PK testing.
Results for plasma concentrations of SCY-078 and voriconazole analyzed by the central laboratory will not be available in real time for any subject.

19.8.2 Pharmacokinetic Analyses

The sparse samples collected in this study will be analyzed using Population PK (Pop PK) analysis methods to estimate PK parameters (C_{max}, AUC, clearance/fraction absorbed [CL/F]) as applicable.
Key collection and analysis timepoints include Day 1, Day 7 (i.e., steady state) and Day 14. After the first 20 subjects have been treated for at least 7 days, an interim PK evaluation will be conducted to ensure there are no clinically relevant effects of the co-administration of SCY-078 and voriconazole on the PK exposure (predicted AUC and C_{max} based on updated population PK model) of both drugs. The data from this analysis will inform, and if necessary adjust, the doses of the study drug for subjects subsequently randomized. The overall goal, considering that IPA is a life-threatening condition, is to ensure that >80% of subjects achieve an exposure that is at least equal to that reported as efficacious in the mice models of invasive aspergillosis (15.6 µg•mL/hr). The results from the PK analyses will be presented in a separate report.

The interim analysis will be focused on PK parameters only. Unblinded information will

be provided to the independent pharmacokinetics team doing the analysis and the remaining of the study team will remain blinded. The statistical team responsible for randomization will confirm if at least 10 subjects have been randomized to SCY-078 and voriconazole at the time of the planned interim analysis. If less than 10 subjects have been randomized to SCY-078 and voriconazole at that point, the interim analysis will be postponed until 24 subjects are randomized.

20.0 Ethics and Protection of Human Patients

20.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, the ethical principles established by the Declaration of Helsinki (as amended in Fortaleza, Brazil, October 2013), the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, the US Code of Federal Regulations (CFR) sections that address clinical research studies, applicable European Union regulations and/or other national and local ethical and legal requirements, as applicable.

20.2 Institutional Review Board/Ethics Committee Review

The PI must provide the IRB/EC with all appropriate materials, including a copy of the subject ICF. The study will not be initiated until the PI obtains written approval of the protocol and the subject ICF from the appropriate IRB/EC, and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the PI to the IRB/EC, medical monitor, and Sponsor in accordance with applicable government regulations and in agreement with policy established by the Sponsor.

20.3 Informed Consent

The ICH issued guidelines to provide protection for human subjects in clinical investigations. The ICH Tripartite Guideline for Good Clinical Practice establishes the general requirements for informed consent. Each subject will be provided with oral and written information in a language they can understand that describes the nature and duration of the study. Before undergoing screening, each subject must consent in writing to study participation. The patient (or the subject's legal representative) will sign and personally date the subject ICF. The person rendering consent will also sign and personally date the subject ICF as the person who obtained the consent of the subject. For subjects who were unable to provide consent due to incapacity and their legally authorized representative (LAR) provided consent on their behalf, and if during the course of the study, the subject regains the ability to make decisions he/she will be informed of the decisions made by the LAR during the time of their incapacity and any

effects that may have occurred as a result. The subject will then be asked to provide consent and decide whether to continue in the study. Alternatively, the site may choose not to include patients in the study, who are not able to provide consent on their own. The original signed subject ICF will be retained with the study center's records. Each subject will receive a copy of his/her signed subject ICF. In addition, the PI, or his or her designee, must document in the case history that informed consent was obtained before study participation.

20.4 Future Use of Samples

Mold isolates including *Aspergillus* spp. (see Section 15.14) collected in this study may be maintained in repositories for potential future use. Future research of isolates may include *in vitro* susceptibility testing of new or existing antifungals or analysis of mechanisms of resistance.

20.5 Subject Privacy and Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number to maintain subject privacy and confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be performed with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the medical monitor, IRB/EC, the Food and Drug Administration (FDA), the Sponsor or where required by law. All local privacy laws must be followed.

20.6 Study Termination

The PI, the Sponsor, the FDA, and the IRB/EC each reserve the right to terminate the study, due to unjustifiable risk, relevant toxicity, and/or unknown and new adverse event findings, in the interest of subjects' safety and welfare. The Sponsor reserves the right to terminate the study at any time for administrative or any reasons.

20.7 Financial Disclosure

The financial interests of all investigators from all participating clinical centers must be collected prior to study initiation and 1 year following the completion of the clinical trial.

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22.0 Appendices

22.1 Appendix A: Prohibited Medications and Medications to be Administered with Caution

Below are a few examples relevant for hematological patients. Details and flexible medical monitor guidance will be available, with consideration to local label, local standard practice and best interest of the patient.

22.1.1 Prohibited Medications

In addition to the prohibited medications listed below, the Voriconazole label should be consulted and followed for additional warnings and precautions related to concomitant medications.

Investigational Drugs

No other investigational drugs are allowed during the study from at least 28 days or 5.5 half-lives of the investigational product (whichever is longer) before signing the informed consent through the 6-Week Follow-up visit.

Antifungals

- No antifungal treatment other than the study drug is allowed during the study.
- Prior mold-active antifungal agents for the treatment of the IPA episode are not allowed for more than 4 days (96 hours) in the 7 days preceding enrollment (Baseline/Treatment Day 1), except for those subjects who have received more than 4 days but less than 7 days of prior mold-active antifungal therapy for the treatment of the IPA episode in the 7 days preceding enrollment into the study and are approved for randomization by the medical monitor.
- Prophylaxis with a mold-active azole antifungal (i.e., voriconazole, posaconazole, isavuconazole or itraconazole) is not allowed in the 14 days preceding enrollment into the study (Baseline/Treatment Day 1).

Other Prohibited Medications

In addition, the medications listed below are also prohibited.

Strong CYP3A4/5 inhibitors and CYP3A4/5 inducers

CYP	Strong Inhibitors[a]	Inducers[a]

3A4/5	• boceprevir • clarithromycin • conivaptan • indinavir • lopinavir • mibefradil	• nefazodone • nelfinavir • ritonavir • saquinavir • telaprevir • telithromycin	• avasimibe • carbamazepine • phenytoin • rifampin • St. John's wort

a: The CYP3A4/5 inhibitors and CYP3A4/5 inducers listed in this table are not permitted during the 14 days prior to Baseline/Treatment Day 1 and during study treatment.

P-glycoprotein (P-gp) substrates

P-gp Drug Substrates[a]
digoxin, colchicine, vinblastine and talinolol

a. The P-gp substrates listed in this table are not permitted during the 48 hours prior to Baseline/Treatment Day 1 and during study treatment.

22.1.2 Medications to be administered with Caution and Monitored as Appropriate

CYP3A4 substrates

CYP	Substrates
3A4	*In vitro*, SCY-078 was an inhibitor of CYP3A mediated metabolism of midazolam, but was only a weak inhibitor of metabolism of testosterone. The clinical significance of this inhibition is unknown; caution should be exercised when administering SCY-078 with drugs known to be CYP3A sensitive substrates with narrow therapeutic index, such as midazolam and cyclosporine. Subjects receiving sirolimus, tacrolimus or warfarin, cyclosporine or amiodarone are permitted for enrollment in the study and these medications may be administered concomitantly with SCY-078 with close monitoring. Dosing adjustments and subsequent monitoring of sirolimus and warfarin should be undertaken in accordance with product prescribing information for the respective agents.

OATP1B3 substrates

OATP	Substrate
1B3	*In vitro*, SCY-078 is an inhibitor of the OATP1B3 liver uptake transporter. The clinical significance of this inhibition is unknown; however, there is a potential risk for increased exposure of the concomitant medications (arising from lowered hepatic clearance) when administering SCY-078 with drugs known to be OATP1B3 selective substrates. Therefore, caution should be exercised when administering SCY-078 with drugs known to be OATP1B3 selective substrates such as telmisartan, including monitoring the subject for signs of overexposure associated with the concomitant medications as described in the product prescribing information.

Sources:

- FDA Draft Guidance for Industry. Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling. 2012.
- Drug interactions in infectious disease by Stephen C. Piscitelli, Keith Rodvold (2007)
- UCSF-FDA Transportal

22.2 Appendix B: Voriconazole Label

Voriconazole prescribing information in the Unites States of America:
https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=e985d908-22ca-4849-8ac3-c081301b65f0&type=display

Voriconazole prescribing information in Europe:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000387/WC500049756.pdf

22.3 Appendix C: Definitions of Invasive Fungal Disease (IFD)

Adapted from the Diagnostic Criteria published by the EORTC-MSG[15]

A DRC charter will provide detailed criteria to be used for the baseline and outcome analysis of subjects in this study. The analysis criteria will be based on EORTC-MSG Consensus Criteria as outlined below. Adaptations to the EORTC-MSG criteria adopted by the DRC will be documented in the DRC charter.

Proven Invasive Fungal Disease

Subjects with a positive diagnostic test of either:

- Histopathologic, cytopathologic, or wet mount examination of a needle aspiration or biopsy specimen showing hyphal forms with evidence of associated tissue damage (either microscopically or as an infiltrate or lesion by imaging);

  OR
- Recovery of a mould by culture from a sample obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage (BAL).

Probable Invasive Fungal Disease

At least one host factor (definitions see below) PLUS at least one clinical feature of acute lower respiratory tract disease (definitions see below) PLUS at least one mycological criterion (definitions see below).

Possible Invasive Fungal Disease

All subjects with at least one host factor who meet criteria for clinical features of lower respiratory tract disease (as defined below), but for which mycological criteria are absent.

Definitions of Diagnostic Criteria:

Host Factors

a. Recently resolved (<4 weeks) or ongoing neutropenia (neutropenia defined as absolute neutrophil count $<0.5 \times 10^9$/L [$<500/mm^3$] for ≥10 days), associated with the onset of the fungal disease; or
b. Receipt of an allogeneic haematopoietic stem cell transplant (HSCT) or BMT; or
c. Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for > 3 weeks;
d. Treatment with other recognized T-cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days;
e. Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency).

Clinical Features of Acute Lower Respiratory Tract Disease with:

At least one of the following imaging signs on CT:

a. Dense well-circumscribed lesion(s) (nodules) ± halo sign
b. Air crescent sign
c. Cavity
d. A "non-specific" focal infiltrate ("Tree-in-bud", "Wedge shapes")

(Review of the medical history does not suggest a different etiology for the syndrome; syndrome onset within 2 weeks prior to the first dose of study medication. The presence of other clinical findings (pleural rub, pleural pain, or haemoptysis) will be recorded but these features are not thought sufficiently predictive to be used alone.)

Note: Only subjects with lower respiratory tract disease are eligible for the study. Subjects with clinical features of non-lower respiratory tract disease, such as sino-nasal infection, tracheobronchitis as the only manifestation of invasive aspergillosis are not eligible.

Mycological Criteria (all available GMI results from serum or BAL within 7 days prior to enrollment should be included in the CRF):

- Serum galactomannan (GM) with at least one GMI value of ≥0.5 are adequate mycological evidence for considering an IPA as probable in this study.
    - Subjects receiving concomitant amoxicillin/clavulanate, piperacillin/tazobactam or Plasma-Lyte™ (Baxter) that could potentially induce false positive GM should be discussed with the Medical Monitor.

- BAL galactomannan (GM) with at least one GMI value of ≥1.

- Cytology, direct microscopy, culture or polymerase chain reaction (PCR) from bronchoalveolar lavage (BAL) fluid, bronchial brush, or other lung samples indicating presence of Aspergillus spp.

22.4 Appendix D: Karnofsky Performance Status Scale

Value	Level of functional capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work; no special care needed
90	Able to carry on normal activity, minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do active work	Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed
60	Requires occasional assistance but is able to care for most needs	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly
30	Severely disabled, hospitalization is indicated although death is not imminent	
20	Hospitalization is necessary, very sick, active supportive treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

22.5 Appendix E: Previous Protocol Revisions

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
Clinical Trial Protocol (Title) Section 2 (Protocol Approvals) Investigator Agreement Statement (Title)	• Removed "Combination Therapy" and replaced with "Coadministration" for clarity.
Section 1 (Contact Information) Section 2 (Protocol Approvals)	Updated Study Medical Monitor from [redacted] to [redacted]
Section 5 (Abbreviations)	Added Amphotericin B (AMB) and Standard of Care (SOC).
Synopsis (Title, Primary Objective, Secondary Objective, Exploratory Objective, Study Design, Study Treatment Groups)	Provided clarification to the study drug and voriconazole coadministration by removing "combination therapy" and "monotherapy" since the study treatment is coadministration of SCY-078 and voriconazole compared to the coadministration of SCY-078 placebo and voriconazole.
Section 8.1 (Background Information)	In the Drug-Drug Interaction Potential section: • Removed "combination" and replaced with "where SCY-078 is coadministered with voriconazole" to read: As a precautionary measure, the SCY-078 dose administered in this study where SCY-078 is co-administered with voriconazole, will be reduced by 30% until the results of the model are confirmed in an interim PK analysis that will include the first 20 randomized subjects." In the Conclusion section: • Replaced "Combination therapy" with "Coadministration" to read: Co-administration of SCY-078 with a mold-active azole such as voriconazole has the potential to improve clinical outcomes in patients with life-threatening IPA.

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
Section 8.2 (Rationale for the Study)	In the first paragraph: • Replaced "in combination" with "coadministered" to read: The two components of the combination therapy proposed in this protocol are voriconazole, an approved mold-active azole coadministered with SCY-078, an investigational GSI. • Added "taken with placebo" to read: In line with these guidelines, the only monotherapy arm in this study is with a mold-active azole (voriconazole) taken with placebo, and monotherapy with SCY-078 is not included in this design. In the Rationale for the objectives of the study section: • Replaced "given in combination" with "coadministered" to read: This study will evaluate the safety of SCY-078 when coadministered with voriconazole to the intended population. • Replaced "combination therapy" with "coadministation of SCY-078 with voriconazole" to read: This Phase 2 study also aims to investigate the effect of the coadministration of SCY-078 with voriconazole on multiple outcome endpoints including ACM and global response (typical endpoints for this indication) but also investigates other biological markers of therapeutic response such as serum galactomannan index. In the Rationale for proposed doses (Voriconazole) section: • Replaced "used in combination" with "coadministered" to read: The drug-drug interaction simulation PBPK-based model does not indicate any need for a modification to the approved dose of voriconazole when coadministered with SCY-078.

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
	In the Rationale for proposed doses (SCY-078) section (last paragraph): • Removed "combination" from sentence to read: As a precautionary measure, the SCY-078 dose administered in this study will be reduced by 30% until the results of the model are confirmed in an interim PK analysis that will include the first 20 randomized subjects. • Replaced "combination" with "SCY-078 and voriconazole" to read: Specifically, the first 10 subjects assigned to SCY-078 and voriconazole therapy will receive an oral SCY-078 loading dose of 500 mg BID on Days 1 and 2 followed by a maintenance dose of 500 mg QD from Day 3 onwards.
Synopsis (Study Design) Section 11.1 (Overall Description of the Study) Section 12.1 (Inclusion Criterion #6)	Addition of statement to clarify enrollment of patients who may have received mold active prophylaxis as follows: This study is intended for subjects with an IPA episode that, in the investigator´s judgement, requires antifungal therapy and is reasonable to expect that be adequately treated with voriconazole (i.e., the IPA is not due to a voriconazole-resistant isolate or a breakthrough infection while receiving a mold-active azole antifungal [voriconazole, posaconazole, isavuconazole or itraconazole] that requires therapy with a non-azole antifungal agent). Subjects with breakthrough IPA while receiving a mold-active azole antifungal may be considered for enrollment in circumstances in which the antifungal prophylaxis is considered not optimally administered (e.g. only few doses were given, frequent interruptions, subject not achieving adequate plasma exposures) and/or if the *Aspergillus* spp. isolate (when available) is known or expected to be susceptible to voriconazole.
Section 9.1 (Primary Objectives) Section 9.2 (Secondary Objectives)	Provided clarification to the study drug and voriconazole coadministration by removing "combination therapy" and "monotherapy" since the treatment is

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
Section 9.3 (Exploratory Objectives) Section 11.1 (Overall Description of the Study) Section 11.2 (Blinding, Randomization and Stratification) Section 16 (Study Schedule: footnote t)	coadministration of SCY-078 and voriconazole compared to the coadministration of SCY-078 placebo and voriconazole.
Synopsis (Study Design and Target Population) Section 11.1 (Overall Description of the Study) Section 11.1.1.1 [Screening Period (Days -4 to -1)]	Removal of "HM or a myelodysplastic syndrome or aplastic anemia or HCT" since the target subject population was broadened.
Synopsis (Key Inclusion Criteria) Section 12.1 (Inclusion Criteria)	Expanded Inclusion Criteria #4 and added last 3 bullets below to allow additional target subject population to enroll in the study. Added "OR" between each bulleted criterion below, since subjects should have one of the 4 criteria. • a diagnosis of a hematological malignancy or a myelodysplastic syndrome or aplastic anemia or has undergone hematopoietic cell transplantation, **OR** • Subject who either recently resolved or ongoing neutropenia (neutropenia defined as absolute neutrophil count < 0.5 x 10^9/L [< 500/mm3] for > 10 days), temporally related to the onset of fungal disease **OR** • Subject who received treatment with other recognized T-cell immunosuppressants (such as cyclosporine, tacrolimus, monoclonal antibodies or nucleoside analogs) during the past 90 days including solid organ transplant patients **OR** • Subject with inherited severe immunodeficiency (e.g. chronic granulomatous disease, severe combined immunodeficiency).

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
Section 12.1 (Inclusion Criteria – criterion 8c)	Added "highly effective" to hormonal contraceptive as the allowable form of contraception.
Synopsis (Key Exclusion Criteria) Section 12.2 (Exclusion Criteria)	For criterion 6: • Changed the AST or ALT value from >10 to ≥ 5 and total bilirubin value from > 5 to > 2.5 to exclude subjects with Grade 3 and beyond elevations in LFT tests. Criterion now states: Subject has abnormal liver test parameters: AST or ALT ≥ 5 x ULN and/or total bilirubin > 2.5 x ULN. • For subjects with Gilbert's disease, provided a limit of <7 mg/dL for unconjugated hyperbilirubinemia since a limit was not previously provided.
Section 12.2 (Exclusion Criteria)	• For criterion 9: added " and prolonged QTcF interval (Fridericia's correction: QTc= QT/$(RR)^{0.33}$) >450 ms for males". Criterion now reads: Subject has a prolonged QTcF interval (Fridericia's correction: QTc= QT/$(RR)^{0.33}$) >480 ms for females and prolonged QTcF interval (Fridericia's correction: QTc= QT/$(RR)^{0.33}$) >450 ms for males, on the baseline ECG or other abnormalities deemed clinically significant by the investigator that would put the subject at unacceptable risk for participation in the study. • For criterion 10: added "including history of conditions or medications that may increase the risk for QTc prolongation". Criterion now reads: Subject has any other condition including history of conditions or medications that may increase the risk for QTc prolongation, or laboratory abnormality that, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study or may interfere with the assessments included in the study.

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
Synopsis (Study Blinding, Randomization and Stratification) Section 17.13 (Procedures for Emergency Unblinding)	Added: In the event that the web-based IWRS system is not available, emergency unblinding can occur by contacting the [redacted] help-desk as follows: [redacted]
Synopsis (Safety Evaluations) Section 15.17 (Safety Laboratory Tests)	• Added 6-Week FU to the timepoints when safety laboratory tests should be performed. • Added clarification to include monitoring serum electrolytes, amylase, lipase. • Added the treatment Day to correspond to the weekly monitoring in the first month of treatment and also added Day 21. • Added sentence as follows: Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.
Section 11.1 (Overall Description of the Study)	Changed Section 22.3 to Section 12.1 since the link should be directed to the Inclusion Criteria.
Section 11.1.1.1 (Screening Period (Days -4 to -1)	For Subjects with Possible IPA - Removed the following sentence: This 4-day mold-active antifungal treatment limit prior to randomization is inclusive of any days of mold-active antifungal that the subject may have received prior to Screening.
Section 11.1.2 (Safety and Tolerability) Section 19.6.1 (Safety Assessments)	Added: Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.
Synopsis and Section 11.2 (Blinding, Randomization and Stratification)	Updated the stratification criterion as a result of broadened target population as follows: • Hematological malignancies and /or hematopoietic cell transplantation recipients • Solid organ transplant recipients • Other immunocompromising conditions

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
Section 11.3 (Study Duration)	• Added "End of Study" to section heading which now reads "Study Duration/End of Study" • Added definition for end of study.
Synopsis (Study Treatment Groups)	• Addition of administration of voriconazole with regard to meals. • Addition of SCY-078 frequency and administration with regard to meals.
Section 13.1.1 (Description of Study Groups)	• Addition of administration of voriconazole with regard to meals and addition of SCY-078 frequency and administration with regard to meals. • Removed row which displayed "Combination Therapy" and "Monotherapy" from Table 3.
Section 13.2 (Dietary Requirements)	• Addition of "oral" to SCY-078. • Removed dosing instruction since it should not belong in the dietary requirements section.
Synopsis and Section 13.3 (Study Drugs)	Removal of Sponsor to provide voriconazole AND addition of statement that Sponsor will provide voriconazole in extenuating circumstances.
Section 15.13 (Other Imaging)	Removed "subsequent imaging studies" and changed to "these other".
Section 15.14 (Mycological Testing Other than Serum GMI, Serum β-D Glucan and Plasma *Aspergillus* PCR)	• BAL and relevant tissue samples to include histopathology along with *Aspergillus* PCR which should be submitted to the central laboratory for additional diagnostic tests. • Clarified by adding mold isolates including Aspergillus to be sent to the central laboratory where isolates are specified
Section 15.16 (Serum β-D Glucan and Plasma *Aspergillus* PCR Test)	Added sentence to state that if blood samples are collected to perform serum β-D-glucan and plasma *Aspergillus* PCR are locally that the results from the local laboratory should be entered in the eCRF.
Section 15.17 (Safety Laboratory Tests)	• Added magnesium, calcium, amylase and lipase and removed "and indirect" for bilirubin in the blood chemistry table.

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
	• Removed 6-Week FU since it is no longer clinically indicated but required.
Section 15.20 (SCY-078 Pharmacokinetic Sample Collection)	Added "In addition to blood, other biological samples such as pleural effusion and tissue biopsies may also analyzed for SCY-078 PK determination, when available" to the of the paragraph.
Section 15.24 (Study Drug Dispensing)	Removed "Screening", "Treatment Day 5", "Treatment Day 14" for Study Drug Dispensing since study drug will now be dispensed at Baseline ((Treatment Day 1) and Every 14 days during treatment.
Section 15.25 (Study Drug Dosing)	• Removed "IV and oral voriconazole" from this section since voriconazole (oral and IV) is standard of care (SOC) therapy. • Added SCY-078 study drug administration, adjustment, frequency and dosing with regard to meals. • Addition of allowable dose administration adjustments for subjects who are intolerant of SCY-078 due to gastrointestinal (GI) related conditions.
Section 15.26 (Study Drug Collection and Treatment Compliance Evaluation)	Revised sentence to state: Study drug use will be recorded for treatment compliance evaluation daily from Baseline (Treatment Day 1) through EoT (see Section 13.5 for further details).
Section 15.27 (Study Diary Dispensing, Collection and Review)	Removed "every 14 days" and replaced with "at clinic visits" for when study diaries will be reviewed.
Synopsis (Safety Evaluations) Section 15.29 (Adverse Event Monitoring) Section 17.9 (Adverse Event Collection Timeframe	Added clarification for when AEs should be collected and evaluated in the first sentence which now reads: "AEs will be collected and evaluated from Baseline (Treatment Day 1), after the first dose of study drug SCY-078, and SOC voriconazole and through the end of the study."
Section 15.9 (Pregnancy Test)	Added "once a month, while on study treatment" regarding when pregnancy test should be performed.

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
Section 16 (Study Schedule)	• Added "+" to "1" for Days (allowable days) under Treatment Day 14. • Added "X" at the 6-Week follow-up visit to indicate Safety Laboratory Assessments to be done at that visit. • Added footnote "f" to indicate that pregnancy test should be done locally, once a month, while on study treatment. Added clarification to footnote "n" to include monitoring serum electrolytes, amylase, lipase. • Added the treatment Day to correspond to the weekly monitoring in the first month of treatment and also added Day 21. • Removed "X" at "Screening", "Treatment Day 5", "Treatment Day 14" for Study Drug Dispensing row since studyh will be now dispensed at Baseline ((Treatment Day 1) and Every 14 days during treatment.
Section 17.3 (Events of Clinical Interest)	Clarified by adding that ECIs must be recorded as such on the AE eCRF when the PI becomes aware of the ECI.
Section 19.0 (Analytical Plan)	Added "When feasible, based on adequate sample size sub-group analyses including by gender and by underlying condition will be conducted."
Section 19.1 (Sample Size Determination)	Added text providing rationale for why no formal sample size is provided for the study.
Section 20.3 (Informed Consent)	Added instructions for subjects who had legally authorized representative (LAR) provide consent on their behalf due to incapacity.
Section 20.4 (Future Use of Samples)	Clarified and added "mold isolates including" *Aspergillus* spp.
Section 20.6 (Study Termination)	Added additional reasons for why the study could be terminated.

Revisions to Protocol dated 12 Nov 2018 (Protocol Version 4.0) **Current Version and Date: Protocol Amendment 4 (Protocol Version 5.0) dated 01 August 2019**	
Protocol Sections	**Change and Rationale**
Section 22.1.1 (Prohibited Medications)	• Add clarification that the voriconazole label should be consulted for additional warning and precautions related to concomitant medications. • Removed "long-lasting barbituates" from the "Strong CYP3A4/5 inhibitors and CYP3A4/5 inducers table". • Addition of vinblastine and talinolol to the "P-gp Drug Substrates" table.
Miscellaneous (throughout protocol)	Corrected minor typographical and grammatical errors.

Revisions to Protocol dated 31 Oct 2018 (Protocol Version 3.0) **Current Version and Date: Protocol Amendment 3 (Protocol Version 4.0) dated 12 Nov 2018**	
Protocol Sections	**Change and Rationale**
Synopsis Section 8.1 (Background Information) Section 8.2 (Rationale for the Study) Section 11.1.2 (Study Assessments) Section 13.1.1 (Description of Study Groups), including Table 3 Section 15.19 (Voriconazole Level Determination) Section 15.20 (SCY-078 PK Sample Collection)	• Revised the number of subjects who will receive a reduced SCY-078 dosing regimen consisting of a loading dose of 500 mg BID on Days 1 and 2 followed by a maintenance dose of 500 mg QD from Day 3 onwards, from an overall of 10 subjects (5 from each treatment group) to an overall of 20 subjects (a minimum of 10 subjects randomized to the combination therapy group).

Revisions to Protocol dated 31 Oct 2018 (Protocol Version 3.0) **Current Version and Date: Protocol Amendment 3 (Protocol Version 4.0) dated 12 Nov 2018**	
Protocol Sections	**Change and Rationale**
Section 16.0 (Study Schedule, Footnotes "p" and "r") Section 19.8 (Pharmacokinetics)	
Revision History	• Corrected error in GMI value for mycological criteria in Section 22.3 (Appendix C: Definitions of Invasive Fungal Disease)
Miscellaneous	• Corrected minor typographical errors.

Revisions to Protocol dated 04 Oct 2018 (Protocol Version 2.0) **Current Version and Date: Protocol Amendment 2 (Protocol Version 3.0) dated 31 Oct 2018**	
Protocol Sections	**Change and Rationale**
Section 8.1 (Background Information) Section 8.2 (Rationale for the Study)	• Clarified that the efficacy SCY-078 target exposure for invasive candidiasis models is 11.2 µg•mL•hr and for invasive aspergillosis models is 15.6 µg•mL/hr.
Section 8.1 (Background Information)	• Removed isavuconazole from the drug-drug interaction discussion to avoid confusion regarding azole used in this study.

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Protocol Sections	**Change and Rationale**
Synopsis Section 12.1 (Inclusion Criteria) Section 15.15 (Galactomannan Index Assessment) Section 16 (Study Schedule), including Table 4	• Clarified that all subjects with IPA (possible, probable or proven) with a positive GMI test at Screening may be enrolled into the study.
Synopsis Section 8.1 (Background Information) Section 8.2 (Rationale for the Study) Section 13.1.1 (Description of Study Groups), including Table 3	• Added that, as a precautionary measure, the first 10 subjects (first 5 subjects in each treatment group) will receive a reduced SCY-078 dosing regimen consisting of a loading dose of 500 mg BID on Days 1 and 2 followed by a maintenance dose of 500 mg QD from Day 3 onwards, which represents a 30% reduction relative to the prior 750 mg dose. • Added that an interim PK analysis will be conducted once the above first 10 subjects have been treated for at least 7 days and that, based on the results from this interim analysis, the SCY-078 dose may be increased for subsequent subjects up to a loading dose of 750 mg BID on Days 1 and 2 followed by a maintenance dose of 750 mg QD from Day 3 onwards
Synopsis Section 13.1.1 (Description of Study Groups)	• Updated the number of SCY-078-matching placebo tablets to be taken before and potentially after the interim PK analysis.
Synopsis Section 11.1.1.1 (Screening Period) Section 11.1.1.2 (Baseline)	• Removed statement indicating that subjects with a possible IPA plus one positive GMI test result would be considered upgraded to probable IPA.
Synopsis Section 11.1.2 (Study Assessments) Section 15.19 (Voriconazole Level Determination)	• Added blood PK sampling time points for voriconazole and SCY-078 for the first 10 randomized subjects and updated sampling time points for subsequent subjects.

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Protocol Sections	**Change and Rationale**
Section 15.20 (SCY-078 Pharmacokinetic Sample Collection) Section 16 (Study Schedule), including Table 4 Section 19.8.1 (Pharmacokinetic Assessments)	
Synopsis Section 19.8.2 (Pharmacokinetic Analyses)	• Updated description of PK analyses to reflect current sampling time points.
Synopsis Section 13.1.1 (Description of Study Groups)	• Clarified that the voriconazole dose may be adjusted for individual subjects based on therapeutic drug monitoring results but that subjects will continue to receive the 500 mg dose of SCY-078 until results of the interim PK analyses are available.
Section 15.10 (Karnofsky Performance Status Scale) Section 16 (Study Schedule), including Table 4 and Table 5	• Added the assessment of Karnofsky scores to the list of study procedures
Section 15.17 (Safety Laboratory Tests) Section 16.0 (Study Schedule)	• Added that for subjects who are still receiving study drug by Day 42 (i.e., EoT has not occurred), an additional safety lab assessment should be conducted on Day 42 or Day 56.
Section 22.3 (Appendix C: Definitions of Invasive Fungal Disease)	• Revised GMI mycological criteria to include at least one GMI value ≥1 OR two consecutive samples with values of ≥0.5.
Miscellaneous	• Corrected minor typographical errors.

Revisions to Protocol dated 20 Aug 2018 (Protocol Version 1.0) **Current Version and Date: Protocol Amendment 1 (Protocol Version 2.0) dated 04 Oct 2018**	
Protocol Sections	**Change and Rationale**
Synopsis	• Clarified that recurrence will be determined by the Data Review Committee (DRC). • Added a new time point (EoT) for the assessment of the percentage of subjects with clinical, mycological and radiological response as determined by the DRC and by the Principal Investigator. • Added the flexibility for each study site pharmacy to supply their own voriconazole (intravenous and oral). • Added the description of study treatment groups. • Added the performance of a visual function assessment as part of the general physical examination at Screening/Baseline and on Treatment Day 28 (if treatment continues beyond Treatment Day 28). • Added the need for liver function tests and bilirubin monitoring as per voriconazole label recommendations. • Added time points for the collection of blood samples at 4-8 hours after dosing for the determination of voriconazole and SCY-078 levels.
Section 9.3 (Exploratory Objectives)	Revised wording to clarify that recurrence will be determined by the DRC.
Section 10.2 (Exploratory Endpoints) Section 11.1.2 (Study Assessments; Efficacy Assessments) 15.20 (Assessment of Treatment Outcome) Section 16.0 (Study Schedule)	Added a new time point (EoT) for the assessment of the percentage of subjects with clinical, mycological and radiological response as determined by the DRC and by the Principal Investigator.
Section 11.1.2 (Study Assessments)	Added the performance of a visual function assessment as part of the general physical examination at

Revisions to Protocol dated 20 Aug 2018 (Protocol Version 1.0) **Current Version and Date: Protocol Amendment 1 (Protocol Version 2.0) dated 04 Oct 2018**	
Protocol Sections	**Change and Rationale**
Section 15.6 (General Physical Examination, Including Visual Function Assessment) Section 16.0 (Study Schedule) Section 19.6.1 (Safety Assessments)	Screening/Baseline and on Treatment Day 28 (if treatment continues beyond Treatment Day 28)
Section 11.1.2 (Study Assessments) Section 15.18 (Voriconazole Level Determination) Section 15.19 (PK Collection) Section 16.0 (Study Schedule) Section 19.8.1 (Pharmacokinetic Assessments)	Added time points for the collection of blood samples at 4-8 hours after dosing for the determination of voriconazole and SCY-078 levels.
Section 13.3 (Study Drugs)	Added the flexibility for each study site pharmacy to supply their own voriconazole (intravenous and oral).
Section 15.16 (Safety Laboratory Tests) Section 16.0 (Study Schedule)	Added the need for liver function tests and bilirubin monitoring as per voriconazole label recommendations.
Section 15.21 (Recurrence) and Section 19.7.1.4 (Recurrence)	Revised the definition of recurrence and clarified that the DRC will be making the final determination of recurrence.
Section 15.24 (Study Drug Dispensing)	Revised the timepoints when study drug will be dispensed by removeing at “Screening”, and “Day 5 and 14” and provided clarification by adding “approximately every” to 14 days thereafter until EoT.
Section 15.28 (Adverse Event Monitoring)	Added wording to reflect information from voriconazole label and to stress the need for the Principal Investigators to be aware of visual disturbances and potential adverse events of voriconazole.
Miscellaneous	Corrected minor typographical errors and provided additional clarifications. Introduced minor changes to Section 15.14 (Galactomannan Index Assessment), Section 15.3 (Subject Enrollment and Assignment of Subject Number), Section 15.10 (Targeted Physical

Revisions to Protocol dated 20 Aug 2018 (Protocol Version 1.0) **Current Version and Date: Protocol Amendment 1 (Protocol Version 2.0) dated 04 Oct 2018**	
Protocol Sections	**Change and Rationale**
	Examination, Including Clinical Evaluation of Signs and Symptoms of Infection), Section 15.26 (Subject Diary Dispensing, Collection and Review), and Appendix C (Definitions of Invasive Fungal Disease [IFD]).