NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	*A non comparative , multi centre observational study: Isavuconazole (Cresemba) in Invasive Mould Infections (Invasive Aspergillosis, Invasive Mucormycosis) in India*
Protocol number	C3791010
Protocol version identifier	*5.0*
Date	*21.05.2021*
EU Post Authorization Study (PAS) register number	*EUPAS37495*
Active substance	*Isavuconazole* J02AC05
Medicinal product	*Cresemba capsule and Cresemba injection, powder, lyophilized, for solution*
Research question and objectives	To describe a case series of patients treated with Isavuconazole (Cresemba) (post approval) for Invasive Mould Infections (Invasive Aspergillosis, Invasive Mucormycosis) in India during a period of two years (post protocol approval)
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reactions
AE	Adverse Events
AUC	Area Under Curve
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
DCGI	Drug Controller General of India
DDI	Drug-drug Interaction
DMP	Data Management Plan
EORTC-MSG	European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group
EOT	End of treatment
GCP	Good Clinical Practice
GM	Galactomannan
IA	Invasive Aspergillosis
ICF	Infomed Consent Form
ICU	Intensive Care Unit
IFI	Invasive Fungal Infections
IM	Invasive Mucormycosis
IMI	Invasive Mould Infections
SAE	Serious Adverse Events
SAP	Statistical Action Plan
SOP	Standard Operating Procedure

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Dr Prithwijit Kundu	Medical Advisor, HBU	Pfizer	Pfizer, BKC, Mumbai
Dr Shweta Kamat	Medical Lead, HBU	Pfizer	Pfizer, BKC, Mumbai

4. ABSTRACT

A non comparative , multi centre observational study: Isavuconazole (Cresemba) in Invasive Mould Infections (Invasive Aspergillosis, Invasive Mucormycosis) in India

The burden of invasive fungal infections (IFIs) is increasing due to an exponential increase in the pool of individuals with classical as well as non-classical risk factors. Although Invasive Candida Infections (ICIs) form the bulk of IFIs, invasive mould infections (IMIs) are steadily on the rise. A significant trend has been the higher incidence of IMIs in patients with non-classical risk factors. In India the incidence of IFI is significantly higher than what was described elsewhere. In a study published in India in 2019, the incidence of IMIs in ICU was reported as 9.5 cases/1000 admissions.[1]The major unmet needs in the management of IMIs are very high mortality/morbidity, difficulty in diagnosis leading to missed diagnosis as well as misdiagnosis and reduced tolerability to current pharmacological agents. The current recommended first line agents are voriconazole for Invasive Aspergillosis (IA) and Amphotericin B (lipid formulations) for Invasive Mucormycosis (IM). The limitations of voriconazole are adverse drug reactions (ADRs), drug-drug interactions (DDIs) and possible accumulation of cyclodextrin with the intravenous formulation in patients with renal insufficiency. Lipid formulations of Amphotericin B use is limited by nephrotoxicity (albeit lesser than conventional formulations), infusion related reactions and unavailability of the option to switch from intravenous to oral therapy. Considering the unmet medical needs, isavuconazole, a broad-spectrum azole covering both *Aspergillus spp.* and *Mucorales spp.*, is an important addition to the armamentarium. This study is being conducted to provide additional safety and effectiveness data during standard of care treatment. A case series of patients treated with Cresemba (post approval) for Invasive Mould Infections (Invasive Aspergillosis, Invasive Mucormycosis) will be evaluated in India.

This is a non comparative, multi centre, observational study. Adult patients with proven, probable or possible Invasive Aspergillosis or Invasive Mucormycosis as decided by the treating clinician and receiving Isavuconazole (Cresemba) (iv,oral) as per standard of care practices will be recruited from tertiary care centers across India. Outcomes: clinical outcome, microbiological outcomes, length of hospital stay, and discharge status. Key covariates: patient demographics, indication, treatment history, clinical characteristic. Data will be abstracted for patients in the study, from patient charts/ electronic health records after end of six weeks. The data will be recorded in the case report forms (CRFs) for further evaluation. Data will be collected from a maximum of 70 patients with diagnosis of proven, probable or possible IMI, as decided by the treating clinician, during a period of two consecutive calendar years from the protocol approval. The study population will be stratified to achieve a number of study subjects of about 50 Invasive Aspergillosis (IA) and about 20 for Invasive Mucormycosis (IM) on IV and/or oral Cresemba formulations. All reasonable efforts will be made to collect data from the target number of patients. After one year of enrolment and due to the relative rare occurrence of these diseases, recruitment feasibility analyses will be performed. Based on the results of such analyses a modification of the population size will be proposed if necessary. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor.

This non-interventional study is designated as a Post Authorisation Safety Study (PASS) and is a commitment to the DCGI.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1.	14.10.2020	Section 9.2.1/9.2.2	Inclusion criteria: "Evidence of a signed and dated data privacy consent form indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study" has been removed Exclusion criteria: "Patient/LAR has not signed the data privacy consent form" has been removed	Data privacy consent form needs to be signed by the investigator and not the patient or LAR.
2.	14.10.2020	Section 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.
3.	14.10.2020	Section 13	Reference number 2: Cresemba LPD	The Local Product Document has been revised
4.	21.05.2021	Section 9.4	Data collection at 1 week added	This milestone of data collection was missing
5.	21.05.2021	Section 9.6	Schedule of Activities section added	The section was missing and needed incorporation in the protocol
6.	21.05.2021	Section 9.7	Data management system changed from INES to InForm	InForm is the current data management system to be utilized
7.	21.05.2021	Section 9.8	Data Analysis section updated	SAP details added; SAS® to be used in place of SPSS
8.	21.05.2021	Section 13	Reference number 2: Cresemba LPD	The Local Product Document has been revised

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	*November 2020*
Start of data collection	*August 2021*
End of data collection	*February 2022*
Study progress report 1	*November 2021*
Recruitment feasibility analyses and population size assessment	*November 2021*
Registration in the EU PAS register	*October 2020*
Final study report	*December 2022*

7. RATIONALE AND BACKGROUND

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the *DCGI.*

The burden of invasive fungal infections (IFIs) is increasing due to an exponential increase in the pool of individuals subject to classical as well as non-classical risk factors. Although, Invasive Candida Infections (ICIs) form the bulk of IFIs, invasive mould infections (IMIs) are steadily on the rise. A significant trend has been the higher incidence of IMIs in patients with non-classical risk factors. In India the incidence of IFI is significantly higher than what was described elswere…… In a study published in India in 2019, the incidence of IMIs in ICU was reported as 9.5 cases/1000 admissions.[1]The major unmet needs in the management of IMIs are very high mortality/morbidity, difficulty in diagnosis leading to missed diagnosis as well as misdiagnosis and reduced tolerability to current pharmacological agents. The current recommended first line agents are voriconazole for Invasive Aspergillosis (IA) and Amphotericin B (lipid formulations) for Invasive Mucormycosis (IM). The limitations of voriconazole are adverse drug reactions (ADRs), drug-drug interactions (DDIs) and possible accumulation of cyclodextrin with the intravenous formulation in patients with renal insufficiency Lipid formulations of Amphotericin B use is limited by nephrotoxicity (albeit lesser than conventional formulations), infusion related reactions and unavailability of the option to switch from intravenous to oral therapy. Considering the unmet medical needs, isavuconazole, a broad-spectrum azole covering both *Aspergillus spp.* and *Mucorales spp.*, is an important addition to the armamentarium.

Clinical efficacy and safety[2]

Treatment of invasive aspergillosis

The safety and efficacy of isavuconazole for the treatment of patients with invasive aspergillosis was evaluated in a double-blind, active-controlled clinical study in 516 patients with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi. 29 patients from India were recruited. In the intent-to-treat (ITT) population, 258 patients received isavuconazole and 258 patients received voriconazole. CRESEMBA was

administered intravenously (equivalent to 200 mg isavuconazole) every 8 hours for the first 48 hours, followed by once-daily intravenous or oral treatment (equivalent to 200 mg isavuconazole). The protocol-defined maximum treatment duration was 84 days. Median treatment duration was 45 days. The overall response at end-of-treatment (EOT) in the myITT population (patients with proven and probable invasive aspergillosis based on cytology, histology, culture or galactomannan testing) was assessed by an independent blinded Data Review Committee. The myITT population comprised 123 patients receiving isavuconazole and 108 patients receiving voriconazole. The overall response in this population was n = 43 (35%) for isavuconazole and n = 42 (38.9%) for voriconazole. The adjusted treatment difference (voriconazole−isavuconazole) was 4.0 (95% confidence interval: −7.9; 15.9). The all-cause mortality at Day 42 in this population was 18.7% for isavuconazole and 22.2% for voriconazole. The adjusted treatment difference (isavuconazole−voriconazole) was −2.7% (95 % confidence interval: −12.9; 7.5). Proportions of patients with treatment-emergent adverse events by system organ class were similar overall. However, isavuconazole-treated patients had a lower frequency of hepatobiliary disorders (23 [9%] *vs* 42 [16%]; p=0·016), eye disorders (39 [15%] *vs* 69 [27%]; p=0·002), and skin or subcutaneous tissue disorders (86 [33%] *vs* 110 [42%]; p=0·037). Drug-related adverse events were reported in 109 (42%) patients receiving isavuconazole and 155 (60%) receiving voriconazole (p<0·001). Isavuconazole was non-inferior to voriconazole for the primary treatment of suspected invasive mould disease. Isavuconazole was well tolerated compared with voriconazole, with fewer study-drug-related adverse events.

Treatment of mucormycosis

In an open-label non-controlled study, 37 patients with proven or probable mucormycosis received isavuconazole at the same dose regimen as that used to treat invasive aspergillosis. 5 patients were recruited from India for the study. Median treatment duration was 84 days for the overall mucormycosis patient population, and 102 days for the 21 patients not previously treated for mucormycosis. For patients with probable or proven mucormycosis as defined by the independent Data Review Committee (DRC), all-cause mortality at Day 84 was 43.2% (16/37) for the overall patient population, 42.9% (9/21) for mucormycosis patients receiving isavuconazole as primary treatment, and 43.8% (7/16) for mucormycosis patients receiving isavuconazole who were refractory to, or intolerant of, prior antifungal therapy (mainly amphotericin B-based treatments). The DRC-assessed overall success rate at EOT was 11/35 (31.4%), with 5 patients considered completely cured and 6 patients partially cured. A stable response was observed in an additional 10/35 patients (28.6%). In 9 patients with mucormycosis due to *Rhizopus* spp., 4 patients showed a favourable response to isavuconazole. In 5 patients with mucormycosis due to *Rhizomucor* spp., no favourable responses were observed. The clinical experience in other species is very limited (*Lichtheimia* spp. n=2, *Cunninghamella* spp. n=1, *Actinomucor* elegans n=1). Overall, the adverse events reported in patients with mucormycosis were similar in distribution to those reported in the SECURE invasive aspergillosis trial. Isavuconazole showed activity against mucormycosis with efficacy similar to amphotericin B.

The overall benefit-risk profile for Isavuconazole (Cresemba) in patients with IA and IM is positive.

8. RESEARCH QUESTION AND OBJECTIVES

This study objective is to provide additional data on clinical outcomes of patients with diagnosis of IMI (IA and IM) treated with isavuconazole (Cresemba) as part of the standard of care in India. A case series of patients treated with Isavuconazole (Cresemba) (post approval) for Invasive Mould Infections (Invasive Aspergillosis, Invasive Mucormycosis) will be evaluated during a period of two years.

9. RESEARCH METHODS

9.1. Study design

This is a single-arm, multi-center, observational study to describe a case series of patients with invasive aspergillosis or invasive mucormycosis treated with Cresemba as per the clinical judgement of the prescriber,

as per routine clinical practice conditions in India and in accordance with the labelling information as per the local product document (LPD) for Cresemba. All reasonable efforts will be made to collect data from about 70 patients (about 50 IA and about 20 patients of IM) on IV and/or oral formulations.
The diagnostic protocol and treatment would be as per the standard of care and per the judgement of the treating physician.

9.2. Setting

This study is performed in accordance with routine clinical practice as per regulatory requirement.
Data will be collected from patients initiated on Cresemba fulfilling the inclusion criteria, continuously up to the maximum planned number, or on completion of the 2-year enrollment period. Feasibility assessment of the recruitment of the proposed population size among IA and IM will be carried out after one year of recruitment.

Data from patients identified by the investigator will be collected from available clinical records. Secondary data collection will be performed using a predeveloped data collection form. Data from the patient will be collected at the following time points : admission, diagnosis, one week, two weeks, four weeks and six weeks of treatment with Cresemba. It may not be possible to collect data up to the six weeks time point if the patient is discharged/released from the hospital, lack of tracking /follow-up or in-hospital death.

9.2.1 Inclusion criteria

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

1. Patients 18 years or older

2. Patients with diagnosis of invasive aspergillosis/invasive mucormycosis meeting the criteria for proven, probable or possible invasive mould disease as per the judgement of the treating physician and must have received Cresemba for at least 48h .

9.2.2 Exclusion criteria

There are no other exclusion criteria for this study.

9.3. Variables

The parameters that will be evaluated and captured in the CRF are diagnosis at admission, patient demographics, underlying co-morbidities, treatment history, duration of IV/oral therapy, concomitant medications, clinical characteristics, clinical outcomes, length of hospital stay, radiological findings, and microbiological/histopathological findings. Post initiation of therapy, clinical response will be recorded for evaluation against the following time-points: end of 7 days, 14 days, 4 weeks and 6 weeks. Identified adverse events will be reported following the requirements established below in section 11.

9.4. Data sources

Data will be collected from the patient charts/electronic health records, at time of therapy initiation, and at week 1, 2, 4 and 6 or until lost patient tracking, death or what happened first. The data collected will be recorded in the case report forms (CRFs) for further evaluation.

9.5. Study size

The study will include about 50 patients for invasive aspergillosis and 20 for invasive mucormycosis. All reasonable efforts will be taken to collect data from the targeted number of patients in a period of two years from the protocol initiation.

9.6. Schedule of Activities

The Schedule of Activities table provides an overview of the protocol visits and procedures.

Visit Identifier	Visit 1 (Day 0)	Visit 2 (Day 7)	Visit 3 (Day 14)	Visit 4 (4 weeks)	Visit 5 (6 weeks)
Inclusion Criteria	x				
Data Privacy Consent[a]	x				
Demographics	x				
Medical History	x				
Physical examination and vital signs	x	x	x	x	x
Diagnosis details	x				
Treatment	x	x	x	x	x
Clinical Outcomes (Improvement in symptoms)		x	x	x	x
Radiological assessment (Not mandatory)	x	x	x	x	x
Mycological assessment (Not mandatory)	x	x	x	x	x
Serious and non-serious adverse events	x	x	x	x	x
Concomitant medications	x	x	x	x	x
All-cause mortality		x	x	x	x
[a]Data privacy consent must be obtained prior to undergoing any study-specific procedures that are not considered standard of care.					

9.7. Data management

An electronic e-CRF will be used to abstract the details and InForm data management system will be used for data entry and management.

9.7.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF*[/DCT]* should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF*[/DCT]* is required and should be completed for each included patient. The completed original CRFs*[/DCTs]* 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*[/DCTs]* are securely stored at the study site in *[encrypted electronic and/or paper]* form and will be *[password protected or secured in a locked room]* 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*[/DCTs]* 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*[/DCTs]* must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs*[/DCTs]* are true. Any corrections to entries made in the CRFs*[/DCTs]* or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart/ electronic health records. In these cases, data collected on the CRFs*[/DCTs*] must match those charts.

9.7.2. 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, e.g., CRFs*[/DCTs]* and hospital records),all original signed data privacy consent forms copies of all CRFs*[/DCTs]*, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., 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 (e.g., 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 *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.

9.8. Data analysis

Descriptive statistics on the study population. Data will be analyzed using standard statistical methods: continuous variables will be described with means, standard deviations, medians [interquartile ranges (IQR)] and range. Categorical variables will be summarized by frequencies and percentages. Data analysis will be performed using the most recent version of SAS® at the time of final analysis.

IMI, for study report evaluation purposes will be defined based on:
1. EORTC-MSG criteria[3]
A "proven" IMI is defined by the presence of septate or aseptate hyphae in the biopsied sample from deep tissue or isolation of mould from sterile sites.
"Probable" IMI is defined based on the host factors, radiological findings and demonstration of the fungi or its components (by either culture or cytology or galactomannan).
"Possible" IMI is defined as cases with the appropriate host factors and with sufficient clinical evidence consistent with IFD but for which there was no mycological support.

2. Criteria proposed by Bulpa et al. in subjects with COPD admitted to the ICU[4],
3. Criteria proposed by Vandewoude et al. in non-COPD subjects admitted to the ICU[5]
4. Criteria for Critically ill patients with Invasive Aspergillosis[6].

Clinical Outcomes are defined as follows:

Complete response: Resolution of all signs and symptoms and radiographic abnormalities compared with baseline;

Partial response: Clinical and radiographic improvement compared with baseline;

No response: Not consistent with any of the categories mentioned above

Frequencies and percentages of the number of subjects corresponding to each of the above defined response categories will be summarized visit wise and their corresponding 95% exact confidence interval will be reported.

Mycological Outcomes are defined as follows:

Mycological cultivation is not mandatory as the study is a non-interventional study. However, if the investigator performed cultivation before and after administration of Cresemba for follow-up, the results will be abstracted and recorded. Assessment of mycological response will be determined according to the following definitions;

Eradication (documented or presumed): None of the baseline isolates are present in a repeat culture taken from the original site of cultivation (documented) or clinical response of cure or improvement precludes the availabiity of a specimen for culture (presumed).

Persistence (documented or presumed): Any baseline isolate is present in a repeat culture obtained from the original site of cultivation (documented) or culture data are not available for a subject with a clinical response of failure (presumed).

Indeterminate: The patient was lost to follow-up, died within 2 days after the first dose of Cresemba for any reason, test not carried out/inconclusive, drop-out or patient withdrawal.

Frequencies and percentages of the number of subjects corresponding to each of the above defined outcome categories (subject to availability and collection of data) will be summarized visit wise and their corresponding 95% exact confidence interval will be reported.

Classical risk factors as any of the following[1]:
(i) neutropenic subjects with absolute neutrophil count < 500 cells/µL
(ii) subjects on cytotoxic chemotherapy formalignancies;
(iii) immunosuppressive therapy for solid organ transplantation; and,
(iv) hematopoietic stem cell transplantation.
All the remaining conditions including diabetesmellitus, COPD, chronic liver and kidney diseases, influenza, sepsis, and glucocorticoid use > 0.3 mg/kg/day of prednisolone (or equivalent) for at least three weeks were taken as non-classic risk factors.

The analyses related to the above mentioned outcomes will be performed on all subjects who receive at least dose of study drug.

Safety events, *as reported per the reporting requirements (details provided in section 11) will be captured in the study report. Serious and non-serious adverse events with explicit attribution to Cresemba or any Pfizer drug that appear in the reviewed information and drug exposure events in the patient charts/electronic health records will be captured in the case report form and analysed.*
Safety data will be tabulated and listed according to Pfizer's standard reporting algorithms. Additional analyses may be done for safety endpoints if needed. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary.
All safety analyses will be performed according to Pfizer Data Standards on all subjects who receive at least one dose of study drug.

9.9. Quality control

The CRO contracted by the Sponsor will conduct a study center visit to verify the qualifications of the Investigator, inspect the facilities and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.
All aspects of the study will be carefully monitored with respect to SOPs for compliance with applicable government regulations. The study monitor will be an authorized individual designated by the Sponsor. The study monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the PI.
Frequent communication between the study site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's medical monitor may review safety information as it becomes available throughout the study.
The Investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the clinical study for each study participant. All information recorded on the CRFs for this clinical study must be consistent with the subject's source documentation.
The CRO will perform selective audits and that adherence to the protocol, SOPs, GCP guidelines and national laws will be checked.

9.10. Limitations of the research methods

Data collection will reflect routine clinical practice rather than mandatory assessments at prespecified time points, which may have an impact on the amount of data and its interpretation. Also, confirmatory result can not be conclued because it is a open-label, single arm study without control group.

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 and/or paper* form and will be *password protected or secured in a locked room* to ensure that only authorized study staff have access. 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, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. 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 clinical study agreement 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..

10.3. Patient withdrawal

Not applicable.

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., data privacy consent forms) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

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 Good Pharmacoepidemiology Practices (GPP) published by The International Society for Pharmacoepidemiology (ISPE).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/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 adverse events (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 a healthcare provider 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 case report form 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 the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.
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

A study progress report will be submitted to the DCGI after a year of enrolment of patients.

In the event of any prohibition or restriction imposed (e.g., 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.

The data will also be published subsequently.

13. REFERENCES

1. Chakrabarti A, et al. Epidemiology and clinical outcomes of invasive mould infections in Indian intensive care units (FISF study). Journal of Critical Care.2019; 51: 64–70
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3. De Pauw B, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious DiseasesMycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813–21.
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14. LIST OF TABLES

Not Applicable

15. LIST OF FIGURES

Not applicable

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

None

ANNEX 3. ADDITIONAL INFORMATION

Not applicable