Statistical Analysis Plan

SCY-078-206

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

US IND Number 107,521

NCT03672292

Investigational Product:	Ibrexafungerp (formerly SCY-078)
Reference Product:	
Phase:	2
Document Type:	Statistical Analysis Plan
Version:	Final v1.1
Date of Issue:	23 Oct 2023

Statistical Analysis Plan Approval Form

Author: _____ _____

[redacted]

Reviewer: _____ _____

[redacted]

Approver: _____ _____

[redacted]

Version History	
Version&Date	Changes
SAP V1.0, 15 Sep 2023	
SAP V1.1, 23 Oct 2023	1. adding additional exploratory endpoints • Relationship between GMI decrease and Global response at Day 42 and EOT • Relationship between GMI decrease and Clinical response at Day 42 and EOT • Relationship between GMI decrease and Radiological response at Day 42 and EOT • Number of subjects with complete response and alive at Days 42 and 84 2. appending the "Definitions for Treatment Outcomes" – detailed in Protocol Section 19.7.1.1 to the SAP.

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
ACM	All-Cause Mortality
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-Time Curve
$AUC_{0\text{-}inf}$	Area under the concentration-time curve extrapolated to infinity
$AUC_{0\text{-}last}$	Area under the curve from the time of dosing to the last measurable concentration
BMI	Body Mass index
CI	Confidence Interval
CL/F	Apparent clearance
C_{max}	Maximum Concentration
CT	Computed Tomography
DRC	Data Review Committee
ECG	Electrocardiogram
EoT	End of Treatment
FU	Follow-Up
GMI	Galactomannan Index
λ_z	Terminal elimination phase rate constant
HCT	Hematopoietic Cell Transplantation
HM	Hematological Malignancy
ICU	Intensive Care Unit
IPA	Invasive Pulmonary Aspergillosis
ITT	Intent-to-Treat
IV	Intravenous
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MITT	Modified Intent-to-Treat
NG	Nasogastric
PEG	Percutaneous Endoscopic Gastrostomy

Abbreviation	Description
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
T_{max}	The first time to maximum observed concentration sampled during a dosing interval
TFL	Table, Figure and Listing
WHODD	World Health Organization Drug Dictionary

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all SDTM datasets,ADaM datasets, tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety, efficacy and pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study.

3. Study Objectives

3.1. Primary Objective

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

3.2. Secondary Objectives

- To evaluate the efficacy of the coadministration of ibrexafungerp and voriconazole compared with that of ibrexafungerp 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 ibrexafungerp and voriconazole.

3.3. Exploratory Objectives

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

- To evaluate the efficacy of the coadministration of ibrexafungerp and voriconzaole compared with coadministration of ibrexafungerp 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 ibrexafungerp and voriconazole compared with coadministration of ibrexafungerp placebo and voriconazole based on overall hospital stay and intensive care unit stay.
- To assess the effect of the coadministration of ibrexafungerp and voriconazole compared with coadministration of ibrexafungerp placebo and voriconazole on on-schedule administration of planned therapies for the underlying condition.

3.4. Brief Description

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

The study will be conducted at approximately 30 sites globally (revised to 8 number of sites with subjects randomized). Approximately 90 subjects will be screened to randomize a total of approximately 60 subjects (revised

to approximately 22 subjects randomized , 11 subjects per group) into one of the two treatment groups of the study (ibrexafungerp plus voriconazole or ibrexafungerp 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.

3.5. Subject Selection

The target population is Male or female subjects 18 years of age and older with a probable or proven IPA.

3.5.1. 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.
   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:
   a. a diagnosis of a hematological malignancy or a myelodysplastic syndrome or aplastic anemia or has undergone 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).
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.

3.5.2. 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 (< 7 mg/dL) with a diagnosis of Gilbert's disease* ***are not excluded.***

3.6. Determination of Sample Size

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

3.7. Treatment Assignment & Blinding

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 20 eligible subjects (10 subjects per treatment arm) will be randomized in a 1:1 ratio to one of the two study treatment arms: voriconazole and ibrexafungerp or voriconazole and ibrexafungerp placebo. For the purpose of maintaining treatment blinding, all randomized subjects will receive ibrexafungerp or ibrexafungerp 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

The study team will be unblinded at the end of the study, following database lock.

3.8. Study Procedures and Flowchart

Detailed schedules of all study visits and procedures are presented in the Schedules of Visits and Procedures (Table 1 and Table 2).

Table 1 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	X	X	X	X	X		X	X	X	X	

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											
including Clinical Evaluation of Signs and Symptoms of Infection											
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 serum GMI, serum β -D Glucan, and plasma *Aspergillus* PCR)	X[k]	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.	If applic.
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.

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											
ibrexafungerp 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

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											

treatment; GM = galactomannan; PK = pharmacokinetic(s), QD = once daily; TD = Treatment Day; TDM = therapeutic drug monitoring; VFA = visual function assessment.

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

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											

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 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 ibrexafungerp PK 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 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 ibrexafungerp + voriconazole or ibrexafungerp placebo + voriconazole.

u. For non-hospitalized patients only.

Table 2 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

4. Endpoints

4.1. Primary Endpoint

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

4.2. 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
- Ibrexafungerp and voriconazole plasma concentrations population PK analysis.

4.3. 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
- Relationship between GMI decrease and Global response at Day 42 and EOT
- Relationship between GMI decrease and Clinical response at Day 42 and EOT
- Relationship between GMI decrease and Radiological response at Day 42 and EOT
- Number of subjects with complete response and alive 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.

5. Analysis Populations

5.1. Screened Population

The Screened Population will include all subjects screened. Unless specified otherwise, this set will be used for subject listings and for summaries of subject disposition. The summary of subject disposition will be according to randomized treatment.

5.2. Intent-to-Treat (ITT) Population

The ITT Population will include all randomized subject who receive at least one dose of randomized study medication. This population will be the primary population for the analysis of efficacy data. Analysis will be according to randomized treatment.

5.3. Safety Population

The Safety Population will include all randomized subject who receive at least one dose of randomized study medication. This population will be the primary population for the analysis of safety data. Analysis will be according to actual treatment received.

5.4. 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. Analysis will be according to randomized treatment.

5.5. 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. Analysis will be according to randomized treatment.

5.6. Pharmacokinetic Population

The PK Population will include all enrolled subjects who provide at least one PK sample. The PK Population is the primary population for the analysis of PK data. Analysis will be according to actual treatment received.

6. General Aspects for Statistical Analysis

6.1. General Methods

- Unless otherwise specified, summaries will be presented for each treatment group.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.
- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.
- All data will be summarized at the nominal time point at which they were collected. Repeat and unscheduled assessments will not be used in the data summaries, however these will be listed.

6.2. Key Definitions

Study Day 1 is defined as the day of the first dose of study medication. Study Day -1 is defined as the day before the day of the first dose of study medication.

For days on or after the day of the first dose of study medication, Study Day will be calculated as:

Study Day = Assessment Date – Date of First Dose of Study Drug + 1.

For days before the day of the first dose of study medication, Study Day will be calculated as:

Study Day = Assessment Date – Date of First Dose of Study Drug.

Baseline is defined as the last non-missing assessment prior to the first dose of study drug.

Change from baseline is defined as:

Post-Baseline Value – Baseline Value.

6.3. Missing Data

Data from subjects who withdraw will be included, where possible, in all summaries and analyses.

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.

6.4. Visit Windows

All data will be summarized at the nominal time point at which they were collected. Visit windows will not be used.

6.5. Pooling of Centres

Data from all centers will be pooled and summarized together. Center is not included as a factor in any of the analysis models.

7. Subject Disposition, Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized for each treatment group and all subjects combined.

7.1. Subject Disposition

Subject disposition will be summarized for all sites combined and for each site individually.

The summary table will be for the Screened Population, however percentages will be calculated out of the number of subjects randomized.

The number of subjects screened and randomized will be presented.

The number and percentage of subjects treated will be summarized.

The number and percentage of subjects completing treatment, discontinuing treatment and reason for discontinuation will be summarized.

The number and percentage of subjects completing the study, discontinuing the study and reason for discontinuation will be summarized.

Inclusion/exclusion criteria subjects meet or don't meet will be listed only.

A summary of the number and percentage of subjects in each of the analysis populations will be presented. Percentages will be calculated out of the number of subjects in the ITT Population. In addition, listings will be provided showing subjects excluded from the ITT, Modified ITT and Per Protocol Populations, including the respective reason for exclusion.

7.2. Demography

Demography will be summarized for the safety Population.

Age, sex, race, ethnicity, country, randomization strata, height at screening, weight at screening and body mass index (BMI) at screening will all be summarized.

7.3. Protocol Deviations

Protocol deviations are captured in the eCRF and classified as major or minor. In addition, each deviation is assigned to one of the following categories:

- Procedures/Assessments
- Missed Visit
- Visit Outside Protocol Window
- Inclusion/Exclusion
- Randomization
- Informed Consent
- Study Drug Administration

- Study Restrictions
- Prohibited/Restricted Medication
- Other.

Protocol deviations will be listed and summarized by category, major/minor status and treatment group.

7.4. Invasive Pulmonary Aspergillosis Diagnosis

IPA diagnosis will be summarized for the Safety Population.

7.5. Underlying Hematological Condition

Underlying hematological condition will be summarized for the Safety Population.

Time since diagnosis of underlying hematological condition will be calculated in weeks as:

Time Since Diagnosis = (Date of Informed Consent – Date of Diagnosis)/7.

Should only a partial date be available for date of diagnosis, if the day is missing then 01 will be imputed, if the day and month are missing then 01 January will be imputed. Should the full date be missing the time since diagnosis will not be calculated.

7.6. Medical and Major Surgical History

Medical and major surgical history will be summarized for the Safety Population.

The number and percentage of subjects with any medical and major surgical history will be summarized.

Medical and major surgical history will be coded using MedDRA 26.0, and will be further summarized by System Organ Class (SOC) and Preferred Term (PT). The summary by SOC and PT will be ordered alphabetically.

Summaries will be for all medical and major surgical history, past history (at the time of screening) and ongoing history.

7.7. Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHODD) Global B3 202303.

Prior medications are those medications taken before the first dose of study drug. Note, this includes medications ongoing at the time of the first dose of study drug.

Concomitant medications are those medications taken after the first dose of study drug. Note, a prior medication ongoing at the time of the first dose of study drug is also concomitant.

Prior medications will be summarized for each treatment group and overall, by Anatomic Therapeutic Chemical (ATC) classification level 3 and preferred term.

Concomitant medications will be summarized by treatment group and overall, by ATC level 3 and preferred term.

Summary tables will be ordered by decreasing frequency for the overall column based on Safety Population.

A listing of prior and concomitant medications will be provided, where the prior/concomitant status is indicated.

8. Efficacy

Efficacy definitions are provided in Appendix 14.1

8.1. Key Efficacy Endpoint and Analysis

The key efficacy endpoint is the assessment of Global Response as determined by the DRC.

The DRC will assess the Global Response at Day 42, Day 84 and EoT.

Analysis of Global Response by the DRC will be for the ITT Population.

Global Response will be summarized at each visit.

In addition, the percentage of subjects with a Global Response, defined as either a complete or partial response at EoT, Day 42 and Day 84 will also be summarized. Subjects with missing data at EoT, Day 42 and Day 84 will be considered as indeterminate response at the corresponding visit. 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 wmethod of Clopper-Pearson.

8.2. Other Efficacy Endpoints and Analyses

8.2.1. Global Response by Principal Investigator

Global Response as determined by Principal Investigator will be analyzed for the ITT Population as for the Global Response by the DRC, see Section 8.1.

8.2.2. Overall Survival

Overall survival is defined as the time from randomization to time of death up to Day 84.

Subjects with death will be censored at Day 84, date of withdrawal or date of last follow up whichever comes earliest.

Overall survival will be expressed in days and calculated using the formula:

Overall Survival = Date of Death/Censoring – Date of Randomization.

The number and percentage of subjects with events and censored will be summarized.

The Kaplan-Meier method will be used to estimate the distribution of overall survival for each treatment group. The 25th percentile, median and 75th percentile overall survival and their 95% CIs will be presented. In addition, the overall survival (%) at Day 42 and Day 84 and their 95% CIs will also be presented.

8.2.3. All-Cause Mortality

All-cause mortality is defined as all deaths following the first dose of study drug, regardless of attribution. The total number of deaths by Day 42 and Day 84 and relationship to the fungal infection will be summarized. The difference in mortality rates between treatments will be presented along with a 95% CI calculated using the method of Clopper-Pearson.

8.2.4. GMI Reduction

GMI is assessed at screening, Day 1, Day 3, Day 5, Day 7, Day 10, Day 14, then every 14 days during treatment, at EoT and at Follow-up.

GMI reduction at a visit will be calculated as the baseline result minus the result at the visit.

GM reduction will be summarized, by treatment, for the Intent-to-Treat Population at Week 1 (Day 7), Week 2 (Day 14), Week 4 (Day 28) and Week 6 (Day 42).

In addition, percentage reduction will also be summarized.

Note, assessment of GMI endpoints will be based on the central laboratory results. Local results will be listed only.

8.2.5. Percentage of Subjects with Target Changes in GMI from Baseline

The percentage of subjects with the following target reductions in serum GMI from baseline will be presented at Weeks 1, 2, 4 and 6:

- Fifty percent reduction or greater
- Twenty-five percent reduction or greater
- Any percent reduction
- Reduction equal to or greater than 0.25
- Reduction to < 0.5

The difference in rates between treatments will be presented along with a 95% CI calculated using the method of Clopper-Pearson.

8.2.6. Time to Achieve Target Changes in GMI from Baseline

The following targets will be considered:

- 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

Time to achieve a target change in serum GMI from baseline will be expressed in days and calculated using the formula:

Time to Achieve = Date of Achievement/Censoring – Date of Randomization.

Subjects not achieving the target by Day 84 will be censored at Day 84 Or date of death, or date of withdraw, or date of last GMI assessment whichever comes earliest.

The number and percentage of subjects with events and censored will be summarized.

The Kaplan-Meier method will be used to estimate the distribution of time to achieve target for each treatment group. The 25th percentile, median and 75th percentile and their 95% CIs will be presented.

8.2.7. Clinical Response, Mycological Response and Radiological Response at EoT, Day 42 and Day 84 as determined by the DRC

Clinical Response, Mycological Response and Radiological Response at EoT, Day 42 and Day 84 as determined by the DRC will be analyzed for the ITT Population as for the Global Response by the DRC, see Section 8.1.

8.2.8. Clinical Response, Mycological Response and Radiological Response at EoT, Day 42 and Day 84 as determined by Principal Investigator

Clinical Response, Mycological Response and Radiological Response at EoT, Day 42 and Day 84 as determined by Principal Investigator will be analyzed for the ITT Population as for the Global Response by the DRC, see Section 8.1.

8.2.9. Absolute and Percentage Changes in Serum β-D-Glucan from Baseline

Serum β-D-glucan is assessed at screening, Day 1, Day 3, Day 5, Day 7, Day 10, Day 14, then every 14 days during treatment, at EoT and at Follow-up.

Absolute change from baseline in serum β-D-glucan will be summarized, by treatment, for the ITT Population at Week 1 (Day 7), Week 2 (Day 14), Week 4 (Day 28) and Week 6 (Day 42).

In addition, percentage change from baseline will also be summarized.

8.2.10. Percentage of Subjects with Target Changes in Serum β-D-Glucan from Baseline

The percentage of subjects with the following target changes in serum β-D-glucan from baseline will be presented at Weeks 1, 2, 4 and 6 for the ITT Population:

- Fifty percent reduction or greater
- Twenty-five percent reduction or greater
- Any percent reduction
- Negative serum β-D-glucan

The difference in rates between treatments will be presented along with a 95% CI calculated using the method of Clopper-Pearson.

8.2.11. Percentage of Subjects that Convert from Positive Plasma *Aspergillus* PCR at Baseline to Negative

The percentage of subjects that convert from positive plasma *Aspergillus* PCR at baseline to negative will be presented at Weeks 1, 2, 4 and 6 for the ITT Population.

The difference in rates between treatments will be presented along with a 95% CI calculated using the method of Clopper-Pearson.

8.2.12. Absolute Change in Karnofsky Score from Baseline to Days 42 and 84

Karnofsky Performance Status is assessed at screening, Day 1, Day 14, Day 28, Day 42, Day 56, Day 70 and Day 84.

Karnofsky Performance Status will be summarized as a categorical variable at each visit.

In addition, taking Karnofsky Performance Status as a continuous variable, absolute change from baseline in Karnofsky score will be summarized, by treatment, for the ITT Population at Day 42 and Day 84.

8.2.13. Time to Achieve a 10-Point Improvement in Karnofsky Score from Baseline

Time to achieve a 10-point improvement in Karnofsky score from baseline will be expressed in days and calculated using the formula:

Time to Achieve = Date of Achievement/Censoring – Date of Randomization.

Subjects not achieving the 10-point improvement by Day 84 will be censored at their last Karnofsky assessment date, date of withdraw, date of deat or at Day 84 whichever comes first.

The number and percentage of subjects with events and censored will be summarized.

The Kaplan-Meier method will be used to estimate the distribution of time to achieve target for each treatment group. The 25^{th} percentile, median and 75^{th} percentile and their 95% CIs will be presented.

8.2.14. Percentage of Subjects with a Recurrence of the Baseline Fungal Infection within 42 Days (Week 6) after EoT

Assessment of recurrence of the baseline fungal infection will take place at the follow-up visit, 6 weeks after EoT.

The percentage of subjects with a recurrence will be summarized, by treatment, for the ITT Population. The denominator for the percentage will be the number of subjects without the baseline fungal infection at EoT.

8.2.15. Relationship Between Serum GMI Decrease and ACM at Days 42 and 84 for subset of patients with positive serum galactomannan at baseline

At Day 42, subjects will be categorized as dead or alive. For each of these two groups of subjects, a boxplot will be presented showing their last available GMI decrease, up to and including Day 42. Should a subject have no post baseline GMI data then they will not be included in the plot. The plot will be based on the ITT Population.

The above plot will be repeated for Day 84.

8.2.16. Relationship between serum GMI decrease and global response at D42 and EOT for subset of patients with positive serum GM at baseline

8.2.17. Relationship between serum GMI decrease and clinical response at D42 and EOT for subset of patients with positive serum GM at baseline

8.2.18. Relationship between serum GMI decrease and radiological response at D42 and EOT for subset of patients with positive serum GM at baseline

8.2.19. Number of subjects with complete response and alive at Day 42 and at Day 84

8.2.20. Days of Hospital Stay and Days of ICU Stay

For each subject the number of days of hospital stay and the number of days of ICU stay will be calculated.

These both will be summarized, by treatment, for the ITT Population.

8.2.21. Percentage of Subjects Who are Able to Receive On-Schedule Administration of the Planned Therapies for their Underlying Condition

The number and percentage of subjects who received on-schedule administration of the planned therapies for their underlying condition will be summarized.

In addition, the number of subjects with a delay to their planned therapy, and the duration of the delay will also be summarized.

Summaries will be for the ITT Population.

8.2.22. Signs and Symptoms of Invasive Aspergillosis

Targeted physical examinations/clinical evaluations of signs and symptoms of IPA will be listed.

8.2.23. Chest CT Scan

Results from the chest CT scans will be listed.

9. Analysis Of Pharmacokinetics

As planned in the protocol population PK analysis will be done and reported in a separate report. This SAP does not include the specifics of PopPK which will be outlined in a separate SAP. The population PK analysis will include the PK data in this study SCY078-206.

9.1. PK Sampling Schedule

PK testing for the determination of ibrexafungerp will be conducted for all subjects. Blood samples for ibrexafungerp 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.

9.2. PK Concentration

The summary statistics of plasma concentrations will be presented per treatment (ibrexafungerp, voriconazole), PK Day (Pre-first dose, Day 1, Day 7 and Day 14) and by time interval (pre-dose, 2-4 and 6-8 hours post dose), and BLQ concentration values should be set to 0. All concentration values presented as BLQ and the number of BLQs (ie, n below the lower limit of quantitationLLOQ) for each time interval will be listed as reported.

10. Safety

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of AEs, clinical laboratory data, vital signs, ECG parameters and physical examinations

10.1. Extent of Exposure

Extent of exposure will be considered separately for study drug (ibrexafungerp or ibrexafungerp placebo) and Voriconazole.

For study drug, duration of treatment (weeks) will be calculated as:

Duration of treatment (weeks) = (Date of last dose – Date of first dose + 1)/7.

In addition, the number of days of treatment will also be calculated, taking into account any dose interruptions.

For the ibrexafungerp arm, the total dose in mg will be calculated from the sum of the number of tablets taken from the study drug dispensing log.

In addition, average daily dose will be calculated as the total dose in mg, divided by the duration of treatment in days.

Duration of treatment, number of days of treatment, total dose and average daily dose will be summarized for the Safety Population.

For Vorinconazole, duration of treatment (weeks) will be calculated as:

Duration of treatment (weeks) = (Date of last dose – Date of first dose + 1)/7.

In addition, the number of days of treatment will also be calculated, taking into account any dose interruptions.

Duration of treatment and number of days of treatment will be summarized for the Safety Population.

10.2. Treatment Compliance

For study drug, compliance (%) will be calculated as:

Compliance (%) = 100*(Number of tablets taken/Expected number of tablets taken),

where the number of tablets taken will be calculated from the sum of the number of tablets taken from the study drug dispensing log, and the expected number of tablets taken will be based on the first and last dose dates, accounting for the loading doses.

Compliance will be summarized for the Safety Population. In addition, compliance will be summarized according to the categories:

- <80%
- 80% to <120%
- ≥120%.

10.3. Adverse Events

Adverse events will be coded into SOCs and PTs using the MedDRA 26.0 .

If the relationship to a study drug is missing then in the summary tables the AE will be classified as related. Similarly, missing severity will be classified as severe in the summary tables.

Treatment-related AEs will be those with relationship to either ibrexafungerp or voriconazole of related.

Summary tables of AEs will be based on treatment emergent adverse events (TEAEs).

A TEAE is defined as any event not present prior to the initiation of the study treatment, or any event already present which worsens either in intensity or frequency following the exposure to the study treatment.

AEs with incomplete start dates will be considered as TEAE if:

- Day and month are missing and the year is equal to or after the year of the first dose date
- Day is missing and the year is after the year of the first dose
- Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date
- Year is missing
- Complete start date is missing.

For summaries by SOC and PT, a subject will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT and maximum severity, a subject will be counted once at the highest severity for which an event occurred at the SOC level and the highest severity for each unique PT within that SOC level. Therefore, subjects may only contribute once to each PT and once to each SOC level.

An overall summary of TEAEs will be provided showing the number and percentage of subjects reporting TEAEs, treatment-related TEAEs, TEAEs with severe severity, TEAEs leading to withdrawal of study treatment, serious TEAEs and treatment-related serious TEAEs, TEAEs leading to Death.

The following TEAE tables will also be provided:

- A summary of TEAEs overall and by SOC and PT
- A summary of treatment-related TEAEs overall and by SOC and PT
- A summary of TEAEs by maximum severity, overall and by SOC and PT
- A summary of TEAEs leading to withdrawal of study treatment, overall and by SOC and PT
- A summary of serious TEAEs, overall and by SOC and PT
- A summary of treatment-related serious TEAEs, overall and by SOC and PT
- A summary of TEAEs leading to Death, overall and by SOC and PT

The above summaries will show the number and percentage of subjects reporting events in the respective categories. All summaries will be by treatment group. Only the TEAEs will be included in the summary tables, however all AEs will be included in the listings.

Listings will be provided for all AEs, AEs leading to study treatment withdrawal and SAEs. TEAEs will be flagged in the listings.

10.4. Laboratory Evaluations

Blood samples are taken at Screening, Day 1, Day 7, Day 10, Day 14, then every 14 days as required, up to EoT and Follow-Up for the central evaluation of hematology, chemistry and urinalysis laboratory tests.

Summaries of laboratory data will be based on the Safety Population.

Continuous laboratory results for hematology, chemistry and urinalysis will be summarized, by treatment, at baseline, Day 7, Day 10, Day 14, and all further scheduled visits, up until EoT and Follow-Up. In addition, for post baseline visits, a summary will also be given for the change from baseline.

10.5. Vital Signs

Vital signs include SBP, DBP, pulse rate, respiratory rate and body temperature, and are collected at Screening, Day 1 and EoT.

Temperatures captured in °F will be converted to °C using the formula:

Temperature (in °C) = 5/9 (Temperature [in °F]-32).>

Vital signs will be summarized, by treatment, for the Safety Population at baseline and EoT. In addition, at EoT a summary will be given for the change from baseline.

10.6. 12-Lead ECG

A 12-lead ECG is collected at Screening, Day 1, Day 10 and EoT.

Summaries of ECG data will be based on the Safety Population.

Overall interpretation will be summarized, by treatment, at baseline, Day 10 and EoT.

ECG parameters, including heart rate, PR interval, RR interval, QRS interval and QTcF interval will be summarized, by treatment, at baseline, Day 10 and EoT. In addition, at Day 10 and EoT a summary will be given for the change from baseline.

10.7. Physical Examination

A general physical examination is done at Screening, Day 1, Day 14, Day 28, Day 42, Day 56, Day 70, Day 84, EoT and at Follow-Up.

Physical examination results will be summarized, by treatment, for the Safety Population.

11. Interim Analyses

The protocol planned for the performance of an interim analysis. However, there is no interim analysis since the study was stopped after enrolment of 22 subjects, due to patient recruitment challenges..

12. Changes from Analysis Planned in Protocol

There are currently no deviations from the analyses planned in the protocol. Enrollment into the study was stopped after 22 subjects were randomized because of the subject recruitment challenges and feasibility to enrol the planned sample size of 60 subjects.

13. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA. Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. General Considerations

- One SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance.

13.2. Table, Listing, and Figure Format

13.2.1. General

- All TFLs will be produced in landscape format on *American letter size / A4 paper size*, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides. Note: No headers or footers from Stats programming to be present in this area . This blank area is required to add additional Publishing text and lines during Final CSR Publishing.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:
- Scynexis, Inc. Protocol SCY-078-206

- Draft/Final Run
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

Each FL are identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

13.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned; and

- Mixtures of whole numbers and numbers containing fractional portions are center aligned.

13.2.5.2. *Table Conventions*

- Units will be included where available

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.

- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Min	XXX
Max	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999.

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Values that round down to <1% will be displayed as '<1'. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the ibrexafungerp + Voriconazole treatment group in decreasing order, assuming all terms are coded. Within

the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available.

13.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.

- Subject specific footnotes are avoided, where possible.

- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

14. Appendices

14.1. Treatment Outcome

(SCY-078-206 Protocol Amendment 5, 13 October 2020 Section 19.7.1.1)

Global Response will be assessed *at Day 42, Day 84 (if applicable) and at EOT,* 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, *****including serum GMI (for patients with positive GMI at baseline), 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.
  (* applicable for DRC assessments)

- 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 *at Day 42, Day 84 (if applicable) and at EOT,* 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

Recurrence*, at 6-week FU visit*

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.

14.2. PopPK analysis plan