NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

Study information

Title	Patterns of Real-World Isavuconazole use, Effectiveness, Safety, and Healthcare Resource Utilization—a Retrospective Chart Review Study of Patients With Mucormycosis or Invasive Aspergillosis (PRISMA)
Protocol number	C3791008
Protocol version identifier	Final version 1.1
Date	27 July 2020
Active substance	Isavuconazole (ATC code J02AC05)
Medicinal product	Cresemba®
Research questions and objectives	Primary objectives: • To document real-world clinical outcomes (all-cause mortality, overall response) of isavuconazole in patients with invasive aspergillosis or mucormycosis who are receiving treatment in routine clinical practice in Europe (France, Germany, Italy, Spain, and the United Kingdom). • To assess real-world safety (isavuconazole-related adverse events or serious adverse events) of isavuconazole in patients with invasive aspergillosis or mucormycosis receiving treatment in routine clinical practice in Europe. Secondary objectives:

	• To describe demographic and clinical characteristics of patients with invasive aspergillosis or mucormycosis receiving isavuconazole in routine clinical practice in Europe. • To document treatment patterns among patients with invasive aspergillosis or mucormycosis receiving isavuconazole in routine clinical practice in Europe. • To quantify HCRU among patients with invasive aspergillosis or mucormycosis receiving isavuconazole in routine clinical practice in Europe.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	Adverse Event Monitoring
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BAL	bronchoalveolar lavage
BDG	beta-(1,3)-D-glucan
CI	confidence interval
CIOMS	Council for International Organization of Medical Sciences
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease of 2019
CRF	Case report form; also referred to as electronic data record
CRO	contract research organization
CSA	clinical study agreement
CT	computed tomography
DHHS	Department of Health and Human Services
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EORTC/MSG	European Organization for Research and Treatment of Cancer/Mycosis Study Group
ER	emergency room
EU	European Union
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
FU	follow up
GEP	Good Epidemiological Practice
GM	galactomannan
GPP	Good Pharmacoepidemiology Practices
HCP	healthcare provider
HCRU	health care resource utilization
HEOR	health economics and outcomes research
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
ICF	informed consent form
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
ID	Identifying number

Abbreviation	Definition
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
LOS	Length of stay
MRI	magnetic resonance imaging
NIS	non-interventional study
NISMF	NIS master file
OHRP	Office for Human Research Protections
PRISMA	Patterns of Real-World Isavuconazole use, Effectiveness, Safety, and Healthcare Resource Utilization—a Retrospective Chart Review Study of Patients With Mucormycosis or Invasive Aspergillosis
QT	QT interval
RTI	Research Triangle Institute
RTI-HS	RTI Health Solutions
RWE	real world evidence
SAE	serious adverse event
SAP	Statistical Analysis Plan
SECURE	A Phase III, Double-Blind, Randomized Study to Evaluate Safety and Efficacy of BAL8557 Versus Voriconazole for Primary Treatment of Invasive Fungal Disease Caused by Aspergillus Species or Other Filamentous Fungi
SOP	standard operating procedure
TDM	therapeutic drug monitoring
UK	United Kingdom
US	United States
VITAL	Open-Label Study of Isavuconazole in the Treatment of Patients with Aspergillosis and Renal Impairment or of Patients with Invasive Fungal Disease Caused by Rare Moulds, Yeasts or Dimorphic Fungi

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Study title: Patterns of Real-World Isavuconazole Use, Effectiveness, Safety, and Healthcare Resource Utilization—a Retrospective Chart Review Study of Patients With Mucormycosis or Invasive Aspergillosis (PRISMA)

Rationale and background: Invasive aspergillosis and mucormycosis are rare, life-threatening fungal infections associated with high mortality.[1,2] Treatment of invasive aspergillosis usually includes antifungal medications such as voriconazole or isavuconazole.[1] Initial treatment of mucormycosis typically includes surgery to remove infected tissues and antifungal treatment with amphotericin B.[1]

Cresemba® (isavuconazole) is an antifungal agent whose mechanism of action involves blocking the production of a key component of the cell membrane of fungi, thus weakening the membrane and preventing fungal cell growth.[3] Isavuconazole demonstrated non-inferiority compared to voriconazole with improved safety profile in the SECURE clinical trial for patients with invasive aspergillosis (phase 3, randomized, double-blind, comparative-group; NCT00412893).[4] Additionally, in the VITAL clinical trial (single-arm, open-label; NCT00634049), isavuconazole was well tolerated and showed activity against mucormycosis with efficacy comparable to that of amphotericin B in a matched case-control analysis.[5] Isavuconazole was subsequently approved by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2015.

Following market authorization in 2015, real-world evidence (RWE) from European Union (EU) is needed for further insight into isavuconazole use outside of a trial setting. The current study is a retrospective, multi-country chart review to be conducted in five European countries (France, Germany, Italy, Spain, and the United Kingdom [UK]), designed to obtain RWE to increase the knowledge of isavuconazole patterns of use, clinical response, HCRU, and safety in clinical practice.

Research objectives: The primary objectives are to document real-world clinical outcomes (all-cause mortality, overall response) and assess real-world safety (isavuconazole-related adverse events [AEs] and serious adverse events [SAEs]) of isavuconazole for patients with invasive aspergillosis or mucormycosis receiving treatment in routine clinical practice in Europe (France, Germany, Italy, Spain and the United Kingdom). The secondary objectives include describing demographic and clinical characteristics, documenting treatment patterns, and quantifying health care resource utilization (HCRU) among patients with invasive aspergillosis or mucormycosis receiving isavuconazole in routine clinical practice in Europe.

Study design: A retrospective observational cohort study will be conducted, involving the review and abstraction of data from the medical records of patients diagnosed with invasive aspergillosis or mucormycosis who received treatment with isavuconazole. The target sample is approximately 600 patients across 22 sites located in Europe.[a] De-identified data on patient demographics, disease characteristics, treatment effectiveness, safety outcomes,

[a] Dependent on interest in participation and the number of eligible patients each site can contribute, the total number of sites enrolled as well as patients per site could increase/decrease.

isavuconazole treatment patterns, and HCRU will be collected from patient medical records and entered into an electronic data capture (EDC) system by site staff. As this study is retrospective, information pertaining to patient care will already be documented in patient medical records at the time of chart abstraction.

Population: Adult patients (aged ≥18 years) who received isavuconazole for the treatment of invasive aspergillosis or mucormycosis in the hospital setting.

Study sites: Although the target number of sites is 22 sites, the total number of sites enrolled will depend on site interest, availability of its staff (considering the COVID-19 pandemic), and access to eligible medical records. Invasive aspergillosis and mucormycosis are rare fungal infections; thus, it is expected that the pool of potential patients across sites will be small. The sites will be hospital based; thus, the patient population will consist of those who were either hospitalized or attending a hospital at the initiation of isavuconazole therapy.

Patient population: Inclusion criteria: Patients must be aged ≥18 years at isavuconazole initiation, have a record of a diagnosis of invasive aspergillosis or mucormycosis at the time isavuconazole was initiated (regardless of whether this diagnosis is suspected or confirmed),[b] and have received at least one dose of isavuconazole during the eligibility period (October 15, 2015, to June 30, 2019).

Exclusion criteria: Patients who did not receive at least one dose of isavuconazole for treatment of invasive aspergillosis or mucormycosis within the eligibility period.

Data source/data collection: Retrospective data will be abstracted from the medical records of patients and entered into an EDC system by trained local site staff. It is estimated that data abstraction will be completed in approximately 7 months from the point at which the first patient is included in the study (estimated to be from August 2020 to March 2021 for all countries except Italy, and from October 2021 to January 2022 for Italy).[c]

[b] Documented cases of invasive aspergillosis or mucormycosis will be included (providing the patient meets all other study inclusion criteria), regardless of whether the diagnosis is classified as being 'suspected' or confirmed via mycological or radiological assessments (this includes European Organization for Research and Treatment of Cancer/Mycosis Study Group [EORTC/MSG] classification of "proven," "probable," and "possible" invasive fungal disease). All available sources will be used to confirm diagnosis (including any text in the medical records [eg, discharge diagnosis] and *International Classification of Diseases, 10th Revision* [ICD-10] codes, if available). The level of documentation in the medical records is expected to vary by healthcare provider (HCP) and by site/country.

[c] Dates of medical record abstraction are subject to change based on the volume of potentially eligible patients during the timeframe of the current eligibility period, the timing of study start-up, and the impact of the COVID-19 pandemic on site staff availability.

Patients who initiate isavuconazole treatment (index event) during the eligibility period (October 15, 2015, to June 30, 2019)[d] will be identified and screened for inclusion/exclusion criteria for enrollment into the study. The two main study periods for data collection from each patient's medical chart are as follows:

- **Pre-index event period:** Baseline data on demographics and medical history will be collected based on all available information in medical records before the index event.

- **Post-index event period:** The timeframe for follow-up data collection will begin one day post-index treatment initiation and end at the earliest of the following: six-months post-index treatment discontinuation, death, loss to follow-up, or December 31, 2019. Key timepoints of interest for assessment of clinical outcomes (mortality and overall response), and safety will be assessed at 6 weeks, 12 weeks, and 24 weeks after initiation of index treatment.

Variables: Categories to be abstracted from the medical records if available include, but are not limited to, the following:

- Demographic, medical history, and clinical characteristics (eg, age, sex, history of invasive fungal infection and prior antifungal treatments, fungal disease characteristics such as diagnosis, mycological confirmation, date of diagnosis, and other comorbidities including underlying illness/risk factors for invasive aspergillosis and mucormycosis).

- Clinical outcomes (eg, overall response [including clinical response, mycological response, radiological response], and mortality).

- Safety outcomes (AEs and SAEs).

- Isavuconazole treatment patterns (eg, formulation, dosage [loading and maintenance], duration, treatment changes (including dosage adjustments, switching, and discontinuation), and concomitant medication).

- Health care resource utilization (eg, length of stay [LOS], emergency room [ER] visits, intensive care unit [ICU] visits and LOS, inpatient hospitalizations, and planned and unplanned outpatient visits).

Study size: Precision estimates were generated based on the all-cause mortality rate at day 42 for patients with invasive aspergillosis who received isavuconazole in the SECURE trial.[4] A sample size of 150 to 200 patients is expected to yield a reasonable margin of error (between 5.00% and 6.25%) for estimating a 95% confidence interval (CI) for the mortality

[d] The eligibility period end date is subject to change based on timing of medical record abstraction and anticipated number of potentially eligible patients during the proposed eligibility timeframe.

rate. However, 95% CIs may be wider for analyses of rare events or analyses conducted in small subgroups.

As mucormycosis is rare, sample size for this population is expected to be low and limited by the availability of patient medical records at sites. All eligible patients with mucormycosis will be included. Based on the observed weighted all-cause mortality rate in the sample of mucormycosis patients (n = 37) in the VITAL trial of 33%, such a sample would allow to estimate the mortality rate within a precision of 15%.

Data analysis: Data analysis will be primarily descriptive. Mean, standard deviation, median, minimum, and maximum, interquartile range, and range will be provided for continuous variables; numbers and percentages for each category will be provided for categorical variables. Time to event outcomes will be assessed using the Kaplan-Meier (KM) method and will be reported as descriptive statistics (eg, median time to event) with 95% CIs. The statistical analysis plan (SAP) will provide a detailed description of analytic populations, analyses to be performed, and methods to deal with missing data and censoring.

Milestones:

Completion of feasibility assessment: October 15, 2019

Start of data collection: August 10, 2020

End of data collection: January 22, 2022

Interim study report (ex-Italy): July 22, 2021

Final study report: May 26, 2022

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	October 15, 2019
Start of data collection	August 10, 2020
End of data collection	January 22, 2022
Interim study report (ex-Italy)	July 22, 2021
Final study report	May 26, 2022[e]

[e] Anticipated date; subject to change based on the impact of the COVID-19 pandemic on the availability of members of ethics review committee, staff at the institutional review board, and site staff.

7. RATIONALE AND BACKGROUND

7.1. Study Background

Invasive aspergillosis and mucormycosis are rare, life-threatening fungal infections associated with high mortality.[1,2] Causative agents for fungal infections can vary across geographic locations; however, *Aspergillus fumigatus* and *Rhizopus arrhizus* are associated with the majority (approximately 70%) of invasive aspergillosis and mucormycosis cases, respectively.[1] Although the epidemiology of rare fungal diseases is not well studied, the incidence rates (per 100,000 persons) for invasive aspergillosis and mucormycosis are estimated to be 4.6 and 0.09 in the UK, 2.8 and 0.04 in Spain, and 1.8 and 0.1 in France, respectively.[2] Incidence rates are difficult to estimate due to a lack of a reliable denominator.[2,5]

Cresemba® (isavuconazole) is an antifungal agent that contains the active substance isavuconazole. Its mechanism of action involves blocking the production of a key component of the cell membrane of fungi, thus weakening the membrane and preventing fungal cell growth.[3] Isavuconazole can be administered orally or by infusion. Isavuconazole demonstrated non-inferiority compared to voriconazole with improved safety profile in the SECURE clinical trial for patients with invasive aspergillosis (phase 3, randomized, double-blind, comparative-group; NCT00412893).[4] Isavuconazole was approved by the EMA on October 15, 2015, for use in adults for the treatment of (i) invasive aspergillosis and (ii) mucormycosis in patients for whom amphotericin B is inappropriate.

7.2. Invasive Aspergillosis

Invasive aspergillosis usually occurs in immunocompromised patients with hematological malignancies, oncology patients receiving chemotherapy, and immunosuppressed patients (eg, as a result of taking immunosuppressive drugs after transplant surgery). Other risk factors include comorbidities such as diabetes, renal or liver dysfunction, chronic obstructive pulmonary disease, and neutropenic sepsis. Patients with comorbidities also are at higher risk for stays in the ICU.[6] Diagnosis of invasive aspergillosis is typically made by the combination of host status, imaging, and mycological findings.[1] Treatment of invasive aspergillosis usually includes antifungal medications such as voriconazole or isavuconazole.[1]

The SECURE clinical trial (NCT00412893) was a phase 3 randomized, double-blind, comparative-group study designed to compare the efficacy and safety of isavuconazole vs. voriconazole in the treatment of patients with invasive aspergillosis. The primary outcome measure was all-cause mortality at day 42. In the intention-to-treat population, all-cause mortality was 19% for isavuconazole and 20% for voriconazole, adjusted treatment difference = –1.0% (95% CI: –7.8, 5.7).[4] Patients treated with isavuconazole also had a lower frequency of hepatobiliary disorders (9% vs. 16%; $P = 0.016$), eye disorders (15% vs. 27%; $P = 0.002$), and skin or subcutaneous tissue disorders (33% vs. 42%; $P = 0.037$). Additionally, treatment-related AEs were reported in 42% and 60% of patients receiving isavuconazole and voriconazole, respectively ($P < 0.001$). Guidelines therefore recommend isavuconazole and voriconazole for first-line treatment of invasive aspergillosis.

7.3. Mucormycosis

The main risk factors for mucormycosis include diabetes mellitus, hematological malignancies, stem cell/organ transplantations, corticosteroid therapy, and neutropenia.[2] Mucormycosis is usually diagnosed through identification of causative agents by histopathological analysis of tissue specimens, in patients showing symptoms of the infection.[1] However, diagnosis is challenging, and cultures are only occasionally positive. Initial treatment of mucormycosis typically includes surgery to remove infected tissues and antifungal treatment with amphotericin B.[1]

The VITAL clinical trial (NCT00634049) was a single-arm, open-label trial, that included an assessment of the efficacy and safety of isavuconazole for treatment of mucormycosis in 37 patients. The primary outcome was independent data review committee-determined overall response (complete or partial response [treatment success] or stable or progressive disease [treatment failure]) at day 42, day 84, and end of treatment. The results demonstrated that by day 42, 11% of patients had a partial response, 43% had stable disease, 3% had disease progression, 8% had missing assessments, and 35% had died.[7] The efficacy of isavuconazole and amphotericin B was also compared in a matched case-control analysis.[7] At day 42, all-cause mortality was similar in cases with isavuconazole as the primary treatment and amphotericin B-treated matched controls (weighted all-cause mortality: 33% vs. 41%; $P = 0.595$).[7]

Although the use of some antifungals are restricted in patients with renal impairment, in a pooled analysis of the SECURE and VITAL trials, isavuconazole was reported to be well tolerated in patients with renal impairment.[8]

7.4. Study Rationale

Isavuconazole obtained market authorization in the US and the EU in 2015. The generation of RWE will provide additional insight into isavuconazole use and related outcomes in clinical practice. The current study is a retrospective cohort study based on a multi-country chart review to be conducted in five European countries (France, Germany, Italy, Spain, and the UK), designed to obtain RWE of isavuconazole patterns of use, clinical response, HCRU, and safety in clinical practice.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objectives:

- To document real-world clinical outcomes (all-cause mortality, overall response) of isavuconazole in patients with invasive aspergillosis or mucormycosis receiving treatment in routine clinical practice in Europe (France, Germany, Italy, Spain, and the United Kingdom).

- To assess real-world safety (isavuconazole-related AEs and SAEs) of isavuconazole in patients with invasive aspergillosis or mucormycosis receiving treatment in routine clinical practice in Europe.

Secondary objectives:

- To describe demographic and clinical characteristics of patients with invasive aspergillosis or mucormycosis receiving isavuconazole in routine clinical practice in Europe.

- To document treatment patterns among patients with invasive aspergillosis or mucormycosis receiving isavuconazole in routine clinical practice in Europe.

- To quantify HCRU among patients with invasive aspergillosis or mucormycosis receiving isavuconazole in routine clinical practice in Europe.

9. RESEARCH METHODS

9.1. Study Design

This is an observational retrospective cohort study involving the review and abstraction of pertinent data from the medical records of patients diagnosed with invasive aspergillosis or mucormycosis who received treatment with isavuconazole (index event) between October 15, 2015, and June 30, 2019.[f] The target sample size for this study is approximately 600 patients (with a minimum of 200) across 22 sites located in Europe.[g]

De-identified data (ie, anonymous to non-site staff) on patient demographics, disease characteristics, isavuconazole treatment patterns, clinical response, safety outcomes, and HCRU will be collected from patient medical records and entered into an EDC system by site staff between August 2020 and March 2021 for Germany, Spain, and the UK, and between October 2021 and January 2022 for Italy.[h] The differences in the data abstraction timelines are due to ethics and contracting processes in Italy taking between 6 to 12 months to complete, compared with an estimated maximum of 4 months in the remaining countries. As this study is retrospective, information pertaining to patient care will already be documented in patient medical records at the time of chart abstraction.

A steering committee composed of experts within hematology and infectious diseases will provide input and guidance on the study design and implementation, as well as the interpretation of results.

[f] The eligibility period end date is subject to change based on timing of medical record abstraction and anticipated number of potentially eligible patients during the proposed eligibility timeframe.

[g] Dependent on interest in participation and the number of eligible patients each site can contribute, the total number of sites enrolled as well as patients per site could increase/decrease.

[h] Dates of medical record abstraction are subject to change based on the volume of potentially eligible patients during the timeframe of the current eligibility period and the timing of study start-up.

9.2. Setting

9.2.1. Study Sites

A feasibility assessment was conducted, and a total of 22 sites meeting the study criteria were identified: 6 in Germany, 5 in Italy, 5 in Spain, 4 in the UK, and 2 in France. All sites are hospital-based facilities and had access to eligible medical records of patients treated within oncology, hematology, and/or transplantation wards and ICUs. During this feasibility assessment, sites were evaluated on the following parameters, to determine their suitability for participation:

- Number of eligible patients treated with isavuconazole for either invasive aspergillosis or mucormycosis.
- Location of medical records and continuity of data across wards and staff resources, to be able to abstract the required data.
- Frequency and availability of follow-up data.

The total number of sites who participate in the study may differ from the anticipated number (22), depending on a site's interest and the availability of its staff (considering the COVID-19 pandemic), and access to eligible medical records. The sites will be hospital based; thus, the patient population will consist of those who were either hospitalized or attending a hospital at the initiation of isavuconazole therapy. As invasive aspergillosis and mucormycosis are rare fungal infections, we expect that the pool of potential patients across sites will be small. The total number of patients eligible patient records to which the sites have access was estimated to be about 583.

9.2.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patient must be aged ≥18 years at the time of isavuconazole initiation.
2. Patient must have a record of a diagnosis of invasive aspergillosis or mucormycosis in their medical record at the time isavuconazole was initiated (regardless of whether this diagnosis is suspected or confirmed).[i]
3. Patient must have received at least one dose of isavuconazole during the eligibility period (October 15, 2015, to June 30, 2019).[j]

[i] Documented cases of invasive aspergillosis or mucormycosis will be included (providing the patient meets all other study inclusion criteria), regardless of whether the diagnosis is classified as being 'suspected' or confirmed via mycological or radiological assessments (this includes EORTC/MSG classification of "proven," "probable," and "possible" invasive fungal disease). All available sources will be used to confirm diagnosis (including any text in the medical records [eg, discharge diagnosis] and ICD-10 codes, if available). The level of documentation in the medical records is expected to vary by HCP and by site and/or country.

[j] The eligibility period end date is subject to change based on timing of medical record abstraction and anticipated number of potentially eligible patients during the proposed eligibility timeframe.

9.2.3. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients who did not receive at least one dose of isavuconazole for treatment of invasive aspergillosis or mucormycosis within the eligibility period.

9.3. Data Source and Data Collection Process

The source for all data collected will be patient medical records. Retrospective data will be abstracted from the medical records of patients and entered into an EDC system by trained local site staff. It is estimated that data abstraction will be completed in approximately 7 months from the point at which the first patient is included in the study for Germany, France, Spain, and the UK (estimated to be from August 2020 to March 2021). For Italy, data collection is anticipated to begin at a later date, and data abstraction will be completed in approximately 3 months from the point at which the first patient is enrolled (estimated to be from October 2021 to January 2022).[k]

9.3.1. Study Periods

9.3.1.1. Index Event

This is defined as the first initiation of isavuconazole treatment for the invasive fungal infection that was diagnosed during the eligibility period.

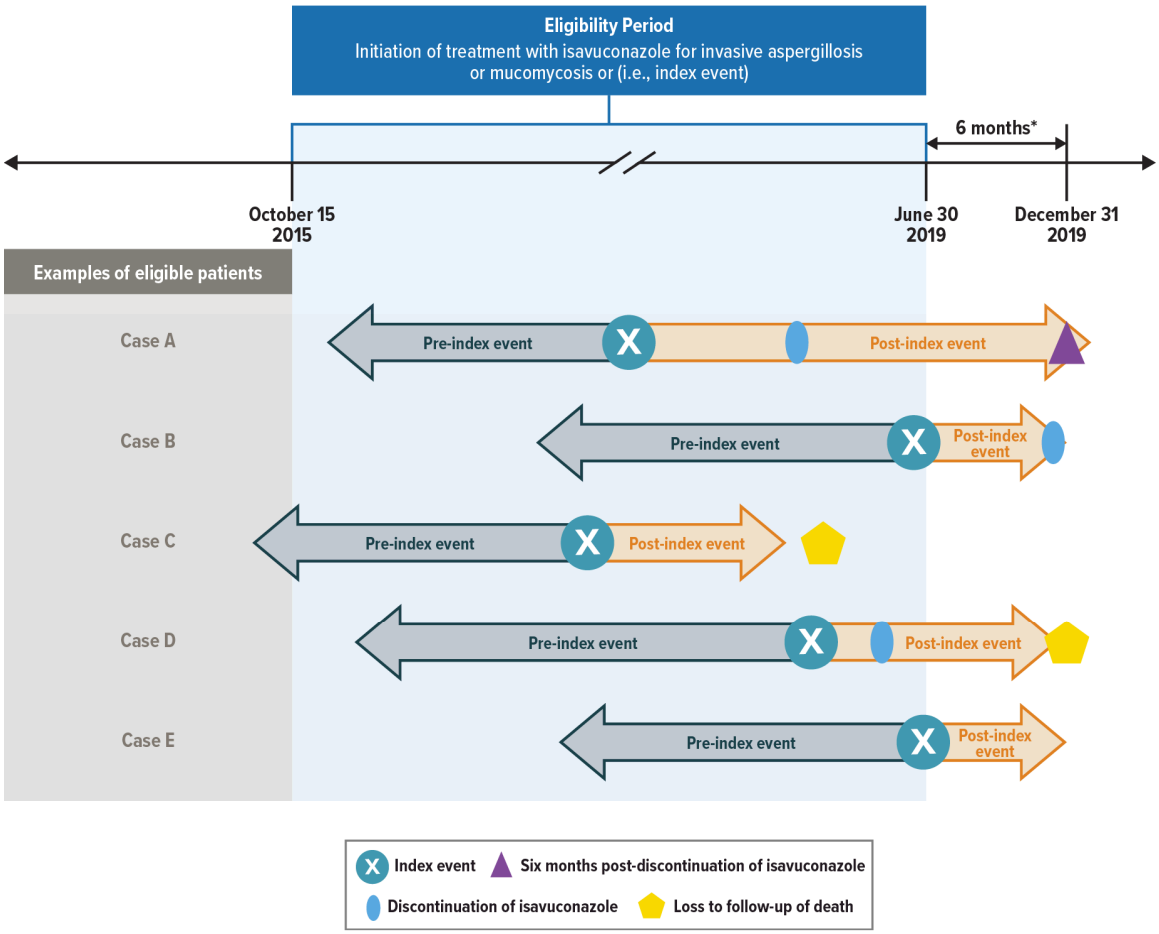
9.3.1.2. Eligibility Period

The eligibility period, wherein potentially eligible patients are identified for enrollment, will be from October 15, 2015 (date of isavuconazole approval by the EMA in the EU), to June 30, 2019.[l] The end date of the eligibility period ensures that the latest date of isavuconazole initiation will occur at least 6 months before the end of December 2019 (after which point the medical records may contain data related to the COVID-19 pandemic, which is not of interest for this study). This will allow a minimum of 6 months of follow-up from the date of isavuconazole initiation unless the patient dies or is lost to follow-up within this timeframe (see Figure 1).

[k] Dates of medical record abstraction are subject to change based on the volume of potentially eligible patients during the timeframe of the current eligibility period, the timing of study start-up, and the effect of the COVID-19 pandemic on the availability of members of ethical review boards, institutional review boards, and availability of site staff.

[l] The eligibility period end date is subject to change based on the timing of medical record abstraction and the anticipated number of potentially eligible patients during the proposed eligibility timeframe.

Figure 1. Overview of Study Periods and Examples of Eligible Cases



9.3.1.3. Data Collection (Chart Abstraction) Periods

Patients who initiate isavuconazole treatment (index event) during the eligibility period (October 15, 2015, to June 30, 2019)[m] will be identified and screened for inclusion/exclusion criteria for enrollment into the study.

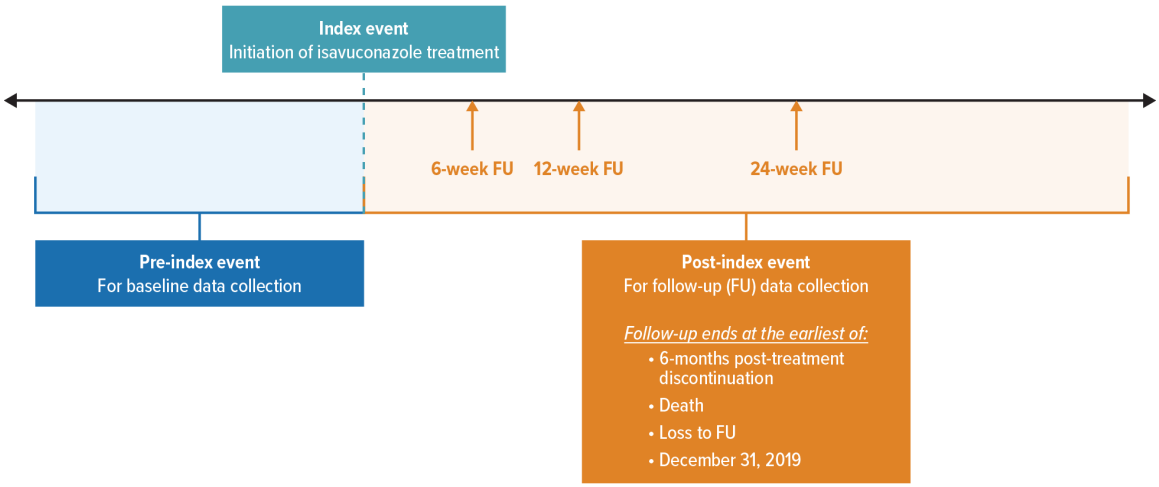
The two main study periods for data collection from each patient's medical chart are:

- **Pre-index event period:** Baseline data on demographics and medical history will be collected based on all available information in medical records before the index event.

[m] The eligibility period end date is subject to change based on timing of medical record abstraction and anticipated number of potentially eligible patients during the proposed eligibility timeframe.

- **Post-index event period:** The timeframe for follow-up data collection will begin one day post-index treatment initiation and end at the earliest of the following: 6 months after post-index treatment discontinuation, death, or loss to follow-up, or December 31, 2019 (see Figure 1 and Figure 2). Key timepoints of interest for assessment of clinical response and safety will be at 6 weeks, 12 weeks, and 24 weeks after initiation of index treatment (see Figure 2).

Figure 2. Data Collection Periods and Timepoints for Each Patient



FU = follow up.

9.4. Variables

Categories of variables to be abstracted from the medical records if available include, but are not limited to, the following (a detailed description of variables and timepoints will be provided in the SAP):

9.4.1. Demographic and Clinical Characteristics

Category	Variable	Timepoint
Demographics and medical history	Age (years)	Index date, closest assessment to index
	Sex: • Male; • Female.	
	Height (centimeters [cm] or feet ['] and inches ["], depending on the country)	
	Weight (kilograms [kg] or stones [st] and pounds [lb], depending on the country)	
	Ethnic/racial group (country-specific options to be used)	
	Smoking status: • Current smoker; • Previous smoker;	

Category	Variable	Timepoint
	• Never smoked; • Unknown.	
	History of illicit drug use: • Yes; specify drug (if documented); • No; • Unknown.	
	If "yes" to history of illicit drug use, specify route of administration: • Inhalation; • Nasal administration; • Intravenous injection; • Intramuscular injection; • Oral administration; • Other (specify).	
	History of alcohol abuse: • Yes; • No; • Unknown.	
Comorbid medical conditions *Note: this refers to comorbidities documented in the chart during the 30 days prior to index and the date of index. However, the onset of the comorbidity may have occurred prior to this.*	• AIDS; • Asthma; • Autoimmune disease; • Bronchiectasis; • Chronic granulomatous disease; • COPD; • Congestive heart failure; • Coronary artery disease; • Cytomegalovirus infection; • Diabetes mellitus or uncontrolled hyperglycemia; • Drug-related AEs; • Fever and neutropenia; • Fungal infection, (specify: fungal, bacterial, other); • Influenza; • Iron overload; • Liver cirrhosis; • Graft-versus-host disease; • Hematologic malignancy; • Herpes virus (including VZV, CMV, etc.); • Hypertension; • Major trauma;	30 days prior to index date, index date

Category	Variable	Timepoint
	• Moderate-to-severe renal disease; • Neutropenia; • Severe burns; • Solid tumor (specify); • Solid organ transplantation (specify); • Stem cell transplantation (specify); • Tuberculosis; • Other (specify); • Unknown.	
Fungal disease characteristics	Disease type • Invasive aspergillosis; • Mucormycosis.	At index date or closest assessment to index during the pre-index period. If no assessments are available in the pre-index period, then assessments closest to index in the post-index period will be used.
	Date of suspected diagnosis (DD MMM YYYY) Date of confirmed diagnosis (DD MMM YYYY) *Note: Documented cases of invasive aspergillosis or mucormycosis will be included (providing the patient meets all other study inclusion criteria), regardless of whether the diagnosis is classified as being "suspected" or confirmed via mycological or radiological assessments (this includes EORTC/MSG classification of "proven," "probable," and "possible" invasive fungal disease). All available sources will be used to confirm diagnosis (including any text in the medical records [eg, discharge diagnosis] and ICD-10 codes, if available). The level of documentation in the medical records is expected to vary by HCP and by site/country.*	
	Mycological confirmation: • Yes; • No; • Unknown.	
	Date of mycological confirmation (DD/MMM/YYYY) (if applicable)	
	Mycological examination type (if applicable):	

Category	Variable	Timepoint
	• Blood or tissue culture; • Bronchoalveolar lavage; • Urine sample; • Biopsy specimen; • Other (specify); • Unknown.	
	Radiological confirmation: • Yes; • No; • Unknown.	
	Date of radiological confirmation (DD/MMM/YYYY) (if applicable)	
	Radiological assessment type (if applicable): • Chest X-ray; • CT scan; • Ultrasound; • MRI; • Other (specify); • Unknown.	
	Radiographic assessment location: • Brain; • Lungs; • Liver; • Kidney; • Stomach; • Intestines; • Other (specify); • Unknown.	
	Other confirmation type: • Yes (specify); • No; • Unknown.	
	EORTC/MSG disease classification (if available): • Proven; • Probable; • Possible; • Unknown.	
	Localization (all that apply): • Lungs; • Sinus;	

Category	Variable	Timepoint
	• Skin; • Stomach; • Intestines; • Central nervous system; • Bones; • Liver; • Kidney; • Blood; • Other (specify); • Unknown.	
Antifungal drug use prior to index treatment	Antifungal type: • Liposomal amphotericin B; • Voriconazole; • Posaconazole; • Caspofungin; • Anidulafungin; • Micafungin; • Other (specify); • Unknown.	1 year prior to index date
	Reason for switch to index treatment (if applicable): • Lack of response to treatment; • AE; • Patient decision (unrelated to AEs); • Other (specify); • Unknown.	
	Date of initiation (DD MMM YYYY)	
	Date of discontinuation (DD MMM YYYY)	
Other prior treatment history	• Antibiotic (specify); • Surgery (specify); • Corticosteroid (specify); • Immunosuppressant (specify); • Chemotherapy (specify); • Other (specify); • Unknown.	30 days prior to index date

AE = adverse event; COPD = chronic obstructive pulmonary disease; CT = computed tomography; EORTC/MSG = European Organization for Research and Treatment of Cancer/Mycosis Study Group; HCP = healthcare provider; ICD-10 = *International Classification of Diseases, 10th Revision*; MRI = magnetic resonance imaging.

9.4.2. Isavuconazole Treatment Patterns

Category	Variable	Timepoint

Index treatment (isavuconazole) administration	Setting of treatment administration:
	• Inpatient setting:
	  • Oncology ward;
	  • Hematology ward;
	  • Transplantation ward;
	  • ICU;
	  • General medicine ward;
	  • Other ward (specify).
	• Outpatient setting;
	• Other (specify);
	• Unknown.
		Index date, post-index period

	Loading-dose method of administration: • Infusion; • Oral; • Unknown; • Not applicable.	
	Date of first loading-dose administration (DD MMM YYYY)	
	Date of last loading-dose administration (DD MMM YYYY)	
	Loading dose: • 372 mg of isavuconazonium sulfate; • Other (specify).	
	Loading-dose frequency: • Every 8 hours for 48 hours (ie, 6 doses); • Other (specify).	
	Maintenance therapy method of administration: • Infusion; • Oral; • Maintenance therapy not administered; • Unknown; • Not applicable.	
	Date of first dose of maintenance therapy (DD MMM YYYY)	
	Date of last dose of maintenance therapy (DD MMM YYYY)	
	Maintenance dose (mg): • 372 mg of isavuconazonium sulfate;	

Category	Variable	Timepoint
	• Other (specify).	
	Maintenance dose frequency: • Every 24 hours (ie, once daily); • Other (specify).	
Modification of index treatment	Treatment modification (eg, dose adjustment, mode of administration change): • Yes; • No; • Unknown.	Post-index period
	Date of index therapy modification (DD MMM YYYY)	
	Type of therapy modification (all that apply): • Change from infusion to oral capsule; • Change from oral capsule to infusion; • Dose increase; • Dose decrease; • Frequency increase; • Frequency decrease; • Other (specify); • Unknown.	
	Reason for index therapy modification: • Lack of response to treatment; • AE; • Patient decision (unrelated to AEs); • TDM; • Drug-drug interaction; • Other (specify); • Unknown.	
TDM	Was TDM conducted? • Yes; • No; • Unknown.	Post-index period
	Date of TDM (DD MMM YYYY)	
	Outcome of TDM: • Treatment modification; • Treatment discontinuation; • None; • Other (specify);	

Category	Variable	Timepoint
	• Unknown.	
Discontinuation of index treatment	Discontinuation of index treatment: • Yes; • No; • Unknown.	Post-index period
	Date of discontinuation (DD MMM YYYY)	
	Reason for discontinuation: • Patient completed planned course of treatment; • Lack of response to treatment; • AE; • Patient decision (unrelated to AEs); • Treatment success (resolution of invasive fungal infection); • Death (unrelated to therapy); • TDM; • Drug-drug interaction; • Other (specify); • Unknown.	
Switch to a new antifungal drug after discontinuation of index treatment	Switch to a new antifungal agent after discontinuation: • Yes; • No; • Unknown.	Post-index period
	Start date of subsequent antifungal agent (DD MMM YYYY)	
	End date of subsequent antifungal agent (DD MMM YYYY)	
	Type of new antifungal agent: • Liposomal amphotericin B; • Voriconazole; • Posaconazole; • Caspofungin; • Anidulafungin; • Micafungin; • Other (specify); • Unknown.	
Other subsequent antifungal use after end of index treatment	Type of new antifungal drug: • Liposomal amphotericin B; • Voriconazole; • Posaconazole;	Post-index period

Category	Variable	Timepoint
	• Caspofungin; • Anidulafungin; • Other (specify); • Unknown.	
	Start date of subsequent antifungal agent (DD MMM YYYY)	
	End date of subsequent antifungal agent (DD MMM YYYY)	
Index treatment administered as part of antifungal combination therapy	Index treatment administered as part of antifungal combination therapy: • Yes; • No; • Unknown.	Index date, post-index period
	Type of therapy administered in combination with isavuconazole: • Liposomal amphotericin B; • Voriconazole; • Posaconazole; • Caspofungin; • Anidulafungin; • Micafungin; • Other (specify); • Unknown.	
	Start date of therapy administered in combination with isavuconazole (DD MMM YYYY)	
	End date of therapy administered in combination with isavuconazole (DD MMM YYYY)	
Other concomitant treatments (not including combination therapy)	• Antibiotic agent (specify); • Corticosteroid agent (specify); • Immunosuppressant agent (specify); • Chemotherapy (specify); • Other (specify); • Unknown.	Index date, post-index period
	Start date of concomitant treatment (DD MMM YYYY)	
	End date of concomitant treatment (DD MMM YYYY)	

AE = adverse event; ICU = intensive care unit; TDM = therapeutic drug monitoring.

9.4.3. Clinical Effectiveness

Category	Variable	Timepoint
Clinical response[n]	Date of assessment (DD MMM YYYY)	Post-index period
	Clinical response status documented in the medical chart: • Clinical response; • Clinical failure; • Unknown.	
Re-activation of same or new infection	Re-activation documented in the medical chart: • Yes; • No.	Post-index period
	Assessment date (DD MMM YYYY)	
Radiological assessments	Radiographic assessment date (DD MMM YYYY)	Post-index period
	Radiographic examination type: • Chest X-ray; • CT scan; • Ultrasound; • MRI; • Other (specify); • Unknown.	
	Radiographic examination location • Brain; • Lungs; • Liver; • Kidney; • Stomach; • Intestines; • Other (specify); • Unknown.	
Radiological response[o]	Radiological examination date (DD MMM YYYY)	Post-index period

[n] Clinical response will be evaluated according to the following mutually exclusive modalities: **Clinical response**: resolution or partial resolution of all attributable clinical symptoms and physical findings. **Clinical failure**: no resolution of any attributable clinical symptoms and physical findings and/or worsening. When medical record documentation is not clear for the abstractor on which categories to specify, the investigator should review all available medical record documentation to determine classifications. If the investigator determines there is not enough medical record documentation to make the classification, they will indicate unknown. Since clinical response classification is important to the study, participating sites will be selected for participation in the study based on reporting to have diligent medical record documentation for response.

[o] Radiological response will be evaluated according to the following criteria: **Radiological response**: ≥ 50% improvement from initial assessment, or improvement of at least 25% from the initial assessment for the follow-up at 6 weeks (ie, Day 42 [±14 days]) or if end of treatment occurred before this time. . When medical record documentation is not clear for the abstractor on which categories to

Category	Variable	Timepoint
	Radiological examination type • Chest X-ray; • CT scan; • Ultrasound; • MRI; • Other (specify); • Unknown.	
	Radiological response documented in the medical chart: • Yes; • No; • Not applicable (initial assessment); • Unknown.	
Mycological assessments	Mycological examination date (DD MMM YYYY)	Post-index period
	Mycological examination type: • Blood or tissue culture; • Bronchoalveolar lavage; • Urine sample; • Biopsy specimen; • Other (specify); • Unknown.	
Mycological response[p]	Mycological examination date (DD MMM YYYY)	Post-index period
	Mycological examination type: • Blood or tissue culture; • Bronchoalveolar lavage; • Urine sample; • Biopsy specimen; • Other (specify); • Unknown.	
	• Eradication; • Presumed eradication;	

specify, the investigator should review all available medical record documentation to determine classifications. If the investigator determines there is not enough medical record documentation to make the classification, they will indicate unknown. Since radiological response classification is important to the study, participating sites will be selected for participation in the study based on reporting to have diligent medical record documentation for response.

[p] Mycological response will be evaluated according to the following criteria: **eradication** or **presumed eradication** of the original causative organism cultured. **Failure** will be defined as persistence or presumed persistence. When medical record documentation is not clear for the abstractor on which categories to specify, the investigator should review all available medical record documentation to determine classifications. If the investigator determines there is not enough medical record documentation to make the classification, they will indicate unknown. Since mycological response classification is important to the study, participating sites will be selected for participation in the study based on reporting to have diligent medical record documentation for response.

Category	Variable	Timepoint
	• Failure; • Not applicable (initial assessment); • Unknown.	
Biomarkers	• Galactomannan (GM), Serum; • Galactomannan (GM), Bronchoalveolar lavage (BAL); • (1→3)-β-D-Glucan (BDG), serum.	Index date, post-index period
	• Test date (DD MMM YYYY).	

CT = computed tomography; MRI = magnetic resonance imaging.

9.4.4. Safety

Category	Variable	Timepoint

AEs	Type of event (documented by ICD-9 code, ICD-10 code or record in the medical chart):
	• Blood and lymphatic AE:
	  • Neutropenia;
	  • Thrombocytopenia;
	  • Pancytopenia;
	  • Leukopenia;
	  • Anemia;
	  • Other (specify).
	• Immune system AE:
	  • Hypersensitivity;
	  • Other (specify).
	• Metabolism and nutrition AE:
	  • Hypokalemia;
	  • Decreased appetite;
	  • Hypomagnesemia;
	  • Hypoglycemia;
	  • Hypoalbuminemia;
	  • Malnutrition;
	  • Other (specify).
	• Psychiatric AE:
	  • Delirium;
	  • Depression;
	  • Insomnia;
	  • Other (specify);
	• Nervous system AE:
	  • Headache;
	  • Somnolence;
	  • Convulsion;
		Index date, post-index period

Category	Variable	Timepoint
	• Syncope; • Dizziness; • Paresthesia; • Encephalopathy; • Presyncope; • Peripheral neuropathy; • Dysgeusia; • Other (specify). • Ear and labyrinth AE: • Vertigo; • Other (specify). • Cardiac AE: • Atrial fibrillation; • Tachycardia; • Bradycardia; • Palpitations; • Atrial flutter; • Electrocardiogram QT shortened; • Supraventricular tachycardia; • Ventricular extrasystoles; • Supraventricular extrasystoles; • Other (specify). • Vascular AE: • Thrombophlebitis; • Circulatory collapse; • Hypotension; • Other (specify). • Respiratory, thoracic and mediastinal AE: • Dyspnea; • Acute respiratory failure; • Bronchospasm; • Tachypnoea; • Hemoptysis; • Epistaxis; • Other (specify). • Gastrointestinal AE: • Vomiting; • Diarrhea; • Nausea; • Abdominal pain;	

Category	Variable	Timepoint
	• Dyspepsia; • Constipation; • Abdominal distension; • Other (specify). • Hepatobiliary AE: • Elevated liver chemistry tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, bilirubin); • Hepatomegaly; • Hepatitis; • Other (specify). • Skin and subcutaneous tissue AE: • Rash; • Pruritus; • Petechiae; • Alopecia; • Drug eruption; • Dermatitis; • Other (specify). • Musculoskeletal and connective tissue AE: • Back pain; • Other (specify). • Renal and urinary AE: • Renal failure; • Other (specify). • General disorders and administration site condition AE: • Chest pain; • Fatigue; • Injection site reaction; • Edema peripheral; • Malaise; • Asthenia; • Other (specify). • Other AE (specify).	
	AE onset date (DD MMM YYYY)	
	AE resolution: • Yes; • No;	

Category	Variable	Timepoint
	• Unknown.	
	AE resolution date (DD MMM YYYY)	
	AE seriousness: • Was life-threatening; • Required inpatient hospitalization or prolongation of existing hospitalization; • Resulted in persistent or significant incapacity or disability; • Was a congenital anomaly/birth defect; • Was a medically important event; • Resulted in death; • None of the above; • Unknown.	
	AE severity: • Mild; • Moderate; • Severe; • Unknown.	
	Documented relationship to isavuconazole: • Yes; • No; • Unknown.	
	Action taken with isavuconazole: • Treatment discontinuation; • Dose reduced; • Dose increased; • Dose delayed; • Dose not changed; • Not applicable; • Unknown.	
	Outcome of event: • Resolved; • Resolving; • Resolved with sequelae; • Not resolved; • Fatal; • Unknown.	

AE = adverse event; ICD-9 = International Classification of Diseases, 9th Revision; ICD-10 = International Classification of Diseases, 10th Revision.

9.4.5. Survival Status

Category	Variable	Timepoint
Survival status	Date of death (DD MMM YYYY)	Post-index period
	Primary cause of death: • Complications related to invasive aspergillosis or mucormycosis; • Other disease complications; • SAE related to isavuconazole treatment; • SAE unrelated to isavuconazole treatment; • Other (specify); • Unknown.	

SAE = serious adverse event.

9.4.6. Health Care Resource Utilization

Category	Variable	Timepoint
Inpatient hospitalizations (including specialty wards, ICU, ER, general medicine ward, or other)	Inpatient hospitalization occurring after index treatment initiation • Yes; • No; • Unknown.	Post-index period
	Primary reason for hospitalization: • Invasive aspergillosis or mucormycosis disease monitoring; • Other disease monitoring; • AE related to invasive aspergillosis or mucormycosis; • Other (specify); • Unknown.	
	Location for inpatient hospitalization: • Oncology ward; • Hematology ward; • Transplantation ward; • ICU; • ER; • General medicine ward; • Other ward (specify); • Unknown.	
	Use of a mechanical ventilator: • Yes; • No; • Unknown.	
	Admission date (DD MMM YYYY)	

Category	Variable	Timepoint
	Discharge date (DD MMM YYYY)	
	Discharge location (if applicable): • Transferred to another ward for inpatient care; • Discharged to home or self-care (routine discharge); • Discharged to long term care facility/hospice; • Not applicable; • Other (specify); • Unknown.	
Outpatient visits (not associated with a hospital stay)	Outpatient visit/referral occurring after index treatment initiation: • Yes; • No; • Unknown.	Post-index period
	Health care professional visit or referral: • Primary care visit (general practitioner); • Secondary care visit (specialist); • Secondary care referral (specialist); • ER visit.	
	Primary reason for visit/referral: • Planned visit/referral for invasive aspergillosis or mucormycosis disease monitoring; • Unplanned visit/referral for invasive aspergillosis or mucormycosis disease monitoring; • Planned visit/referral for other disease monitoring; • Unplanned visit/referral for other disease monitoring; • Unplanned visit/referral for AE related to invasive aspergillosis or mucormycosis; • Other; • Unknown.	
	Type of health care professional: • Infectious disease specialist;	

Category	Variable	Timepoint
	• Oncologist; • Hematologist; • General internist; • Gastroenterologist; • Cardiologist; • Obstetrician/gynecologist; • Neurologist; • Radiologist; • Dermatologist; • Psychiatric; • Surgeon; • Specialty nurse; • Other (specify); • Unknown.	
	Date of outpatient visit/referral (DD MMM YYYY)	

AE = adverse event; ER = emergency department; ICU = intensive care unit.

9.5. Study Size

As the study is primarily descriptive in nature, formal sample size calculations are not required. Given the rarity of invasive aspergillosis and mucormycosis, we will include all eligible patients identified from sites, up to a target sample size of 600 patients.

Table 1 shows the width of the CI that can be obtained from different sample sizes. Precision estimates were generated based on the all-cause mortality rate at day 42 for patients with invasive aspergillosis who received isavuconazole in the SECURE trial.[4] These estimates suggest that a sample size of 150 to 200 patients initiating isavuconazole would be expected to yield a reasonable margin of error (between 5.00% and 6.25%) for estimating a 95% CI for the mortality rate; thus, an overall sample size of up to 600 patients would yield a reasonable margin of error. However, 95% CIs may be wider for analyses of rare events or analyses conducted in small subgroups.

Table 1. Wilson 95% CI Based on All-Cause Mortality Rate at Day 42 for Patients With Invasive Aspergillosis Who Received Isavuconazole in the SECURE Trial

	Sample Size (N)	95% CI Width
All-cause mortality rate at day 42 in SECURE trial = 19%	292	9.0
	237	10.0
	152	12.5
	106	15.0

CI = confidence interval.

Because mucormycosis is rare, sample size for this population is expected to be low and limited by the availability of patient medical records at sites; therefore, all eligible patients will be included. Based on the observed weighted all-cause mortality rate of 33% in the sample of mucormycosis patients (n = 37) in the VITAL trial, such a sample would allow to estimate the mortality rate within a precision of 15%.

9.6. Data Management

9.6.1. Case Report Forms

Screening results for inclusion and exclusion criteria will be captured in the EDC system for all patients in the initial target cohort.

As used in this protocol, the term CRF should be understood to refer to an electronic data record.

A CRF is required and should be completed for each included patient.

In this study, the clinical research organization (CRO) will provide a password-protected, web-based EDC system to serve as an integrated, transparent tool to collect and manage data and track study progress at the center and at the patient level. Data in the EDC system will be kept in a central location and all data will be transmitted to a central database.

The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source

documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The investigator also has ultimate responsibility for ensuring that data entered are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The investigator or authorized staff member must attest that the data entered in the EDC are true.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

Site staff will be trained by the CRO to perform the medical record abstraction, including data entry and how to retrieve and respond to data queries in the EDC system. To participate in this study, all sites must be able to access the EDC system and complete data entry into the CRFs via the EDC system.

The EDC system will include logic checks to minimize data entry errors. Data inconsistencies outside the logic checks will be managed by manual queries issued by data management within the EDC system for site completion. All queries will be monitored until resolution within the EDC through the electronic query report.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents (if applicable), safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless the CRO and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Monitoring

The CRO will supervise and monitor de-identified data abstraction by site staff into the EDC system.

Quality-control mechanisms (eg, verification of data completeness, validations, and edit checks), which will be automated at the time of data entry, will be built into the EDC. Queries will be generated by the CRO for resolution by site staff within the EDC system.

9.8. Data Cleaning

The EDC system will have built-in methods for data validation (eg, drop-down lists, value range controls, and standardized response formats). However, a data cleaning method will furthermore be employed to correct inconsistencies or errors that were not captured during data entry (eg, outliers or conflicting data). Data will be generated for site resolution. The CRO will follow up on the identified data queries until they are resolved by the site.

9.9. Data Analysis

This study is primarily descriptive in nature. Categorical variables will be reported as counts (n) and frequencies (%). Continuous variables will be reported using mean, standard deviation, median, minimum and maximum, interquartile range, and range. Time to event outcomes will be assessed using the KM method and will be reported as descriptive statistics (eg, median time to event) with 95% CI. Results will be presented for the overall group (both disease types) and separately for invasive aspergillosis and mucormycosis.

The statistical analysis plan (SAP) will provide a detailed description of analytic populations, analyses to be performed, and methods to deal with missing data and censoring.

Depending on the overall sample size, subgroup analyses may be conducted for main study outcomes (eg, by country, by diagnosis).

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary outcome definitions or their analyses would be reflected in a protocol amendment. The SAP will define all planned analytic populations and subpopulations, including definitions of overall response and AEs of interest. The SAP will further provide a detailed description of analyses to be performed.

Any known deviations from the planned analyses, the reason for such deviations and all alternative/additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised SAP before completion of data collection.

9.9.1. Missing Data

It is anticipated that the degree of completeness for the study variables may vary due to unknown or undocumented data in the medical records. The number of patients with missing data for each variable will be summarized and reported. With the exception of the imputation of partial missing date values, no other imputation of missing values is anticipated; however, the impact of missing data on interpretation of findings will be acknowledged and discussed in the final study report. The SAP will further provide a detailed description of methods to deal with missing data and censoring.

9.9.2. Planned Analysis

9.9.2.1. Analysis Plan for Primary Objectives

Mortality/survival rates will be summarized and reported. Clinical, radiological, and mycological response documented in the medical record will be summarized using proportions and counts for each category. Details of radiological and mycological assessments will be reported in a descriptive manner, including the type of assessment and the assessment findings. Definitions of response will be provided in the SAP. Time to response and all-cause mortality will be analyzed using the KM method and quartiles and 95% CIs will be reported.

Descriptive statistics will be used to describe all AEs and SAEs reported during the medical record review. The safety data described will include event type, relationship to isavuconazole treatment (where known), event severity, event seriousness, action taken with isavuconazole treatment and outcome of the event. Definitions of AEs and SAEs will be described in the SAP. Time from index treatment to first AE onset will be summarized.

Key timepoints of interest for assessment of treatment effectiveness, safety and survival outcomes will be at 6 weeks, 12 weeks, and 24 weeks after initiation of index treatment. In the cases that usual care visits do not directly coincide with these timepoints, the time windows for assessment of outcomes will be defined in the SAP.

9.9.2.2. Analysis Plan for Secondary Objectives

Basic summaries of site and patient counts included in the study will be produced. Patients will be characterized by fungal disease type (invasive aspergillosis or mucormycosis) at the time of isavuconazole initiation, in terms of demographics, disease characteristics, medical history, treatment history, prognostic factors, and other factors which may be predictive of clinical outcome.

For isavuconazole treatment patterns, descriptive statistics will be used to summarize details of isavuconazole administration (eg, location, therapy duration, loading dose and frequency, and maintenance dose and frequency), modifications to index therapy, details of therapeutic drug monitoring (therapeutic drug monitoring [TDM], eg, assay type, outcome), discontinuation, switching, antibiotic use before and after index therapy, and concomitant medication.

Health care resource utilization during the post-index period will be reported at 6 weeks, 12 weeks, and 24 weeks after initiation of index therapy. HCRU will include counts and proportions of patients with inpatient visits, outpatient visits, ICU admissions and ER visits and use of mechanical ventilators. Reason for visits and duration of visits will be described. Inpatient LOS and ICU LOS will be derived using admission and discharge dates.

9.9.3. Interim Analysis

There are no planned interim analyses.

9.10. Quality Control

The development of the protocol and SAP will follow Pfizer's internal standard operating procedures (SOPs), which include detailed review rounds. Quality control of the statistical programming will follow the CRO's SOPs.

The CRO will follow SOPs and quality-control processes that address patient data security to ensure that patient data (as well as other confidential data) remain secure and intact. The EDC system has built-in edit checks and validations and supports electronically generated and manual queries.

Patient confidentiality will be strictly maintained. Access to the EDC system will be regulated via a hierarchical username and password control. Subject data will be de-identified through design of data entry fields that do not permit the entry of identifying information such as initials, date of birth, date of diagnoses/treatments/admissions, or center-assigned patient identifiers. Only trained site staff will enter data into the electronic CRFs. Patients' ages in whole years, but not date of birth, will be entered. Dates related to diagnosis, treatments, hospital admissions, discharges, etc. will be entered by the physician; the EDC system will calculate durations. Dates will not be stored by the EDC system and will not exist within the data set. No patient identifiers used by sites will be entered; rather the EDC program will automatically assign a study identifying number (ID) to each patient. The de-identified data as entered into the EDC system will be visible to the CRO and the Sponsor, but only center staff will be able to trace a study ID number to a patient identity, a necessary measure to allow center staff to respond to data queries raised by the CRO later.

9.11. Strengths and Limitations of the Research Methods

In the absence of a suitable existing database, this retrospective medical record review will allow the collection of real-world data in adult patients who received isavuconazole for the treatment of invasive aspergillosis or mucormycosis in the hospital setting. Unlike a prospective study, retrospective cohort designs are not sensitive to the Hawthorne effect (ie, alteration of behavior and/or prescribing practices as a result of being observed).

Limitations of this retrospective study design are acknowledged and will be documented within the study report:

- Data quality will be dependent on completeness and accuracy of the data abstraction and the data documentation in the medical records. Differences in how each site operates, the connections to other health care facilities within the medical record, and the extent to which specific details are documented will affect data availability across medical records. For example, it is expected that the timing of follow-up visits may vary across sites. Additionally, some data are less likely to be comprehensively documented, including reasons for treatment modification/discontinuation/switching, TDM, mycological/radiological response status at end of treatment, AEs, and reason for HCP visits/referrals. Moreover, visits that occur at a different site may not be documented within the medical record to which the site has access; thus, the data may not provide an accurate representation of the true health care burden. A rigorous data review and cleaning process will be undertaken to ensure that the data which is collected is of the highest quality for analysis.

- The study sites will be chosen based on a convenience sampling approach. That is, sites that indicated interest in study participation and that retain pertinent data within patient medical records that meet the study eligibility criteria were identified during the feasibility assessment. Therefore, by study design, the sites are unlikely to be fully representative of all sites in which cases of invasive aspergillosis or mucormycosis are managed with isavuconazole therapy. Thus, the data are unlikely to be representative of the overall usual care patterns for invasive aspergillosis or mucormycosis in Europe, and the study results should not be considered to be generalizable.

- Since invasive aspergillosis and mucormycosis are rare fungal infections, it is expected that the pool of potential patients across sites will be small and will vary by country.

- The sample size might not yield reliable estimates for rare safety outcomes. However, this study will allow assessment of whether commonly occurring safety events in clinical trials also are observed in real-world setting.

- As target patients are likely to have underlying severe diseases, we have designed this study specifically for a patient population found in a hospital setting, including the ER, ICU, or oncology, hematology and/or transplantation wards.

- Inpatients may change wards during isavuconazole treatment, which may impact the availability of follow-up data. Additionally, patients may be discharged from hospital but will continue to receive treatment with isavuconazole. It is possible that the abstracting HCP does not have access to data related to these instances.

9.12. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in *encrypted electronic* form and will be *password protected* to ensure that only authorized study staff have access. No patient-identifying information will be collected for this study or transferred to Pfizer or the CRO. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, the data will not contain patient names (none will be collected). Rather, individual cases will be indicated by a single, specific, numerical code, based on a numbering system defined by Pfizer. The study will not collect any identifiable data; in this way, such data cannot be transferred to Pfizer or other authorized parties. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the CSA and applicable privacy laws.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required and exemption of informed consent will be requested to the Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs). However, informed consent may be required in accordance with local country regulations. If informed consent is required, bias will be introduced into the study since the eligible patient population must be alive at the time of data collection. Where relevant, this will be fully documented in the study report.

If informed consent is required:

- The informed consent form (ICF) will be in compliance with local regulatory requirements and legal requirements. The ICF will be drafted using the Pfizer ICF template, with privacy language per country as required. Additionally, the final ICF and any subsequent amended versions during the study will be prospectively approved by both the IRB or IEC and Pfizer before use.

- Informed consent will be obtained by site study staff prior to data abstraction. The person obtaining consent will be responsible for ensuring that each participant fully understands the nature, purpose, risks, and benefits of the study. Each participating patient will be provided with a copy of his or her signed ICF.

- It will be the investigator's responsibility to ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

10.3. Patient Withdrawal

Not applicable.

10.4. IRB or IEC

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, ICFs, if applicable) from the relevant IRBs or IECs. All correspondence with the IRB or IEC must be retained. Copies of IRB and IEC approvals must be forwarded to Pfizer.

Before study initiation this study will undergo IRB review and clearance in the US by the CRO's IRB, RTI International Committee for the Protection of Human Subjects Research. RTI International, of which RTI Health Solutions (RTI-HS) is a business unit, holds a Federal-Wide Assurance (FWA) (#3331) from the US Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) that allows it to review and approve protocols involving human subjects. The committee also is registered with OHRP for both DHHS- and FDA-regulated research. Our FWA requires IRB review for all studies conducted by RTI-HS that involve human subjects, regardless of the funding source or geographic location from which data are being collected. Depending on the level of risk and the nature of the research, a study may be ruled as exempt from IRB review by an IRB chair or designated IRB member. Studies that are not exempt must be approved either by an IRB chair or designated IRB member (if the study qualifies for expedited review) or by a full IRB committee.

RTI International currently has an IRB committee available to review research protocols. The committee meets monthly to review biomedical clinical trials and has appropriate medical expertise among its members. The IRB has been audited by the FDA and is fully compliant with applicable regulatory requirements. The committee reviews research studies to ensure adherence to appropriate regulations that govern human subjects research, including 45 CFR 46, 21 CFR 50 and 56, and to all applicable Helsinki Declarations and provisions of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use for conduct of multinational studies. All studies involving human subjects undergo a continuing IRB review at least once per year.

A request to classify the study as a 'non-interventional, not human data' research project will be submitted. If the IRB classifies the study as such, no additional reviews will be required.

In addition to review by RTI International's IRB, the protocol will be submitted for review and approval to the appropriate central and/or local IRBs and/or IECs. With assistance from the CRO, each principal investigator will be responsible for obtaining the necessary approval of the study protocol, protocol amendments, and ICFs (if needed), and other relevant documents, if applicable, from the central and/or local IRBs and/or IECs and for ensuring that the study complies with local legislation relating to data protection and privacy. When local approval is obtained, the documentation indicating the IRB's or IEC's (if applicable) approval and the names and qualifications of the committee members must be sent by the principal investigator to the CRO, who will send these documents to the study sponsor before the recruitment process begins.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in:

- Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE);
- Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA);
- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR);
- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on RWE in health care decision making;
- International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS);
- EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology;
- The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies;
- US FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND/OR ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by an HCP linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) Adverse-Event Monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the CRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer. Re-training must be completed on an annual basis using the most current "Your Reporting Responsibilities" training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Results Dissemination

A final study report will be developed. Development of an abstract for presentation at a suitable conference and a study manuscript suitable for submission to an appropriate journal will be considered. All forms of dissemination will describe the rationale for the study, methods, results, and the implications of those findings.

- **Final study report:** A final study report will be developed based on analysis of the final locked dataset and will include all final study tables.

- **Abstract/poster:** In the case that results yield material suitable for generation of a conference abstract, an abstract will be prepared. If selected, the study results (either interim or final) will be used to develop a poster/presentation for the conference.

- **Peer-reviewed publication:** In the case that results yield material suitable for publication of a manuscript in a peer-reviewed journal, a manuscript will be developed. All authors will have to meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship.

12.2. Communication of Issues

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

Table 1. Wilson 95% CI Based on All-Cause Mortality Rate at Day 42 for Patients With Invasive Aspergillosis Who Received Isavuconazole in the SECURE Trial

15. LIST OF FIGURES

Figure 1. Overview of Study Periods and Examples of Eligible Cases

Figure 2. Data Collection Periods and Timepoints for Each Patient

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.