NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	A non-comparative, multicenter observational study: Isavuconazole (Cresemba) in Invasive Mould Infections (Invasive Aspergillosis, Invasive Mucormycosis) in India
Protocol number	C3791010
Version identifier of the final study report	1.0
Date	25thNovember 2022
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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1. ABSTRACT (STAND-ALONE DOCUMENT)

Title: A non-comparative, multicenter observational study: Isavuconazole (Cresemba) in Invasive Mould Infections (Invasive Aspergillosis, Invasive Mucormycosis) in India.

Date: *DD Month YYYY*

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Keywords: Non-Interventional, multicenter, Isavuconazole, Invasive Mould Infections, India

Rationale and background: 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. In India the incidence of IFI is significantly higher than what was described elsewhere. The current recommended first line agents are voriconazole for Invasive Aspergillosis (IA) and Amphotericin B (lipid formulations) for Invasive Mucormycosis (IM) but both have some limitations. Considering the unmet medical needs, Isavuconazole, a broad-spectrum azole covering both Aspergillus spp. and Mucorales spp., is an important addition to the armamentarium. Thus, this study was conducted to provide additional safety and effectiveness data during standard of care treatment.

The overall benefit-risk profile for Isavuconazole (Cresemba) in patients with IA and IM is positive. This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was a commitment to the Drug Controller General of India (DCGI).

Research question and objectives: This study was carried out to evaluate a case series of patients treated with Isavuconazole (Cresemba) (post approval) for Invasive Mould Infections (IMI) (IA and IM) in India during a period of two years (post protocol approval).

The study objective was 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.

Study design: This was a single-arm, multicenter, observational study to describe a case series of patients with IA and IM treated with Cresemba as per the clinical judgement of the prescriber, in accordance with the label instructions.

Setting: This study was performed in accordance with routine clinical practice as per regulatory requirement. Data was collected from patients initiated on Cresemba fulfilling the inclusion criteria, continuously up to the maximum planned number, or on completion of the 2-year enrolment period. Feasibility assessment of the recruitment of the proposed population size among IA and IM was carried out after one year of recruitment. Data from patients identified by the investigator was collected from available clinical records. Secondary data collection was performed using a predeveloped data collection form.

Subjects and study size, including dropouts: The study enrolled patients of age 18 years or older with diagnosis of IA/IM who met the criteria for proven, probable or possible invasive mould disease as per the judgement of the treating physician and had received Cresemba for at least 48h. The target was to collect data from about 70 patients (about 50 with IA and about 20 with IM) on intravenous (IV) and/or oral formulations.

Variables and data sources: The parameters like 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 were evaluated and captured in the case report form (CRF).

Results: A total of 70 patients (48 with IA, 20 with IM and 2 with both IA & IM) were screened and evaluated in this study. Of 70 patients in treatment phase, 27 (38.6%) patients completed the study and 43 (61.4%) patients discontinued from the study. The most common reason for discontinuation was death (41 (58.6%) patients), and the primary cause of death was COVID-19 pneumonia (31.4%) followed by septic shock (11.4%), multiple organ dysfunction syndrome (4.3%) and COVID-19, multi-organ disorder, rhinocerebral mucormycosis (2.9 % each). Secondary cause of death was recorded for 5.7% patients due to sinusitis aspergillus, sinusitis fungal, rhinocerebral mucormycosis, sepsis and multiorgan disorder.

All the patients were Asian (100.0%) with non-Hispanic/Latino (100.0%) ethnicity. Majority of the patients were male (74.3%), with median age of 61.5 years, ranging from 26.0 to 78.0 years.

Overall, clinical outcome was reported in total of 41/70 (58.6%) patients and was missing for 29/70 (41.4%) patients. Complete response was observed in 8/41 (19.5%) evaluable patients, of which 6/41 (14.6%) were in the IA group and 2/41 (4.9%) in the IM group and none out of 2 patients in the mixed infection (IA + IM) group. Partial response was observed in 29/41 (70.7%) evaluable patients of which 18/41 (43.9%) were in IA group, 1/41 (2.4%) in IM group and 1/2 (50.0%) in the mixed infection (IA + IM) group. No response was observed in 4/41 (9.8%) patients, which was only in the IA group.

Overall, mycological outcome was observed for total 4/70 (5.7 %) patients and was missing for 66/70 (94.3%) patients. Eradication was observed in 3/4 (75%) and persistence for 1/4 (25%) evaluable patients, only from the IA group. The observed radiological results were abnormal for 8/14 (57.1%) patients on Day 7, for 4/7 (57.1%) patients on Day 14, and 2/3 (66.7%) patients by Week 4 all from IA group.

Discussion:

Overall, complete response was observed in 19.5% evaluable patients, mycological outcome of eradication for 75% evaluable patients only from the IA group. Observed radiological outcome was abnormal for 57.1% patients on Day 7, 57.1% patients on Day 14, and 66.7% patients by Week 4, and all patients were only from the IA group.

Total number of deaths during the study was 41 (58.6%), which were majorly COVID-19 related. No treatment related adverse drug reactions (ADR), serious ADR or ADRs leading to treatment discontinuation were reported. Overall, isavuconazole was safe and well tolerated in this study.

Considering the nature of the study being observational, there were insufficient data to observe the trend at post-baseline visits.

Names and affiliations of principal investigators:

Dr Prithwijit Kundu, Medical Advisor, HBU, Pfizer, BKC, Mumbai

Dr Akshata Mane, Medical Lead, HBU, Pfizer, BKC, Mumbai

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reactions
AE	Adverse Events
AUC	Area Under Curve
BMI	Body Mass Index
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
DBP	Diastolic Blood Pressure
DCGI	Drug Controller General of India
DDI	Drug-drug Interaction
DRC	Data Review Committee
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
FSFV	first subject first visit
GCP	Good Clinical Practice
GM	Galactomannan
GPP	Good Pharmacoepidemiology Practices
IA	Invasive Aspergillosis
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	Invasive Candida Infection
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFI	Invasive Fungal Infections
IM	Invasive Mucormycosis

IMI	Invasive Mould Infections
IQR	Interquartile Ranges
IRB	Institutional Review Board
ISPE	The International Society for Pharmacoepidemiology
ITT	Intent-to-treat
IV	Intravenous/Intravenously
LAR	Legally Accepted Representative
LPD	Local Product Document
LSLV	last subject last visit
PASS	Post-Authorization Safety
PE	Physical examination
SADR	Serious Adverse Drug Reaction
SAP	Statistical Action Plan
SAS	Safety analysis set
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOP	Standard Operating Procedure

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

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. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
Dr Prithwijit Kundu Medical Advisor, HBU Pfizer, BKC, Mumbai	Principal Investigator

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Completion of feasibility assessment	November 2020	November 2020	
<Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol> The IEC/IRB approval dates for the protocol and any amendments is provided in Appendix 3.2.	November 2021	November 2021	
Start of data collection	October 2021	January 2022	
End of data collection	April 2022	May 2022	
Registration in the EU PAS register.	October 2020		
Study progress report I	November 2021		
Recruitment feasibility analyses and population size assessment	November 2021		
Final report of study results	December 2022		

6. RATIONALE AND BACKGROUND

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 elsewhere. In a study published in India in 2019, the incidence of IMIs in intensive care unit (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 IA 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 IV (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 IA. 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.

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

7. RESEARCH QUESTION AND OBJECTIVES

This study was carried out to evaluate a case series of patients treated with Isavuconazole (Cresemba) (post approval) for IMI (IA and IM) in India during a period of two years (post protocol approval).

The study objective was 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.

8. AMENDMENTS AND UPDATES

Table 1: Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1.	14 Oct 2020	Substantial	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 Oct 2020	Substantial	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 Oct 2020	Administrative	Section 13	Reference number 2: Cresemba LPD	The Local Product Document has been revised
4.	21 May 2021	Substantial	Section 9.4	Data collection at 1 week added	This milestone of data collection was missing
5.	21 May 2021	Administrative	Section 9.6	Schedule of Activities section added	The section was missing and needed incorporation

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
					in the protocol
6.	21 May 2021	Substantial	Section 9.7	Data management system changed from INES to InForm	InForm is the current data management system to be utilized
7.	21 May 2021	Substantial	Section 9.8	Data Analysis section updated	SAP details added; SAS® to be used in place of SPSS
8.	21 May 2021	Administrative	Section 13	Reference number 1: Cresemba LPD	The Local Product Document has been revised

9. RESEARCH METHODS

A detailed description of the research methods of study is presented in the following sections and in the protocol (Appendix 2).

9.1. Study design

This was a single-arm, multicenter, 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.[1] The target was to collect data from about 70 patients (about 50 patients of IA and about 20 patients of IM) on IV and/or oral formulations.

The diagnostic protocol and treatment were to be as per the standard of care and per the judgement of the treating physician.

9.2. Setting

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

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

9.3. Subjects

The study enrolled patients of age 18 years or older with diagnosis of IA/IM 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.

There are no exclusion criteria for this study.

9.4. Variables

The parameters like 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 were evaluated and captured in the case report forms (CRFs). Post initiation of therapy, clinical response was recorded for evaluation against the following time-points: end of 7 days, 14 days, 4 weeks and 6 weeks. Identified ADRs were reported as per the requirements of protocol.

9.5. Data sources and measurement

Data was 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 was recorded in the CRFs for further evaluation.

All data relating to the study were recorded in the CRF. This CRF was developed to record the data requested by the protocol. The Investigator ensured the accuracy, completeness, and timeliness of the data recorded in the CRFs.

At the beginning of the study, a site master file was established at the investigational site. The Investigator maintained the study documents as specified in the ICH Guideline of good clinical practice (GCP) and as required by the applicable regulatory requirements. The Investigator took measures to prevent accidental or premature destruction of these documents.

Prior to the start of the study, a signature and delegation list were completed showing the signatures and hand-written initials of all who were authorized to enter data or make corrections in the CRF.

The Investigator permitted study-related monitoring, audits, and regulatory inspection, providing direct access to source data/documents.

9.6. Bias

Not Applicable

9.7. Study Size

The study was planned to include about 50 patients for IA and 20 for IM. All reasonable efforts were given to collect data from the targeted number of patients in a period of two years from the protocol initiation.

9.8. Data transformation

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

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP) (Appendix 4).

9.9. Statistical methods

Detailed methodology for summarization and statistical analyses of the data collected in this study was documented in a SAP (Appendix 4).

9.9.1. Main summary measures

- Main summary measures include n, mean, standard deviation, median [interquartile ranges
- (IQR)] and range, frequencies and percentages.

9.9.2. Main statistical methods

- Descriptive statistics (n, mean, standard deviation, median [interquartile ranges (IQR)] and range [Min – Max]) are presented in the summary tables for continuous data of the study population. The Mean and Median up to one more decimal place from the original value, standard deviation (SD) two decimal places from the original value and Min – Max as an original value are presented.
- For categorical data, frequency counts (n) and percentage (%) are presented. The percentages are presented up to 1 decimal place.
- No hypothesis testing was performed for this study. The two-sided 95% confidence interval for the proportion was provided using the exact method. All statistical analysis were performed using the most recent version of SAS® at the time of final analysis.
- **Safety analysis set (SAS)**
  - All subjects who receive at least one dose of Isavuconazole (Cresemba) in the study were included in SAS.
  - All dosed subjects were included in safety, and those with evaluable data included for the corresponding outcome.

9.9.3. Missing values

No imputation for missing values was to be performed.

9.9.4. Sensitivity analyses

None

9.9.5. Amendments to the statistical analysis plan

Statistical analysis plan was updated to version 2.0 to accommodate minor changes as per protocol in Section 7.2.6.2 (Updated AEs to ADRs and SAEs to SADRs) and section 7.2.6.6 (Updated normal ranges for respiratory rate). These changes did not have impact on the analysis plan.

There were some changes made to planned statistical analysis as mentioned below:

- Additional analysis was done for the patients who died during the study due to Coronavirus disease 2019 (COVID-19) infection. As part of mortality/death analysis, the outcome measurements (Clinical, Mycological and Radiological) were additionally summarized for patients who died due to COVID-19 during the study.
- Patients who had both IA & IM were grouped separately in the summaries to provide clarity on the overlapping response data. A patient was counted in either one of the following primary diagnosis summary groups: IA, IM and both IA & IM.
- For outcome measurements, overall response and missing responses were additionally added considering the nature of the study and data availability. The impact of missing data was substantial in this study and all clinical, mycological and radiological measurements were summarized with number of missing responses at each corresponding visit. Overall response summary was provided for clinical and mycological outcomes. The best outcome of each patient across post-baseline visits was considered as an overall response. For clinical outcomes, Complete Response was considered as the best outcome followed by Partial Response and No response. For mycological outcomes, Eradication was considered as the best outcome followed by Persistence, Indeterminate and Not Done.
- The mycological outcomes were presented as Detected/Not Detected at baseline visit and Eradication/ Persistence corresponding to the pathogen test result at post-baseline visits.

9.10. Quality control

The investigator and the study monitor (or designee) were to ensure that the study staff receives appropriate training and that any information relevant to the conduct of this study was forwarded to other staff as appropriate.

Quality assurance and quality control systems were implemented and maintained using written standard operating procedures (SOPs) to ensure that the study was conducted, and data were generated, documented (recorded) and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

Quality control was applied to each stage of data handling to ensure that all data were reliable and had been processed correctly.

This Clinical Study Report has been subject to quality control processes reviewed by the sponsor’s own independent quality assurance group.

9.11. Protection of human subjects

Subject information and consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer was not required.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by IRB(s) and/or IEC(s) for each site participating in the study.

Ethical conduct of the study

The study was 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).

10. RESULTS

10.1. Participants

For this current study, patients on treatment with Isavuconazole (Cresemba) for IMIs were screened and enrolled across 2 centers in India. A total of 70 patients (48 patients with IA, 20 patients with IM and 2 with both invasive aspergillosis and mucormycosis (IA & IM) were screened, enrolled and evaluated/observed in this study. (Table 2)

The detail of individual patient's evaluation groups is presented in Table 16.2.1.1.1.

Table 2: Patients Evaluation Groups - All Patients

	Invasive Aspergillosis (N=48)	Invasive Mucormycosis (N=20)	Invasive Aspergillosis and Mucormycosis (N=2)	Total (N=70)
	n (%)	n (%)	n (%)	n (%)
Screened				70
Screened Failure				0
Treated	48 (100.0)	20 (100.0)	2 (100.0)	70 (100.0)

Patients with only one primary diagnosis are counted under their respective groups. Patients with both primary diagnoses are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All patients are counted once under 'Total'.

	Invasive Aspergillosis (N=48)	Invasive Mucormycosis (N=20)	Invasive Aspergillosis and Mucormycosis (N=2)	Total (N=70)
	n (%)	n (%)	n (%)	n (%)

Reference: Table 14.1.1.1

Median time since primary diagnosis was 1 day for patients with aspergillus infection (range 1 to 48), 3 days for patients with mucormycosis (range 1 to 34) and 1 day for patients with invasive aspergillus and mucormycosis (range 1 day). (Table 3)

The detail of individual patient's primary diagnosis and durations is presented in Table 16.2.4.2.2.

Table 3: Primary Diagnosis and Durations - Safety Analysis Set

Total (N=70)	Aspergillus infection	Mucormycosis	Invasive Aspergillosis and Mucormycosis
Number of Patients	48	20	2
Time since primary diagnosis[a] (Days)			
Mean (SD)	2.6 (7.15)	7.1 (8.25)	1.0 (0.00)
Median (Min,Max)	1.0 (1.0, 48.0)	3.0 (1.0, 34.0)	1.0 (1.0, 1.0)
Unspecified (N)[b]		1	1

Patients with only one primary diagnosis are counted under their respective groups. Patients with both primary diagnoses are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All patients are counted once under 'Total'.
a. Time since primary diagnosis = (Date of Visit 1/ Day 0 - Date of Primary Diagnosis) + 1
b. For Patient ID C3791010 1002 10021025, date of primary diagnosis was incomplete, so the duration was not calculated.
MedDRA v25.0 coding dictionary applied.

Reference: Table 14.1.3.2

Of 70 patients enrolled in the treatment phase, 27 (38.6%) patients completed the study, and 43 (61.4%) patients discontinued the study. The most common reason for discontinuation was death in 41 (58.6%) patients. (Table 4).

The detail of individual patient's disposition events is presented in Table 16.2.1.2.2.

Table 4: Disposition Events Summary - Safety Analysis Set

	Invasive Aspergillosis (N=48)	Invasive Mucormycosis (N=20)	Invasive Aspergillosis and Mucormycosis (N=2)	Total (N=70)
Number (%) of Patients	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Disposition phase: Screening				
Patients Entered:	48 (100.0)	20 (100.0)	2 (100.0)	70 (100.0)
Discontinued	0	0	0	0
Completed	48 (100.0)	20 (100.0)	2 (100.0)	70 (100.0)
Disposition phase: Treatment				
Patients Entered:	48 (100.0)	20 (100.0)	2 (100.0)	70 (100.0)
Discontinued	35 (72.9)	6 (30.0)	2 (100.0)	43 (61.4)
Reason for discontinuation				
Death	34 (70.8)	5 (25.0)	2 (100.0)	41 (58.6)
Other	1 (2.1)	1 (5.0)	0	2 (2.9)
Completed	13 (27.1)	14 (70.0)	0	27 (38.6)

Patients with only one primary diagnosis are counted under their respective groups. Patients with both primary diagnosis are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All patients are counted once under 'Total'.

Source: Table 14.1.1.2.1

10.2. Descriptive data

The demographic and baseline characteristics were generally comparable in both evaluation groups in the SAS. All the patients were Asian (100.0%) with non-Hispanic/Latino (100.0%) ethnicity. Majority of the patients were male (74.3%), with a median age of 61.5 years, ranging from 26.0 to 78.0 years. (Table 5)

The detail of individual patient's demographic characteristics is presented in Table 16.2.4.1.1.

Table 5: Demographic and Baseline Characteristics - Safety Analysis Set

	Invasive Aspergillosis (N=48)	Invasive Mucormycosis (N=20)	Invasive Aspergillosis and Mucormycosis (N=2)	Total (N=70)
Age (Years), n[a] (%)				
<65	28 (58.3)	15 (75.0)	1 (50.0)	44 (62.9)
>=65	20 (41.7)	5 (25.0)	1 (50.0)	26 (37.1)
Mean (SD)	59.4 (11.67)	54.5 (10.91)	57.0 (19.80)	57.9 (11.67)
Median (Min, Max)	63.0 (26.0, 78.0)	57.0 (33.0, 71.0)	57.0 (43.0, 71.0)	61.5 (26.0, 78.0)
(Q1,Q3)	(53.5, 68.5)	(44.0, 64.0)	(43.0, 71.0)	(51.0, 67.0)
Sex, n (%)				
Male	36 (75.0)	15 (75.0)	1 (50.0)	52 (74.3)
Female	12 (25.0)	5 (25.0)	1 (50.0)	18 (25.7)
Race, n (%)				
Asian	48 (100.0)	20 (100.0)	2 (100.0)	70 (100.0)
Not reported	0	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	48 (100.0)	20 (100.0)	2 (100.0)	70 (100.0)
Not reported	0	0	0	0
Body mass index (BMI) (kg/m^2)				
n[a]	45	10	2	57
Mean(SD)	23.1 (3.86)	25.1 (3.75)	21.0 (2.25)	23.4 (3.85)
Median (Min, Max)	22.6 (19.1, 44.4)	25.1 (19.0, 33.2)	21.0 (19.4, 22.6)	22.7 (19.0, 44.4)
(Q1,Q3)	(21.9, 23.4)	(23.7, 26.0)	(19.4, 22.6)	(21.9, 24.7)
Height (cm)				
n[a]	45	10	2	57

	Invasive Aspergillosis (N=48)	Invasive Mucormycosis (N=20)	Invasive Aspergillosis and Mucormycosis (N=2)	Total (N=70)
Mean(SD)	165.0 (7.72)	166.5 (4.82)	158.8 (8.98)	165.0 (7.33)
Median (Min, Max)	165.1 (152.4, 193.0)	167.8 (156.0, 172.0)	158.8 (152.4, 165.1)	165.1 (152.4, 193.0)
(Q1,Q3)	(160.0, 167.6)	(164.0, 170.0)	(152.4, 165.1)	(161.0, 167.6)
Weight (kg)				
n[a]	48	18	2	68
Mean(SD)	63.4 (10.98)	66.9 (8.31)	53.3 (11.67)	64.0 (10.49)
Median (Min, Max)	63.4 (45.0, 115.0)	65.6 (55.0, 87.0)	53.3 (45.0, 61.5)	63.8 (45.0, 115.0)
(Q1,Q3)	(59.2, 69.2)	(60.0, 70.2)	(45.0, 61.5)	(59.2, 70.0)

Age at Screening (years) = (date of screening - date of birth + 1)/365.25
The denominator to calculate percentages is N, the number of patients in the safety analysis set within each cohort.
a. n is the number of patients with non-missing age.
Patients with only one primary diagnosis are counted under their respective groups. Patients with both primary diagnoses are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All patients are counted once under 'Total'.

Source: Table 14.1.2.1

Commonly observed medical conditions at the time of enrollment were diabetes mellitus in 41 (58.6 %) patients followed by hypertension in 34 (48.6%) patients. As this is an observational study, COVID-19 testing was not done at screening and data for subjects with COVID-19 infection at the time of enrollment is not available. Summary of pre-specified significant medical history for SAS and individual patient's pre-specified significant medical history has been presented in Table 14.1.3.1 and Table 16.2.4.2.1 respectively.

10.3. Outcome data

The data sets planned for outcome analysis in this study are defined in Section 9.9.2.

All the 70 patients enrolled in the study were included in SAS. Data for clinical, mycological and radiological outcome were presented separately for all 70 patients and additionally for 24 patients who died due to COVID-19.

As part of mortality/death analysis, the outcome measurements (Clinical, Mycological and Radiological) were additionally summarized for patients who died due to COVID-19 (N=24) during the study. The objective was to analyze the outcome measurement trends for clinical, mycological, and radiological measurements additionally for patients who died due to COVID-19 related infections and determine whether this had any impact on the outcome measurement analysis.

10.4. Main results

10.4.1. Clinical outcomes

Clinical outcomes were recorded at Days 7, and 14, and weeks 4 and 6. The results were summarized by visit, per primary diagnosis group and for total patients for safety analysis set and additionally, for patients who died due to COVID-19.

10.4.1.1. Clinical Outcomes by Visit - Safety Analysis Set

Clinical outcome was not available for all 70 patients at the assessment periods (Day 7, Day 14, Week 4 and Week 6) due to significant number of missing data. Clinical response was evaluated taking the number of available patient level data as the denominator and not the total number of patients (Table 6).

Overall response was available for 41 patients and there were missing data of 29 patients. In IA patients complete, partial and no response was seen in 6 (21.4%), 18 (64.3%) and 4 (14.3%) respectively. In IM patients complete, partial and no response was seen in 2 (16.7%), 10 (83.3%) and 0 respectively. In the mixed infection group (IA+IM), complete, partial and no response was seen in 0, 1 (100%) and 0 respectively.

On Day 7, clinical response data for IA was available for 27 patients and there was missing data of 21 patients. In those patients complete, partial and no response was seen in 6 (22.2%), 17 (63%) and 4 (14.8%) respectively. In IM patients, clinical response data was available for 12 patients and there was missing data of 8 patients. In those patients complete, partial and no response was seen in 0, 12 (100%) and 0 respectively. In the mixed infection group (IA+IM), data was available for 1 patient and was unavailable for the other. The clinical response was complete, partial and no response was seen in 0, 1 (100%) and 0 respectively.

On Day 14, clinical response data for IA was available for 14 patients and there was missing data of 34 patients. In IA patients complete, partial and no response was seen in 4 (28.6%), 9 (64.3%) and 1 (7.1%) respectively. In IM patients, clinical response data was available for 10 patients and there was missing data of 10 patients. In those patients complete, partial and no response was seen in 0, 10 (100%) and 0 respectively. In the mixed infection group (IA+IM), no data was available.

On Week 4, clinical response data for IA was available for 5 patients and there was missing data of 43 patients. In those patients complete, partial and no response was seen in 1 (20%), 4 (80%) and 0 respectively. In IM patients, clinical response data was available for 4 patients and there was missing data of 16 patients. In those patients complete, partial and no response

was seen in 1 (25%), 3 (75%) and 0 respectively. In the mixed infection group (IA+IM), no data was available.

On Week 6, clinical response data for IA was unavailable. In IM patients, clinical response data was available for 1 patient and there was missing data of 19 patients. In this patient complete response was seen. In the mixed infection group (IA+IM), no data was available.

The detail of individual patient's clinical response by visit is presented in Table 16.2.6.1.

Table 6: Summary of Clinical Outcomes by Visit - Safety Analysis Set

Visit	Clinical Outcome	Invasive Aspergillosis (N=48)		Invasive Mucormycosis (N=20)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=70)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
Day 7	Complete Response	6 (22.2)	(8.6, 42.3)	0	-	0	-	6 (15.0)	(5.7, 29.8)
	Partial Response	17 (63.0)	(42.4, 80.6)	12 (100.0)	-	1 (100.0)	-	30 (75.0)	(58.8, 87.3)
	No Response	4 (14.8)	(4.2, 33.7)	0	-	0	-	4 (10.0)	(2.8, 23.7)
	Missing[b]	21	-	8	-	1	-	30	-
Day 14	Complete Response	4 (28.6)	(8.4, 58.1)	0	-	0	-	4 (16.7)	(4.7, 37.4)
	Partial Response	9 (64.3)	(35.1, 87.2)	10 (100.0)	-	0	-	19 (79.2)	(57.8, 92.9)
	No Response	1 (7.1)	(0.2, 33.9)	0	-	0	-	1 (4.2)	(0.1, 21.1)
	Missing[b]	34	-	10	-	2	-	46	-
Week 4	Complete Response	1 (20.0)	(0.5, 71.6)	1 (25.0)	(0.6, 80.6)	0	-	2 (22.2)	(2.8, 60.0)
	Partial Response	4 (80.0)	(28.4, 99.5)	3 (75.0)	(19.4, 99.4)	0	-	7 (77.8)	(40.0, 97.2)
	No Response	0	-	0	-	0	-	0	-
	Missing[b]	43	-	16	-	2	-	61	-
Week 6	Complete Response	0	-	1 (100.0)	-	0	-	1 (100.0)	-

Visit	Clinical Outcome	Invasive Aspergillosis (N=48)		Invasive Mucormycosis (N=20)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=70)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
	Partial Response	0	-	0	-	0	-	0	-
	No Response	0	-	0	-	0	-	0	-
	Missing[b]	48	-	19	-	2	-	69	-
Overall[c]	Complete Response	6 (21.4)	(8.3, 41.0)	2 (16.7)	(2.1, 48.4)	0	-	8 (19.5)	(8.8, 34.9)
	Partial Response	18 (64.3)	(44.1, 81.4)	10 (83.3)	(51.6, 97.9)	1 (100.0)	-	29 (70.7)	(54.5, 83.9)
	No Response	4 (14.3)	(4.0, 32.7)	0	-	0	-	4 (9.8)	(2.7, 23.1)
	Missing[b]	20	-	8	-	1	-	29	-

Participants with only one primary diagnosis are counted under their respective groups. Participants with both primary diagnosis are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All participants are counted once under 'Total'.
Percentages are based on participants who reported responses in the corresponding visit. For overall, percentages are based on participants who reported responses at any of the visits.
a. 95% exact confidence interval for the proportions is calculated using the Clopper-Pearson method.
b. Participants not reported/died/discontinued are counted under 'Missing' at the respective visits.
c. For overall, the best outcome of each participant across post-baseline visits are considered.

10.4.1.2. Clinical Outcomes based on patients died due to COVID-19 by Visit

The primary cause of death in 24 patients out of the total 70 was reported as due to COVID-19 in the study. The clinical response data for these 24 patients has been studied in detail.

Clinical outcome was not available for all 24 patients at the assessment periods (Day 7, Day 14, Week 4 and Week 6) due to significant number of missing data. Clinical response was evaluated taking the number of available patient level data as the denominator and not the total number of patients (Table 7).

Overall response was available for 16 patients and there were missing data of 8 patients. In IA patients complete, partial and no response was seen in 0, 12 (80%) and 3 (20%) respectively. In IM patients, no death was attributed to COVID-19 as the primary cause. In the mixed infection group (IA+IM), complete, partial and no response was seen in 0, 1 (100%) and 0 respectively. There was no data available for the other patient.

On Day 7, clinical response data for IA was available for 15 patients and there was missing data of 7 patients. In those patients complete, partial and no response was seen in 0, 12 (80%)

and 3 (20%) respectively. In IM patients, no death was attributed to COVID-19 as the primary cause. In the mixed infection group (IA+IM), complete, partial and no response was seen in 0, 1 (100%) and 0 respectively. There was no data available for the other patient.

On Day 14, clinical response data for IA was available for 7 patients and there was missing data of 15 patients. In IA patients complete, partial and no response was seen in 0, 6 (85.7%) and 1 (14.3%) respectively. In IM patients, no death was attributed to COVID-19 as the primary cause. No data was available for the mixed infection patients.

On Week 4, clinical response data for IA was available for 3 patients and there was missing data of 19 patients. In those patients complete, partial and no response was seen in 0, 3 (100%) and 0 respectively. In IM patients, no death was attributed to COVID-19 as the primary cause. No data was available for the mixed infection patients.

On Week 6, clinical response data for IA, IM and mixed infection was unavailable.

Table 7: Summary of Clinical Outcomes based on patients who died due to COVID-19 by Visit - Safety Analysis Set

Visit	Clinical Outcome	Invasive Aspergillosis (N=22)		Invasive Mucormycosis (N=0)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=24)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
Day 7	Complete Response	0	-	0	-	0	-	0	-
	Partial Response	12 (80.0)	(51.9, 95.7)	0	-	1 (100.0)	-	13 (81.3)	(54.4, 96.0)
	No Response	3 (20.0)	(4.3, 48.1)	0	-	0	-	3 (18.8)	(4.0, 45.6)
	Missing[b]	7	-	0	-	1	-	8	-
Day 14	Complete Response	0	-	0	-	0	-	0	-
	Partial Response	6 (85.7)	(42.1, 99.6)	0	-	0	-	6 (85.7)	(42.1, 99.6)
	No Response	1 (14.3)	(0.4, 57.9)	0	-	0	-	1 (14.3)	(0.4, 57.9)
	Missing[b]	15	-	0	-	2	-	17	-
Week 4	Complete Response	0	-	0	-	0	-	0	-

Visit	Clinical Outcome	Invasive Aspergillosis (N=22)		Invasive Mucormycosis (N=0)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=24)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
	Partial Response	3 (100.0)	-	0	-	0	-	3 (100.0)	-
	No Response	0	-	0	-	0	-	0	-
	Missing[b]	19	-	0	-	2	-	21	-
Week 6	Complete Response	0	-	0	-	0	-	0	-
	Partial Response	0	-	0	-	0	-	0	-
	No Response	0	-	0	-	0	-	0	-
	Missing[b]	22	-	0	-	2	-	24	-
Overall[c]	Complete Response	0	-	0	-	0	-	0	-
	Partial Response	12 (80.0)	(51.9, 95.7)	0	-	1 (100.0)	-	13 (81.3)	(54.4, 96.0)
	No Response	3 (20.0)	(4.3, 48.1)	0	-	0	-	3 (18.8)	(4.0, 45.6)
	Missing[b]	7	-	0	-	1	-	8	-

Participants with only one primary diagnosis are counted under their respective groups. Participants with both primary diagnosis are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All participants are counted once under 'Total'.
Percentages are based on participants who reported responses in the corresponding visit. For overall, percentages are based on participants who reported responses at any of the visits.
a. 95% exact confidence interval for the proportions is calculated using the Clopper-Pearson method.
b. Participants not reported/died/discontinued are counted under 'Missing' at the respective visits.
c. For overall, the best outcome of each participant across post-baseline visits are considered.

10.4.2. Mycological outcomes

Mycological findings were recorded at baseline, Day 7, and 14, and week 4. The results were summarized by visit, per primary diagnosis group and for total patients for safety analysis set and additionally, for patients who died due to COVID-19.

10.4.2.1. Mycological Outcomes by Visit - Safety Analysis Set

Mycological outcome was not available for all 70 patients at the assessment periods (Day 7, Day 14, Week 4 and Week 6) due to significant number of missing data. Response was evaluated taking the number of available patient level data as the denominator and not the total number of patients (Table 8).

Overall, mycological data was observed for 4 patients and was missing for 66 patients. In IA patients eradication and persistence was seen in 3 (75%) and 1 (25%) respectively. In IM and mixed infection patients, no data was available.

At baseline, mycological data for IA patients were available for 39 patients and was missing for 9 patients. In those patients detection, non-detection, indeterminate and not done were 32 (82.1%), 6 (15.4%), 1 (2.6%) and 0 respectively. In IM patients data was available for 3 patients and missing for 17 patients. In those patients, detection, non-detection, indeterminate and not done were 3 (100%), 0, 0 and 0 respectively. In the mixed infection patients 2/2 (100%) cases showed mycological detection.

On Day 7, mycological data for IA patients were available for 3 patients and was missing for 45 patients. In those patients eradication, persistence, indeterminate and not done were 2 (67.3%), 1 (33.3%), 0 and 0 respectively. No data was available for IM and mixed infection patients.

On Day 14, mycological data for IA patients were available for 2 patients and was missing for 46 patients. In those patients eradication, persistence, indeterminate and not done were 1 (50%), 1 (50%), 0 and 0 respectively. No data was available for IM and mixed infection patients.

On Week 4, mycological data for IA patients were available for 2 patients and was missing for 46 patients. In those patients eradication, persistence, indeterminate and not done were 1 (50%), 0, 0 and 1 (50%) respectively. No data was available for IM and mixed infection patients.

The details of individual patient's mycological outcome and pathogen by visit is presented in Table 16.2.6.2 and 16.2.6.3 respectively.

Table 8: Summary of Mycological Findings/Outcomes by Visit - Safety Analysis Set

Visit	Mycological Outcome	Invasive Aspergillosis (N=48)		Invasive Mucormycosis (N=20)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=70)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
Baseline	Detected	32 (82.1)	(66.5, 92.5)	3 (100.0)	-	2 (100.0)	-	37 (84.1)	(69.9, 93.4)
	Not Detected	6 (15.4)	(5.9, 30.5)	0	-	0	-	6 (13.6)	(5.2, 27.4)
	Indeterminate	1 (2.6)	(0.1, 13.5)	0	-	0	-	1 (2.3)	(0.1, 12.0)
	Not Done	0	-	0	-	0	-	0	-
	Missing[b]	9	-	17	-	0	-	26	-
Day 7	Eradication	2 (66.7)	(9.4, 99.2)	0	-	0	-	2 (66.7)	(9.4, 99.2)
	Persistence	1 (33.3)	(0.8, 90.6)	0	-	0	-	1 (33.3)	(0.8, 90.6)
	Indeterminate	0	-	0	-	0	-	0	-
	Not Done	0	-	0	-	0	-	0	-
	Missing[b]	45	-	20	-	2	-	67	-
Day 14	Eradication	1 (50.0)	(1.3, 98.7)	0	-	0	-	1 (50.0)	(1.3, 98.7)
	Persistence	1 (50.0)	(1.3, 98.7)	0	-	0	-	1 (50.0)	(1.3, 98.7)
	Indeterminate	0	-	0	-	0	-	0	-
	Not Done	0	-	0	-	0	-	0	-
	Missing[b]	46	-	20	-	2	-	68	-
Week 4	Eradication	1 (50.0)	(1.3, 98.7)	0	-	0	-	1 (50.0)	(1.3, 98.7)
	Persistence	0	-	0	-	0	-	0	-
	Indeterminate	0	-	0	-	0	-	0	-
	Not Done	1 (50.0)	(1.3, 98.7)	0	-	0	-	1 (50.0)	(1.3, 98.7)
	Missing[b]	46	-	20	-	2	-	68	-
Overall[c]	Eradication	3 (75.0)	(19.4, 99.4)	0	-	0	-	3 (75.0)	(19.4, 99.4)

Visit	Mycological Outcome	Invasive Aspergillosis (N=48)		Invasive Mucormycosis (N=20)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=70)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
	Persistence	1 (25.0)	(0.6, 80.6)	0	-	0	-	1 (25.0)	(0.6, 80.6)
	Indeterminate	0	-	0	-	0	-	0	-
	Not Done	0	-	0	-	0	-	0	-
	Missing[b]	44	-	20	-	2	-	66	-

Participants with only one primary diagnosis are counted under their respective groups. Participants with both primary diagnosis are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All participants are counted once under 'Total'.
Percentages are based on participants who reported responses in the corresponding visit. For overall, percentages are based on participants who reported responses at any of the visits.
a. 95% exact confidence interval for the proportions is calculated using the Clopper-Pearson method.
b. Participants not reported/died/discontinued are counted under 'Missing' at the respective visits.
c. For overall, the best outcome of each participant across post-baseline visits are considered.

10.4.2.2. Mycological Outcomes based on patients died due to COVID-19 by Visit

The primary cause of death in 24 patients out of the total 70 was reported as due to COVID-19 in the study. The mycological response data for these 24 patients has been studied in detail.

Overall, mycological data was observed for 2 patients and was missing for 22 patients. In IA patients eradication and persistence was seen in 1 (50%) and 1 (50%) respectively. In IM and mixed infection patients, no data was available.

On baseline, mycological data for IA patients were available for 17 patients and was missing for 5 patients. In those patients detection, non-detection, indeterminate and not done were 15 (88.2%), 2 (11.8%), 0 and 0 respectively. In IM patients data no death was attributed to COVID-19. In the mixed infection patients 2/2 (100%) cases showed mycological detection.

On Day 7, mycological data for IA patients were available for 1 patient and was missing for 21 patients. In those patients eradication, persistence, indeterminate and not done were 0, 1 (100%), 0 and 0 respectively. In IM patients data no death was attributed to COVID-19. No data was available for mixed infection patients.

On Day 14, mycological data for IA patients were available for 1 patient and was missing for 21 patients. In those patients eradication, persistence, indeterminate and not done were 0, 1

(100%), 0 and 0 respectively. In IM patients data no death was attributed to COVID-19. No data was available for mixed infection patients.

On Week 4, mycological data for IA patients were available for 1 patient and was missing for 21 patients. In those patients eradication, persistence, indeterminate and not done were 1 (100%), 0, 0 and 0 respectively. In IM patients data no death was attributed to COVID-19. No data was available for mixed infection patients.

Table 9: Summary of Mycological Findings/Outcomes based on patients who died due to COVID-19 by Visit - Safety Analysis Set

Visit	Mycological Outcome	Invasive Aspergillosis (N=22)		Invasive Mucormycosis (N=0)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=24)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
Baseline	Detected	15 (88.2)	(63.6, 98.5)	0	-	2 (100.0)	-	17 (89.5)	(66.9, 98.7)
	Not Detected	2 (11.8)	(1.5, 36.4)	0	-	0	-	2 (10.5)	(1.3, 33.1)
	Indeterminate	0	-	0	-	0	-	0	-
	Not Done	0	-	0	-	0	-	0	-
	Missing[b]	5	-	0	-	0	-	5	-
Day 7	Eradication	0	-	0	-	0	-	0	-
	Persistence	1 (100.0)	-	0	-	0	-	1 (100.0)	-
	Indeterminate	0	-	0	-	0	-	0	-
	Not Done	0	-	0	-	0	-	0	-
	Missing[b]	21	-	0	-	2	-	23	-
Day 14	Eradication	0	-	0	-	0	-	0	-
	Persistence	1 (100.0)	-	0	-	0	-	1 (100.0)	-
	Indeterminate	0	-	0	-	0	-	0	-
	Not Done	0	-	0	-	0	-	0	-
	Missing[b]	21	-	0	-	2	-	23	-
Week 4	Eradication	1 (100.0)	-	0	-	0	-	1 (100.0)	-
	Persistence	0	-	0	-	0	-	0	-

Visit	Mycological Outcome	Invasive Aspergillosis (N=22)		Invasive Mucormycosis (N=0)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=24)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
	Indeterminate	0	-	0	-	0	-	0	-
	Not Done	0	-	0	-	0	-	0	-
	Missing[b]	21	-	0	-	2	-	23	-
Overall[c]	Eradication	1 (50.0)	(1.3, 98.7)	0	-	0	-	1 (50.0)	(1.3, 98.7)
	Persistence	1 (50.0)	(1.3, 98.7)	0	-	0	-	1 (50.0)	(1.3, 98.7)
	Indeterminate	0	-	0	-	0	-	0	-
	Not Done	0	-	0	-	0	-	0	-
	Missing[b]	20	-	0	-	2	-	22	-

Participants with only one primary diagnosis are counted under their respective groups. Participants with both primary diagnosis are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All participants are counted once under 'Total'.
Percentages are based on participants who reported responses in the corresponding visit. For overall, percentages are based on participants who reported responses at any of the visits.
a. 95% exact confidence interval for the proportions is calculated using the Clopper-Pearson method.
b. Participants not reported/died/discontinued are counted under 'Missing' at the respective visits.
c. For overall, the best outcome of each participant across post-baseline visits are considered.

10.4.3. Radiological outcomes

Radiological outcomes were recorded at baseline, Day 7, Day 14, and week 4. The results were summarized by visit, per primary diagnosis group and for total patients for safety analysis set and additionally, for patients who died due to COVID-19.

10.4.3.1. Radiological Outcomes by Visit - Safety Analysis Set

The radiological results in IA at baseline were available for 31 patients and missing for 17 patients. Among the available data, abnormal, indeterminate, normal, unknown, and not evaluable was 24 (77.4%), 0, 0, 1 (3.2%) and 6 (19.4%) respectively. The data for IM was available for 11 and missing for 9 patients. Among the available data, abnormal, indeterminate, normal, unknown and not evaluable was 11 (100%), 0, 0, 0 and 0 respectively. For mixed infection, data was available for 1 and missing for the other patient. Abnormal radiological result was seen in that 1 evaluable patient.

The radiological results in IA on Day 7 were available for 14 patients and missing for 34 patients. Among the available data, abnormal, indeterminate, normal, unknown and not

evaluable was 8 (57.1%), 0, 0, 1 (7.1%) and 5 (35.7%) respectively. No data was available for the IM and mixed infection group of patients.

The radiological results in IA on Day 14 were available for 7 patients and missing for 41 patients. Among the available data, abnormal, indeterminate, normal, unknown, and not evaluable was 4 (57.1%), 0, 1 (14.3%), 0 and 2 (28.6%) respectively. No data was available for the IM and mixed infection group of patients.

The radiological results in IA on Week 4 were available for 3 patients and missing for 45 patients. Among the available data, abnormal, indeterminate, normal, unknown, and not evaluable was 2 (66.7%), 0, 1 (33.3%), 0 and 0 respectively. No data was available for the IM and mixed infection group of patients.

The detail of individual patient's radiological outcome by visit is presented in Table 16.2.6.4.

Table 10: Summary of Radiological Outcomes by Visit - Safety Analysis Set

Visit	Radiological Outcome	Invasive Aspergillosis (N=48)		Invasive Mucormycosis (N=20)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=70)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
Baseline	Abnormal	24 (77.4)	(58.9, 90.4)	11 (100.0)	-	1 (100.0)	-	36 (83.7)	(69.3, 93.2)
	Indeterminate	0	-	0	-	0	-	0	-
	Normal	0	-	0	-	0	-	0	-
	Unknown	1 (3.2)	(0.1, 16.7)	0	-	0	-	1 (2.3)	(0.1, 12.3)
	Not Evaluable	6 (19.4)	(7.5, 37.5)	0	-	0	-	6 (14.0)	(5.3, 27.9)
	Missing[b]	17	-	9	-	1	-	27	-
Day 7	Abnormal	8 (57.1)	(28.9, 82.3)	0	-	0	-	8 (57.1)	(28.9, 82.3)
	Indeterminate	0	-	0	-	0	-	0	-
	Normal	0	-	0	-	0	-	0	-
	Unknown	1 (7.1)	(0.2, 33.9)	0	-	0	-	1 (7.1)	(0.2, 33.9)
	Not Evaluable	5 (35.7)	(12.8, 64.9)	0	-	0	-	5 (35.7)	(12.8, 64.9)
	Missing[b]	34	-	20	-	2	-	56	-

Visit	Radiological Outcome	Invasive Aspergillosis (N=48)		Invasive Mucormycosis (N=20)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=70)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
Day 14	Abnormal	4 (57.1)	(18.4, 90.1)	0	-	0	-	4 (57.1)	(18.4, 90.1)
	Indeterminate	0	-	0	-	0	-	0	-
	Normal	1 (14.3)	(0.4, 57.9)	0	-	0	-	1 (14.3)	(0.4, 57.9)
	Unknown	0	-	0	-	0	-	0	-
	Not Evaluable	2 (28.6)	(3.7, 71.0)	0	-	0	-	2 (28.6)	(3.7, 71.0)
	Missing[b]	41	-	20	-	2	-	63	-
Week 4	Abnormal	2 (66.7)	(9.4, 99.2)	0	-	0	-	2 (66.7)	(9.4, 99.2)
	Indeterminate	0	-	0	-	0	-	0	-
	Normal	1 (33.3)	(0.8, 90.6)	0	-	0	-	1 (33.3)	(0.8, 90.6)
	Unknown	0	-	0	-	0	-	0	-
	Not Evaluable	0	-	0	-	0	-	0	-
	Missing[b]	45	-	20	-	2	-	67	-

Participants with only one primary diagnosis are counted under their respective groups. Participants with both primary diagnosis are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All participants are counted once under 'Total'.
Percentages are based on participants who reported responses in the corresponding visit.
a. 95% exact confidence interval for the proportions is calculated using the Clopper-Pearson method.
b. Participants not reported/died/discontinued are counted under 'Missing' at the respective visits.

10.4.3.2. Radiological Outcomes based on patients died due to COVID-19 by Visit

The radiological results at baseline were reported in 16/24 (66.7%) patients and missing for 8/24 (33.3%) patients. Among the available data, abnormal, indeterminate, normal, unknown, and not evaluable was 9 (60%), 0, 0, 1 (3.7%) and 5 (3.3%) respectively. The data for IM was unavailable. For mixed infection, data was available for 1 and missing for the other patient. Abnormal radiological result was seen in that 1 evaluable patient.

The radiological results in IA on Day 7 were available for 9 patients and missing for 13 patients. Among the available data, abnormal, indeterminate, normal, unknown, and not

evaluable was 4 (44.4%), 0, 0, 1 (11.2%) and 4 (44.4%) respectively. No data was available for the IM and mixed infection group of patients.

The radiological results in IA on Day 14 were available for 4 patients and missing for 18 patients. Among the available data, abnormal, indeterminate, normal, unknown, and not evaluable was 3 (75%), 0, 0, 0 and 1 (25%) respectively. No data was available for the IM and mixed infection group of patients.

The radiological results in IA on Week 4 were available for 2 patients and missing for 20 patients. Among the available data, abnormal radiological assessment was reported for both the patients. No data was available for the IM and mixed infection group of patients.

Table 11: Summary of Radiological Outcomes based on Patients who died due to COVID-19 by Visit - Safety Analysis Set

Visit	Radiological Outcome	Invasive Aspergillosis (N=22)		Invasive Mucormycosis (N=0)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=24)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
Baseline	Abnormal	9 (60.0)	(32.3, 83.7)	0	-	1 (100.0)	-	10 (62.5)	(35.4, 84.8)
	Indeterminate	0	-	0	-	0	-	0	-
	Normal	0	-	0	-	0	-	0	-
	Unknown	1 (6.7)	(0.2, 31.9)	0	-	0	-	1 (6.3)	(0.2, 30.2)
	Not Evaluable	5 (33.3)	(11.8, 61.6)	0	-	0	-	5 (31.3)	(11.0, 58.7)
	Missing[b]	7	-		-	1	-	8	-
Day 7	Abnormal	4 (44.4)	(13.7, 78.8)	0	-	0	-	4 (44.4)	(13.7, 78.8)
	Indeterminate	0	-	0	-	0	-	0	-
	Normal	0	-	0	-	0	-	0	-
	Unknown	1 (11.1)	(0.3, 48.2)	0	-	0	-	1 (11.1)	(0.3, 48.2)
	Not Evaluable	4 (44.4)	(13.7, 78.8)	0	-	0	-	4 (44.4)	(13.7, 78.8)
	Missing[b]	13	-		-	2	-	15	-
Day 14	Abnormal	3 (75.0)	(19.4, 99.4)	0	-	0	-	3 (75.0)	(19.4, 99.4)

Visit	Radiological Outcome	Invasive Aspergillosis (N=22)		Invasive Mucormycosis (N=0)		Invasive Aspergillosis and Mucormycosis (N=2)		Total (N=24)	
		n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]	n(%)	95% CI[a]
	Indeterminate	0	-	0	-	0	-	0	-
	Normal	0	-	0	-	0	-	0	-
	Unknown	0	-	0	-	0	-	0	-
	Not Evaluable	1 (25.0)	(0.6, 80.6)	0	-	0	-	1 (25.0)	(0.6, 80.6)
	Missing[b]	18	-		-	2	-	20	-
Week 4	Abnormal	2 (100.0)	-	0	-	0	-	2 (100.0)	-
	Indeterminate	0	-	0	-	0	-	0	-
	Normal	0	-	0	-	0	-	0	-
	Unknown	0	-	0	-	0	-	0	-
	Not Evaluable	0	-	0	-	0	-	0	-
	Missing[b]	20	-		-	2	-	22	-

Participants with only one primary diagnosis are counted under their respective groups. Participants with both primary diagnosis are counted under the group 'Invasive Aspergillosis and Mucormycosis'. All participants are counted once under 'Total'.
Percentages are based on participants who reported responses in the corresponding visit.
a. 95% exact confidence interval for the proportions is calculated using the Clopper-Pearson method.
b. Participants not reported/died/discontinued are counted under 'Missing' at the respective visits.

10.4.4. Safety outcomes

The safety analysis was performed on patients who received at least one dose of study drug.

10.4.4.1. Treatment compliance:

The proportion of patients receiving IV and/or Oral therapy and summary statistics of dosage administration (duration of IV and/or oral therapy, formulation and total dose administered) for safety analysis set were summarized and presented in Table 12.

Median (min, max) total dose administered was 3100.0 (400.0, 38000.0) mg for a treatment duration of 6.0 (2.0, 184.0) days. Injection formulation was administered to majority of the patients (52 [74.3%]).

No medication errors were reported during the study period.

The detail of individual patient dosage administration are provided in Table 16.2.5.1.1.

Table 12: Summary of Dosage Administration- Safety Analysis Set

	Total (N=70)
	N (%)
Number (%) of Patients under IV/Oral therapy	70 (100.0)
Duration of treatment (Days)[a]	
N	70
Mean (SD)	13.7 (25.23)
Median (Min, Max)	6.0 (2.0, 184.0)
(Q1,Q3)	(3.0, 13.0)
Total Dose Administered (mg)[b]	
N	70
Mean (SD)	4546.4 (5524.46)
Median (Min, Max)	3100.0 (400.0, 38000.0)
(Q1,Q3)	(1600.0, 5400.0)
Formulation[c]	
Capsule	18 (25.7)
Injection	52 (74.3)
Capsule and Injection	5 (7.1)

a. The Total Number of Dosing Days on which the study drug was actually administered
b. Total dose (mg) = Total daily dose x Number of dosed days x Frequency.
c. Patient may have taken either capsule, Injection or both during the course of study
Reference: Table 14.4.1.1

10.4.4.2. Concomitant Medications

Prior medications are recorded at the time of enrollment and concomitant medications were recorded at Day 0, Day 7, Day 14, week 4 and week 6. Descriptive summaries of prior and concomitant medications for safety analysis set listed in terms of preferred terms is presented in Table 14.1.4.1 and Table 14.4.2.1 respectively.

Proportion of patients received any prior medication were 53 (75.7%). Most commonly administered prior medications were pantoprazole in 30 (42.9%), enoxaparin sodium in 15 (21.4%), minocycline in 12 (17.1%), paracetamol in 11 (15.7%), meropenem in 10 (14.3%), dexamethasone in 9 (12.9%), avibactam/ceftazidime and lactulose in 8 (11.4%) and remdesivir in 7 (10.0%) patients.

A total of 66 (94.3%) patients received any concomitant medication. Most commonly administered concomitant medications were pantoprazole to 41 (58.6%), paracetamol to 21 (30.0%), avibactam/ceftazidime in 17 (24.3%), enoxaparin sodium in 19 (27.1%), minocycline 16 (22.9%), meropenem to 15 (21.4%), lactulose to 12 (17.1%), amphotericin B, dexamethasone and tigecycline to 11 (15.7%).

The detail of individual patient prior and concomitant medications is provided in Table 16.2.5.2.1.

10.4.4.3. Vital signs

Vital signs (height, weight, body mass index [BMI], systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiratory rate, and temperature) were recorded at Baseline, Day 7, Day 14, week 4 and week 6. Descriptive statistics of observed values and change from baseline for vital signs parameters were summarized by parameter and visit in Table 14.3.5.1.1.

Summary of abnormal vital signs findings for safety analysis set without regard to baseline is presented in Table 13. Fifty four (77.1%) patients were reported with abnormal respiratory rate (value > 20 rpm) and 14 (20.0%) patients with increased pulse rate (value >120 bpm). Abnormal diastolic blood pressure (change ≥ 20 mmHg increase/DBP <50 mmHg) were reported in 8 (11.4%) patients and DBP (Value >90mmHg) in 7 (10.0%) patients. Abnormal findings in SBP, DBP (change ≥ 20mmHg decrease) and weight change were noted in less than 10% patients. No vital sign abnormalities were reported as an ADR.

The detail of individual patient vital signs findings is presented in Table 16.2.8.2.1.

Table 13: Summary of Abnormal Vital Signs Findings - Safety Analysis Set

		Total	
Parameter (units)	**Criteria**	**N**	**n (%)**
Weight (kg)	Pchg >=10% decrease	68	1 (1.5)
Diastolic Blood Pressure (mmHg)	Value <50 mmHg	70	8 (11.4)
	Chg >= 20mmHg increase	70	8 (11.4)
	Chg >= 20mmHg decrease	70	5 (7.1)
	Value >90mmHg	70	7 (10.0)
Pulse Rate (bpm)	Value >120 bpm	70	14 (20.0)
Respiratory Rate (breaths/min)	Value >20 rpm	70	54 (77.1)
Systolic Blood Pressure (mmHg)	Value <90mmHg	70	3 (4.3)
	Chg >= 30mmHg increase	70	3 (4.3)
	Chg >= 30mmHg decrease	70	6 (8.6)

N=number of patients evaluated against criteria. n=number of patients that met criteria.
PFIZER CONFIDENTIAL SDTM Creation: 30JUN2022 (12:25) Source Data: advs Table Generation: 09AUG2022 (01:28)
(Data cutoff date: 20MAY2022 Database snapshot date : 20MAY2022) Output File: ./csr_cresemba/India_C3791010_CSR/advs_s501

Source: Table 14.3.5.2

10.4.4.4. Physical examination

Physical examination (PE) were performed and recorded at baseline, Day 7, Day 14, week 4 and week 6. The results were summarized by visit, body system and presented in Table 14.3.7.1.

No PE abnormalities were reported as an ADR.

The details of individual patients physical examination - Safety Analysis Sets is presented in Table 16.2.8.4.1.

10.4.4.5. Death

Death by cause (primary or secondary) were summarized and provided in Table 14. Total number of deaths during the study was 41 (58.6%) and the primary cause of death was COVID-19 pneumonia (31.4%) followed by septic shock (11.4%), multiple organ dysfunction syndrome (4.3%) and COVID-19, multi-organ disorder, rhinocerebral mucormycosis (2.9 % each). Secondary cause of death was recorded for 5.7% patients due to sinusitis aspergillus, sinusitis fungal, rhinocerebral mucormycosis, sepsis and multi-organ disorder.

The details of death are provided in Table 16.2.7.3.

Table 14: Summary of Deaths - All Patients

	Total (N=70)
Deaths	**n (%)**
Total Number of Death	41 (58.6)
Primary Cause of Death	41 (58.6)
Acute Respiratory Distress Syndrome	1 (1.4)
Covid-19	2 (2.9)
Covid-19 Pneumonia	22 (31.4)
Multi-Organ Disorder	2 (2.9)
Multiple Organ Dysfunction Syndrome	3 (4.3)
Respiratory Failure	1 (1.4)
Rhinocerebral Mucormycosis	2 (2.9)
Septic Shock	8 (11.4)
Secondary Cause of Death	4 (5.7)
Multi-Organ Disorder	1 (1.4)
Rhinocerebral Mucormycosis	1 (1.4)
Sepsis	1 (1.4)

	Total (N=70)
Deaths	**n (%)**
Sinusitis Aspergillus	1 (1.4)
Sinusitis Fungal	1 (1.4)
A patient may have more than one cause of death reported. Source: Table 14.3.2.2.8	

10.5. Other analyses

Summary statistics on the length of hospital stay has been provided using the safety analysis set in Table 15. All 70 subjects were hospitalized at some point of time during the study, the median length of hospitalization was 18 days with a range for 3 to 200* days.

The detail of individual patient hospitalization status is presented in Table 16.2.7.2.

Table 15: Summary of Hospitalization - Safety Analysis Set

	Total (N=70)
Number (%) of Hospitalized Patients	70 (100.0)
Length of Hospital Stay (Days)[a]	
N	70
Mean (SD)	25.2 (26.68)
Median (Min,Max)	18.0 (3.0, 200.0*)
(Q1,Q3)	(13.0, 27.0)
a. Length of Hospital Stay (Days) = Date of discharge – date of admission + 1; For Patients with discharge status Ongoing or missing, the last available date/death date (End of study) is considered as the discharge date to calculate the duration. * For Patients with discharge status ongoing or missing, the last available date/death date (End of study) is considered as the discharge date to calculate the duration Source: Table 14.3.2.5.1	

10.6. Adverse events / adverse reactions

There were no ADRs, serious ADRs, ADRs leading to treatment discontinuation reported in this study. The deaths in the study were due to COVID-19 pneumonia and COVID-19 (primary cause) and fungal infections (including sinusitis aspergillus, sinusitis fungal, rhinocerebral mucormycosis), sepsis and multi organ disorder (secondary cause).

11. DISCUSSION

11.1. Key results

The study objective was 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) was evaluated during a two-year period. A detailed analysis of the clinical and mortality outcome data has been done to evaluate the effectiveness and safety of Isavuconazole in this study for the management of IA and IM.

Clinical Response

11.1.1. Invasive Aspergillosis

Overall clinical response was seen in 24/28 (85%) evaluable patients. Data was unavailable for 20/48 (41.7%) patients. The SECURE study reported 85/137 (62%) clinical response in IA patients treated with Isavuconazole.[1] In this study, complete and partial clinical response was seen in 6/28 (21%) and 18/28 (64%) respectively.

11.1.2. Invasive Mucormycosis

Overall clinical response was seen in 12/12 (100%) evaluable patients. Data was unavailable for 8/20 (40%) patients. The VITAL study reported 10/18 (56%) clinical response in IM patients treated with Isavuconazole.[2] In this study, complete and partial clinical response was seen in 2/12 (17%) and 10/12 (83%) respectively.

11.2. Mycological Response

11.2.1. Invasive Aspergillosis

Mycological response was seen in 3/4 (75%) evaluable patients. Data was unavailable for 44/48 (91.7%) patients. The SECURE study reported 54/143 (38%) mycological response in IA patients treated with Isavuconazole.[1] In this study, persistence of infection was seen in 1/4 (25%) evaluable patient.

11.2.2. Invasive Mucormycosis

Mycological response was not captured in the 20 patients of IM in this study. The VITAL study reported 6/19 (32%) clinical response in IM patients treated with Isavuconazole.[2] The current study has a retrospective, secondary data collection design as opposed to VITAL which was an open label, prospective study.

11.3. Mortality Analysis

Overall mortality reported in this study was 58.6% (41/70) in which 70.8% (34/48) and 25% (5/20) were in IA and IM respectively. Both the patient with mixed infection (IA + IM) did not survive. The all-cause mortality at Day 42 in the SECURE study (IA treated with Isavuconazole) and VITAL study (IM treated with Isavuconazole) were 19% and 33% respectively.[2,3]

11.3.1. Analysis of COVID association with Mortality in IA & IM

COVID-19 and COVID-19 Pneumonia were reported as the primary cause of death in *58.5% (24/41)* IA patients treated with Isavuconazole. All the patients recruited in this retrospective, secondary data collection study received treatment for IA/IM with Isavuconazole during the COVID-19 pandemic. COVID Associated Pulmonary Aspergillosis (CAPA) was a distinct entity that was reported during the pandemic with a very high mortality and morbidity.[4-8] The following table shows the mortality associated with CAPA in studies conducted worldwide as well as in India:

Table 16: Mortality in COVID Associated Pulmonary Aspergillosis (Literature review)

S/N	Study Design	Site/Country	Sample Size	Mortality
1.	Gangneux (2022)[3]: Retrospective + Prospective	France	128	61.8%
2.	Ergun (2021)[4]: Case control (retrospective)	Europe	58	53.8%
3.	Marta (2022)[5]: Prospective	Spain	35	31.4%
4.	Mitaka (2021)[6]: Meta analysis (observational)	Global	314	54.9%
5.	Zia (2021)[7]: Retrospective+ Prospective, observational	SGPGI, Lucknow, India	81	47.3%

In the MYCOVID study, the mortality in IA patients was 32.1% as opposed to the 61.8% seen in CAPA patients.[4] In a review of 34 studies on CAPA by G. Dimopoulos et al., the cumulative all-cause mortality was 55% (105/190) with a range of 22.2% to 100%.[9] The available literature corroborates the very high mortality associated with CAPA compared to non-CAPA patients.

11.3.2. Analysis of COVID Associated Mortality in Study Subjects

COVID-19 status at baseline was not an exclusion criterion in the current retrospective, secondary data collection study. Hence, data on COVID-19 seropositivity status was not collected in the CRF. We analyzed the concomitant medications which were used by clinicians to treat COVID-19 patients and evaluated their start date with the initiation of Isavuconazole treatment. Out of the 22 patients of IA whose primary cause of death was COVID-19, 10 patients had received treatment with COVID-19 medications (methylprednisolone, dexamethasone, remdesivir, hydrocortisone, etc.) prior to initiation of Isavuconazole treatment for IA (see Table 17). This can be due to the patients getting admitted in the hospital due to COVID-19 infection and subsequently getting treatment for proven/probable/possible IA. Also, clinical response (partial) to Isavuconazole therapy for IA was seen in 80.0% (8/10) of the patients who succumbed with a primary cause of death attributed to COVID-19 (see Table 17).

Table 17: Relationship of Concomitant COVID-19 Medication with Initiation of Isavuconazole Treatment for Invasive Aspergillosis and Clinical Response to Isavuconazole Treatment

Patient ID	Diagnosis	Medication Name	Start Day w.r.t# Isavuconazole start day	Reason for Administration	Patient Outcome	Clinical Response to Isavuconazole Treatment
1001	IA	Methylprednisolone	-5	Hypoxia	Death	Partial Response
1003	IA	Methylprednisolone	1	Prophylactic for hypoxia	Death	Partial Response
1006	IA	Dexamethasone/ Methylprednisolone/Remdesivir	-12/-10/-12	Prophylactic for hypoxia/ Prophylactic for hypoxia/Prophylaxis for viral infection	Death	Partial Response
1010	IA	Dexamethasone/ Remdesivir	-3/-3	Prophylactic for hypoxia/ Prophylaxis for viral infection	Death	Partial Response
1019	IA	Dexamethasone	-3	Prophylactic for hypoxia	Death	Partial Response
1025	IA	Remdesivir	-2	Prophylaxis for viral infection	Death	No response
1032	IA	Hydrocortisone	-1	Prophylactic for hypoxia	Death	Partial Response
1033	IA	Dexamethasone	-12	Prophylactic for hypoxia	Death	Partial Response
1035	IA	Methylprednisolone/Remdesivir	-6/-10	Prophylactic for hypoxia/ Prophylaxis for viral infection	Death	No Response
1036	IA	Dexamethasone/ Remdesivir	-1/-4	Prophylactic for fever/ Prophylaxis for viral infection	Death	Partial Response

With respect to

The mortality in patients treated with Isavuconazole for IM in this study was 25% (5/20), but none of the deaths were reported to be due to COVID-19 infection as the primary cause. The cause of death was rhinocerebral mucormycosis in 2/5 (40%) patients who received Isavuconazole for IM treatment. Available literature from India have reported IM mortality rates ranging from 23% to 46.7%.[10-12] Hence, the mortality observed in this study in IM patients is similar to those reported in various clinical studies on IM done worldwide. Untreated patients have 100% mortality. Two patients with mixed mold infection (IA+IM) succumbed to their illness and COVID-19 was reported as the primary cause.

No treatment related ADR, serious ADR or ADRs leading to treatment discontinuation were reported indicating that study drug was generally well tolerated safe.

11.4. Limitations

This was a single-arm, multicenter, observational study to describe a case series of patients with IA or IM 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 LPD for Cresemba. Data was collected from 70 patients (48 IA, 20 patients of IM and 2 with both IA & IM) on IV and/or oral formulations.

Overall, the study design, conduct and execution of the study were adequate to assess study objectives. As the patients died due to the ongoing conditions, complete data was not received for all enrolled 70 patients. This being an observational study with smaller sample size, the results and its significance cannot be justified as there was a significant amount of missing data. Moreover, COVID-19 infection was an important confounding factor during the treatment phase of the patients of IA/IM with Cresemba. Due to the retrospective, non-interventional nature of the study, COVID-19 infection status of the patients was not accounted for at baseline.

11.5. Interpretation

Considering the nature of the study being observational, there was missing data and data available was not sufficient to observe the trend at post-baseline visits. Overall, clinical response, mycological outcome of eradication was observed.

Total number of deaths during the study was 41 (58.6%), which were majorly COVID-19 related. No treatment related ADR, serious ADR or ADRs leading to treatment discontinuation were reported indicating that study drug was generally well tolerated safe.

11.6. Generalizability

Not Applicable

12. OTHER INFORMATION

Not Applicable

13. CONCLUSIONS

This study objective was 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 IMIs (IA and IM) was evaluated during a two-year period.

Although data are limited the results appear generally consistent with previous studies and support a continued positive benefit-risk profile for Cresemba The study drug was observed to be generally safe and well tolerated.