PRODUCT: MK5592	PROTOCOL/AMENDMENT VERSION NO.: 2
REVOPS ID NO: NIS102646 EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08047.004	CORE DRC APPROVAL DATE: 18-SEP-2024

PASS INFORMATION

Title	Post Marketing Surveillance of Effectiveness (All-Cause Mortality) of Posaconazole Injection and Tablet Treatment of Invasive Aspergillosis in Chinese patients
Protocol Version identifier	MK5592-141/Version 2
Date of last version of protocol	26-April-2023
EU PAS Register No:	EUPAS108481
Active substance	Posaconazole Enteric-coated Tablets (NOXAFIL™): 100mg of posaconazole Posaconazole Injection (NOXAFIL™): 300mg of posaconazole
Medicinal product(s):	NOXAFIL™ (MK5592)
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s) (MAH)	Merck Sharp & Dohme LLC 126 East Lincoln Ave., P.O. Box 2000, Rahway, New Jersey 07065 USA.
Joint PASS	No

PRODUCT: MK5592	PROTOCOL/AMENDMENT VERSION NO.: 2
REVOPS ID NO: NIS102646 EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08047.004	CORE DRC APPROVAL DATE: 18-SEP-2024

Research question and objectives	**Primary objective:** 1. To assess all-cause mortality at day 42 of invasive aspergillosis (IA; proven, probable, possible) in Chinese adult patients who receive at least 7 days of posaconazole injection and/or tablet formulations. **Secondary objectives：** 1. To assess the overall response rate (complete or partial response) of posaconazole injection and/or tablet for the first-line treatment of IA (proven, probable, possible) at the end of posaconazole treatment (minimum duration of treatment 42 days and maximum treatment duration 12 weeks [84 days]) in Chinese adult IA patients. 2. To assess the overall response rate (complete or partial response) of posaconazole injection and/or tablet for the salvage treatment of IA (proven, probable, possible) at the end of posaconazole treatment (minimum duration of treatment 7 days and maximum treatment duration 12 weeks [84 days]) in Chinese adult patients with disease that is refractory to amphotericin B, voriconazole, itraconazole, isavuconazole, or other antifungal medicines with activity against Aspergillus, or in patients who are intolerant to these medicinal products. 3. To describe the characteristics of the study population, including baseline demographics, clinical characteristics, and treatment patterns, for Chinese adult patients treated with posaconazole injection and/or tablet for the first-line or salvage treatment of IA.
Country(-ies) of study	China

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Author	PPD Sr. Scientist, Biostatistics and Research Decision Sciences (BARDS)-Epidemiology, MSD R&D (China) Co., Ltd PPD
Marketing authorisation holder(s) including MAH Contact Person	Merck Sharp & Dohme LLC 126 East Lincoln Ave., P.O. Box 2000, Rahway, New Jersey 07065 USA.
Merck Final Repository (REDS) Date	13-DEC-2024
Date of Health Authority Approval of Protocol	Not applicable

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LIST OF ABBREVIATIONS

ACM	All-cause Mortality
AE	Adverse Event
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CRF	Case Report Form
DMP	Data Management Plan
EDC	Electronic Data Capture
ERC	Ethics Review Committee
EORTC/MSGERC	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
GM	Galactomannan
HSCT	Hematopoietic Stem Cell Transplant
PR	Partial Response
IA	Invasive Aspergillosis
IDL	Imported Drug License
IFI	Invasive Fungal Infections
IRB	Institutional Review Board
NMPA	National Medical Products Administration
NRDL	National Reimbursement Drug List
ORR	Overall Response Rate
SAP	Statistical Analysis Plan
RCT	Randomized Control Trial

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1 RESPONSIBLE PARTIES

Principal investigator	Prof. PPD, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Coordinating investigator for each country in which the study is to be performed	Not applicable
Sponsor contacts	PPD MSD R&D (China) Co., Ltd
Other contacts	PPD MSD R&D (China) Co., Ltd
Supplier/Collaborator	Hangzhou Tigermed Consulting Co., Ltd
Investigators	To be determined
Shared responsibilities	Not applicable

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2 ABSTRACT

Title	Post Marketing Surveillance of Effectiveness (All-Cause Mortality) of Posaconazole Injection and Tablet Treatment of Invasive Aspergillosis (IA) in Chinese patients
Protocol Number / Version	5592-141/Version 2
Date	Not applicable
Author	PPD , MSD R&D (China) Co., Ltd
Rationale & Background	Noxafil (posaconazole) (MK-5592) injection and tablet has been approved by the National Medical Products Administration (NMPA) for the treatment of IA in adult patients on 29 Mar 2022. CCI [redacted] IA is a serious fungal infection with a mortality rate of 39-100%; therefore, reduction in all-cause mortality among treated patients is also a measure of real-world effectiveness. All-cause mortality was also a clinical endpoint in the Phase 3 study (MK5592-069) used for marketing approval in this indication.

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Research Question & Objectives	**Primary objective:** 1. To assess all-cause mortality at day 42 of IA (proven, probable, possible) in Chinese adult patients who receive at least 7 days of posaconazole injection and/or tablet formulations. **Secondary objectives:** 1. To assess the overall response rate (complete or partial response) of posaconazole injection and/or tablet for the first-line treatment of IA (proven, probable, possible) at the end of posaconazole treatment (minimum duration of treatment 42 days and maximum treatment duration 12 weeks [84 days]) in Chinese adult IA patients. 2. To assess the overall response rate (complete or partial response) of posaconazole injection and/or tablet for the salvage treatment of IA (proven, probable, possible) at the end of posaconazole treatment (minimum treatment duration of treatment 7 days and maximum treatment duration of 12 weeks [84 days]) in Chinese adult patients with disease that is refractory to amphotericin B, voriconazole, itraconazole, isavuconazole, or other antifungal medicines with activity against Aspergillus, or in patients who are intolerant to these medicinal products. 3. To describe the characteristics of the study population, including baseline demographics, clinical characteristics, and treatment patterns, for Chinese adult patients treated with posaconazole injection and/or tablet for the first-line or salvage treatment of IA.
Study Design	This is a multicenter observational (non-interventional) study involving prospective (planned Oct 2023-Dec 2024) and retrospective (planned Mar 2022-Oct 2023) data collection from medical charts in target hospitals using a case report form during the planned recruitment period (planned Oct 2023-Dec 2024).

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Population	The overall study population will consist of IA adult Chinese patients (proven, probable, possible) who received at least 7 days of posaconazole (injection and/or tablet formulations) treatment (including monotherapy and combination therapy) from Mar 2022 to Dec 2024 (planned).
Variables	**Exposure:** • The study exposure of interest is posaconazole injection and/or tablet formulations treatment administered according to local product labeling and medical judgment of the treating physician. The study will include patients who received posaconazole injection and/or tablet formulations treatment in routine clinical practice. **Primary outcome:** • All-cause death among patients who received at least 7 days of posaconazole injection and/or tablet formulations for treatment of proven, probable, possible IA, through Day 42 of posaconazole treatment. **Secondary outcome:** • The secondary outcome is the clinical response of patients who received posaconazole injection and/or tablet formulations treatment as the first line or salvage treatment of proven or probable IA at the end of posaconazole treatment (up to 12 weeks/Day 84). **Other variables:** • Patient demographic, clinical characteristics and treatment patterns (first line or salvage).

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Data Sources	Relevant patient-level information will be collected from multiple information systems, including the Electronic Medical Record (EMR)/paper medical records, Hospital Information System (HIS), Laboratory Information System (LIS), in selected hospitals. Death certificate information will be collected from patients with retrospective data collection with missing dead or alive status in medical record. Data will be collected with the use of a standardized case report form. Hospitals in which posaconazole injection and/or tablet is available and have the most patients using this product will be considered for inclusion in the study.
Study Size	The study size will depend on the number of patients eligible for the study in the study period. No hypothesis test and power calculation will be considered in this study. 55-70 cases with posaconazole treatment are expected to be enrolled during the recruitment period for both primary and secondary objectives, which including 30-40 cases for primary objective. Assuming 15%-50% of all-cause mortality observed through Day 42 for primary objective, the half-width of 95% confidence interval (CI) will range from 12.1%-18.7%.

Data Analysis	• All-cause mortality=total number of patients who die through Day 42 (or number of patients who die through Day 42 by treatment line)/number of all IA patients (or number of IA patients by line) included in the study with dead or alive status reported × 100%. • Overall response rate (ORR)=number of patients with CR or PR by treatment line (first line or salvage treatment)/ number of IA patients included in the study with available evidence on treatment response at the end of treatment by treatment line (first line or salvage treatment) × 100%. • Numerator and denominator of ORR includes those with a classification of proven or probable or possible IA. • Descriptive statistics will include mean (± standard deviation), median, and inter-quartile ranges (upper and lower) for continuous variables and frequency and proportion for categorical variables.
Milestones	
Start of data collection:	Start date of data collection will be a date (planned Oct 2023) after Human Genetic Resource Administration of China (HGRAC) approval
End of data collection:	Jan 2025 (planned date of last patient last visit)
Interim report(s) of study results:	Not applicable
Study progress report(s):	Not applicable
Final report of study results:	Jun 2025

3 AMENDMENTS AND UPDATES

Amendment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
1	20-AUG-2024	PASS INFORMATION, Section 2, Section 6.1, Section 7.1, Section 7.2.5.5, Section 7.3.2.1, Section 7.8.1	Deleted 'as first line treatment' from the primary objective	The text has been removed as it is no longer planned to limit the primary objective to only first-line patients.	18-SEP-2024	2
2	20-AUG-2024	PASS INFORMATION, Section 2, Section 6.2, Section 7.2.2, Section 7.2.3, Section 7.3.2.2.1, Section 7.8.2.1,	Added 'possible' and 'or other antifungal medicines with activity against Aspergillus' to the secondary objectives	The text has been added as it is no longer planned to limit the secondary objective to only proven and probable patients. And to expand the list of salvage patients resistant to or intolerant to medication to include other antifungal medications with activity against Aspergillus, ensuring consistency with the medication list for first-line patients.	18-SEP-2024	2
3	20-AUG-2024	LIST OF ABBREVIATIONS	Added 'Coronavirus disease 2019 (COVID 19)' and 'Electronic Data Capture (EDC)' to the table	Update text to align with the main body of the protocol.	18-SEP-2024	2

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Amendment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
4	20-AUG-2024	Section 2, Section 4, Section 6, Section7.1, Section 7.2.1, Figure 1, Section 7.2.5.2, Section 7.5, Section 7.10	Modified the study timeline: 1) planned overall recruitment period, planned prospective recruitment period, and the date of last patient in (LPI) to Dec 2024; 2) planned end of data collection and the date of last patient last visit (LPLV) to Jan 2025; 3) final report of study results to Jun 2025	Modify the study timeline to strengthen the recruitment by extending the recruitment period.	18-SEP-2024	2
5	20-AUG-2024	Section 2, Section 7.8.1	Modified the all-cause mortality analysis into two analyses: 1) total all-cause mortality analysis; and 2) all-cause mortality analysis by treatment line	The text has been modified as it is no longer planned to limit the primary objective to only first-line patients.	18-SEP-2024	2
6	20-AUG-2024	Section 7.8.2.1	Deleted ‘Numerator and denominator of ORR includes those with a classification of proven or probable IA only’	The text has been removed as it is no longer planned to limit the secondary objective to only proven and probable patients.	18-SEP-2024	2

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Amendment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
7	20-AUG-2024	Section 6.1	Added footnote 2 'Considering the real-world medication adherence of patients, in this study, if the prescribed duration of medication is specified and the actual duration of medication reaches 80% or more of the specified duration, it can be included in the analysis'	Refine the prescribed medication duration by using 80% adherence as the threshold.	18-SEP-2024	2
8	20-AUG-2024	Section 7.2.1, Section 7.2.2, Section 7.2.3, Annex 5	Added one more consensus criterion as the definition criteria for IA: 2021 EORTC/MSGERC-ICU	Include the 2021 EORTC/MSGERC-ICU consensus criteria as the criteria for the IA diagnosis in this study to align with our overall screening population.	18-SEP-2024	2
9	20-AUG-2024	Section 7.2.5.1	Modified identification period to 32 months	Modify the study timeline.	18-SEP-2024	2
10	20-AUG-2024	Section 7.2.5.1, Section 7.2.5.4	Deleted 'no later than March/Mid-May 2024 to meet the report submission deadline'	Modify the study timeline.	18-SEP-2024	2

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Amendment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
11	20-AUG-2024	Section 7.3.2.2.1	Added 'Clinical responses will be defined by using the 2017 Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the fifth version) (Table 1) or by the investigator[7](s)' and footnote 7 'Considering the low compliance with guidelines in real-world clinical practice, it is possible that there may be insufficient information from medical record to support the definition of clinical response according to the guideline (Table 1). Therefore, investigator's professional judgment could be used to define the clinical response. The subgroup analysis by the methods of clinical response definition (guideline vs. investigator's professional judgment) will be conducted depending on data availability. (see 7.7.2.1)'	Add a clinical response assessment method (to be judged by investigator) to correspond to real-world clinical practice.	18-SEP-2024	2
12	20-AUG-2024	Section 7.8.2.1	Added '5. Methods of clinical response definition: guideline vs. investigator judgment' to subgroup analysis	Update text to align with the planned endpoint analyses.	18-SEP-2024	2
13	20-AUG-2024	Annex 5	Added a footnote* 'This criterion comes from the 2021 EORTC/MSGERC-ICU consensus criteria'	A footnote was added as the source to differentiate the use of the two criteria. (2020 EORTC/MSGERC and 2021 EORTC/MSGERC-ICU)	18-SEP-2024	2

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Amendment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
14	20-AUG-2024	Annex 5	Links for both consensus criteria were added: 1) 'Link for 2020 EORTC/MSGERC consensus criteria: https://pubmed.ncbi.nlm.nih.gov/31802125/'; and 2) 'Link for 2021 EORTC/MSGERC-ICU consensus criteria: https://pubmed.ncbi.nlm.nih.gov/33709127/'	Provide the links for both criteria.	18-SEP-2024	2

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Amendment or Update no	Date	Section of Study Protocol	Amendment or Update	Reason	CORE DRC Approval Date	CORE DRC Version No
15	20-AUG-2024	Annex 5	Added additional host factors from 2021 EORTC/MSGERC-ICU consensus criteria for the criteria for diagnosis of invasive aspergillosis of the study: 1) 'OR *Qualitative or quantitative neutrophil abnormality (inherited neutrophil deficiency, absolute neutrophil count of ≤500 cells/mm^3)'; 2) 'OR *Glucocorticoid treatment with prednisone equivalent of 20 mg or more per day'; 3) '*Chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis)'; 4) '*Decompensated cirrhosis'; 5) '*Human immunodeficiency virus infection'; 6) '*Severe influenza (or other severe viral pneumonia, such as coronavirus disease 2019 [COVID-19])'	Additional host factors from 2021 EORTC/MSGERC-ICU consensus criteria.	18-SEP-2024	2
16	20-AUG-2024	Annex 5	Added additional Mycological Evidence from 2021 EORTC/MSGERC-ICU consensus criteria for the criteria for diagnosis of invasive aspergillosis of the study: 1) '*Cytology, direct microscopy, and/or culture indicating presence of Aspergillus spp. in a lower respiratory tract specimen'; 2) '*Galactomannan antigen index >0.5 in plasma/serum and/or Galactomannan antigen >0.8 in BALF'	Additional Mycological Evidence from 2021 EORTC/MSGERC-ICU consensus criteria.	18-SEP-2024	2

4 MILESTONES

Milestone	Planned Date
Registration in the EU PAS register	Within 35 days of protocol finalization in Regulatory Enterprise Document Source (REDS)
Start of data collection	Start date of data collection will be a date (planned Oct 2023) after Human Genetic Resource Administration of China (HGRAC) approval
End of data collection	Jan 2025 (planned date of last patient last visit)
Final report of study results	Jun 2025

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5 RATIONALE AND BACKGROUND

Posaconazole[1], a triazole antifungal agent, is indicated for use in the treatment of the following invasive fungal infections (IFI) worldwide in patients with disease which is refractory to, or in patients who are intolerant of other alternative therapy: Aspergillosis, Candidiasis, Fusariosis, Zygomycosis, Cryptococcosis, Chromoblastomycosis, Mycetoma, and Coccidioidomycosis.

In China, NOXAFIL injection (for intravenous [IV] use) and tablet (for oral use) were approved on 30 Jan 2021 and 7 Dec 2018, respectively, for prophylaxis of invasive aspergillus and candida infections. Later, NOXAFIL injection and tablet, was approved for the treatment of invasive aspergillosis (IA) in adults on 29 Mar 2022.

In China, the current estimated prevalence of IA is around 1.17 million. [Zhou, L. H., et al 2020] The incidence rate of IA is rising. According to conservative estimates, China has reached 160,000 cases/year of IA in 2016. [Yuan, X. U., et al 2018]There are very few publications reporting the mortality of the Chinese national population. Existing literatures are outdated. A study reported the global mortality rate of IA is about 30-95% in 2012. [Brown, G. D., et al 2012]Studies from single site hospital in China reported the mortality rate of 39% among non-neutropenic patients with proven or probable IA and in a separate study, a mortality rate of 100% in among patients with a probable invasive pulmonary aspergillosis diagnosis admitted with HBV-related liver failure [Dai, Z., et al 2013] [Wang, W., et al 2011]. IA patients with underlying disease without timely treatment have the extremely high fatality rate.

Therefore, reduction in mortality among patients with IA is also a measure of real world effectiveness of antifungal treatment. All cause mortality (ACM) was a clinical endpoint in the Phase III study (MK5592-P069) of posaconazole vs. voriconazole for treatment of IA.

[1] The posaconazole mentioned in this protocol is the product of posaconazole injection and/or posaconazole tablets by Merck & Co., with the brand name ‘Noxafil’

Rationale

The new injection and tablet formulations of posaconazole that are able to achieve a higher exposure target with reduced variability compared to posaconazole oral suspension. Noxafil (posaconazole) (MK-5592) injection and tablet has been approved by the National Medical Products Administration (NMPA) for the treatment of IA in adult patients on 29 Mar 2022.

CCI [redacted]

CCI [redacted] to conduct a

multicenter observational study prospectively and retrospectively collecting effectiveness information in Chinese adult IA patients with posaconazole.

The advantage of the observational study is to conduct the study without any intervention, which will obtain information on patients receiving posaconazole to better reflect real-world clinical practice. Currently, there is no database in China that can be used directly to assess the effectiveness of posaconazole. This study using medical records from multicenter as the basic data source is the most feasible research methods.

According to the evaluation of the number of IA patients in the potential research sites, extensiveness of prophylactic use and the enrollment difficulty and speed in clinical trial, the observed number of IA patients with posaconazole treatment in this study might be limited, hence this study proposed a combination of prospective and retrospective study design.

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6 RESEACH QUESTION AND OBJECTIVES

The aim of this study is to assess all-cause mortality of posaconazole injection and/or tablet treatment of IA in Chinese adult patients by an observational study involving prospective and retrospective data from target hospitals using a case report form during the planned recruitment period (Oct 2023-Dec 2024).

6.1 Primary Objective

1. To assess all-cause mortality at day 42 of IA (proven, probable, possible) in Chinese adult patients who receive at least 7 days[2] of posaconazole injection and/or tablet formulations.

[2] Considering the real-world medication adherence of patients, in this study, if the prescribed duration of medication is specified and the actual duration of medication reaches 80% or more of the specified duration, it can be included in the analysis.

6.2 Secondary Objectives

1. To assess the overall response rate (complete or partial response)[3] of posaconazole injection and/or tablet for the first-line treatment of IA (proven, probable, possible) at the end of posaconazole treatment (minimum duration of treatment 42 days and maximum treatment duration 12 weeks [84 days]) in Chinese adult IA patients.

[3]Complete response (CR) or partial response (PR) follow the definition of the 2017 Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the fifth version) [Chinese Invasive Fungal Infection Working Group 2017] (see 7.3.2.2.1).

2. To assess the overall response rate (complete or partial response) of posaconazole injection and/or tablet for the salvage treatment of IA (proven, probable, possible) at the end of posaconazole treatment (minimum duration of treatment 7 days and maximum treatment duration 12 weeks [84 days]) in Chinese adult patients with disease that is refractory[4] to amphotericin B, voriconazole, itraconazole, isavuconazole, or other antifungal medicines with activity against Aspergillus, or in patients who are intolerant to these medicinal products.

[4]Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

3. To describe the characteristics of the study population, including baseline demographics, clinical characteristics, and treatment patterns, for Chinese adult patients treated with posaconazole injection and/or tablet for the first-line or salvage treatment of IA. (see 7.3.2.2.2/7.3.2.2.3 for more details).

7 RESEARCH METHODS

7.1 Study Design

The study does not involve any interventional measurements, e.g., receiving posaconazole injection and/or tablet, laboratory test for IA diagnosis. Under this protocol, all patients accepted posaconazole injection and/or tablet previously in the course of routine clinical practice.

This is a multicenter observational study involving prospective (Planned: Oct 2023-Dec 2024) and retrospective (Planned: Mar 2022- Oct 2023) data collection from target hospitals using a case report form during the planned recruitment period (Oct 2023-Dec 2024).

Chinese adult IA patients (≥18 years old) who have been treated with posaconazole for at least 7 days in accordance with NMPA's approved product information are potential subjects for the study.

After inclusion/exclusion criteria check: (1) The patients who have continued posaconazole treatment for 7 to 42 days and have dead or alive status available through day 42 will be evaluated for primary objective. (2) The patients who have continued posaconazole as first line treatment for 42 to 84 days and have treatment response data available (success or failure at the end of treatment or at a maximum duration of 84 days) will be evaluated for secondary objectives. (3) The patients who have continued posaconazole as salvage treatment for 7 to 84 days and have treatment response data available (success or failure at the end of treatment or at a maximum duration of 84 days) will be evaluated for secondary objectives. The demographic, clinical characteristics and treatment patterns will be described in this study.

Information will be collected by using a case report form during the planned recruitment period (Oct 2023-Dec 2024) including but not limited to outpatient or inpatient medical records, lab reports, prescription records, etc., by qualified investigators.

7.2 Setting

7.2.1 Study Population

The overall study population will consist of IA adult Chinese patients (proven, probable, possible[5]) who received at least 7 days of posaconazole (injection and/or tablet formulations) treatment (including monotherapy and combination[6] therapy) from Mar 2022 to Dec 2024 (planned date of last patient in).

[5] Follow the definition of 2020 EORTC/MSGERC or 2021 EORTC/MSGERC-ICU consensus criteria [Donnelly, J. P., et al 2020] (see Annex 5).

[6]Combination therapy is defined as patient use posaconazole (injection and/or tablet formulations) with any other antifungal medications with activity against aspergillosis, medications used in as combination therapy should be recorded.

7.2.2 Inclusion/Exclusion criteria for subjects receiving first line treatment

Inclusion criteria for subjects receiving first line treatment of IA:

- Chinese and resident in China;
- At least 18 years of age on the day of initiating posaconazole treatment;
- Diagnosed with proven, probable, possible IA per EORTC/MSGERC 2020 or 2021 EORTC/MSGERC-ICU criteria;
- Has received less than 7 days of other antifungal therapy with activity against aspergillosis (amphotericin, voriconazole, isavuconazole, or itraconazole) for treatment of the current episode of IA.

Exclusion criteria for subjects receiving first line treatment of IA:

- Unable to provide written informed consent if Ethics review committee (ERC) requires;
- Participating in any interventional clinical trial;
- Pregnancy or breast feeding during the treatment with posaconazole;
- Prior enrollment in current study (each subject may only be enrolled once);
- History or known aspergillus infection with a strain that is azole-resistance;
- Known or history of efficacy failure of posaconazole to treat a prior or current episode of IA.

7.2.3 Inclusion/Exclusion criteria for subjects receiving salvage treatment

Inclusion criteria for subjects receiving salvage treatment of IA:

- Chinese and resident of China;
- At least 18 years of age on the day of initiating posaconazole treatment;
- Diagnosis of probable, proven, possible IA per EORTC/MSGERC 2020 or 2021 EORTC/MSGERC-ICU criteria;
- Has a diagnosis of IA with disease that is refractory to amphotericin B, voriconazole, itraconazole, isavuconazole or other antifungal medicines with activity against Aspergillus. Refractoriness is defined as progression of infection or failure to improveafter the receipt of 7 or more days of these medicinal products for treatment of the current episode of infection;

- OR

- Has a diagnosis of IA in patients who have shown intolerance to amphotericin B, voriconazole, itraconazole, isavuconazole or other antifungal medicines with activity against Aspergillus after the receipt of 1 or more days of any of these medicinal products given for the treatment of the current episode of infections.

Exclusion criteria for subjects receiving salvage treatment of IA

- Unable to provide written informed consent if ERC requires;

- Participating in any interventional clinical trial;

- Pregnancy or breast feeding during the treatment with posaconazole;

- Prior enrollment into the study (each subject may only be enrolled once);

- Known or history of efficacy failure of posaconazole to treat a prior or current episode of IA.

7.2.4 Study Sites

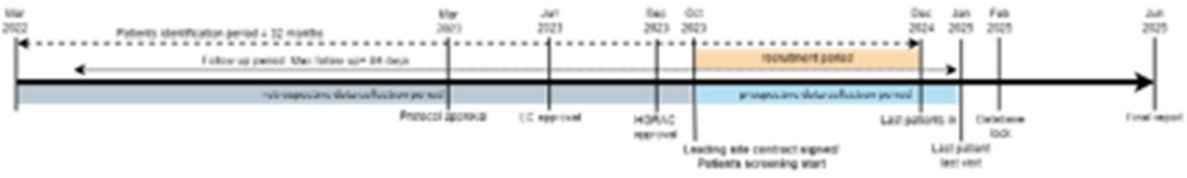
Hospitals in which posaconazole injection and/or tablet is available and have the most patients using this product will be considered for inclusion in the study.

Site selection will depend on availability of posaconazole injections and/or tablets in hospitals, the potential eligible patient number, willingness of PI to participate, the completeness of medical records on study key information as well as the feasibility assessment from the operational perspective. The actual site numbers may be updated according to the actual execution.

7.2.5 Study Period

Figure 1 depicts the planned study period. The study period may be adjusted according to the actual enrollment of patients with available data to confirm the all-cause mortality through day 42 and overall response rate at the end of posaconazole treatment.

Figure 1 Planned Timeline and Study Period for the Study



7.2.5.1 The Patients Identification Period

The patient identification period will be defined as the segment of time from date of posaconazole injection and tablet formulations has been approved by NMPA for the treatment of IA in adult patients (29 Mar 2022) until the planned last patients in date of the study. The whole identification period will last for about 32 months.

IA Patients who admitted to the selected hospitals and received at least 7 days of posaconazole (injection and/or tablet formulations) treatment (including monotherapy and combination^ therapy) during this period should be identified and observed. The procedures of how to identify eligible patients is presented in section 7.4.1.

7.2.5.2 The Recruitment Period

The recruitment period will start after the leading site contract signed (Oct 2023 as planned) and plan to be ended by Dec 2024.

During this period, inclusion/exclusion criteria checking by treatment line should be carried on for patients who are identified and observed during the patients identification period. Qualified patients after inclusion/exclusion criteria check should be recruited into the study and followed up.

7.2.5.3 The Follow up Period

According to treatment line different follow up period should be applied.

For patients who receiving first line treatment, a minimum follow up of 42 days and the maximum follow up of 84 days starting from the patient index date (see 7.2.5.5) are required.

For patients who receiving salvage treatment, a minimum follow up of 7 days and the maximum follow up of 84 days starting from the patient index date (see 7.2.5.5) are required.

7.2.5.4 Data Collection Period

This study involving both prospective and retrospective data collection.

The retrospective data collection period will be defined as date of posaconazole injection and tablet formulations has been approved by NMPA for the treatment of IA in adult patients (29 Mar 2022) until the start of recruitment period (Oct 2023 as planned).

The prospective data collection period will be defined as the start of recruitment period (Oct 2023 as planned) until the the planned patients last visit date of the study (Jan 2025).

7.2.5.5 Patient Index Date and Specific Treatment Assessment Durations

Patient index date is defined as the date of the first treatment of posaconazole injection and/or tablet formulations.

Specific treatment assessment duration for different outcomes are summarized as follows:

- Assessment for all-cause mortality for IA will occur at Day 42. Treatment may continue beyond Day 42.

- Assessment for overall response will occur at the end of treatment (for both first line and salvage treatment). Patients may continue treatment beyond 12 weeks (84 days) however assessment for response to therapy will occur at 84 days for such patients. For patients who receive less than 12 weeks of treatment, assessment will occur at the end of posaconazole treatment.

7.3 Variables

7.3.1 Exposure

The study exposure of interest is posaconazole injection and/or tablet formulations treatment administered in a non-interventional setting. The study will include patients who received posaconazole injection and/or tablet formulations treatment in routine clinical practice.

7.3.2 Outcomes

Health outcomes is definited as clinical events or outcomes which may be represented as diagnoses, treatment or procedures (examples include syncope, disease progression or hypoglycemia collected as study endpoints)

Any herein described health outcomes, collected per the protocol, will be summarized as part of any interim analysis (if required) and in the final study report in addition to being reported in real-time as individual AE/s if the criteria in section 7 are met. Refer to section 9 for AE reporting requirements and procedures.

7.3.2.1 Primary Outcomes

The primary outcome is all-cause death among proven, probable, possible IA patients who received at least 7 days of posaconazole injection and/or tablet formulations treatment through Day 42.

Death is defined as a patient with death is recorded in the medical history or death certificate can be provided through Day 42 or within Day 42. (Data cources see 7.4)

Patients with missing or ‘unable to determine’ dead or alive status through Day 42 will be excluded.

7.3.2.2 Secondary Outcomes

7.3.2.2.1 Clinical response

The clinical response of proven, probable, possible IA patients who received posaconazole injection and/or tablet formulations treatment as the first line or salvage treatment at the end of posaconazole treatment.

Clinical responses will be defined by using the 2017 Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the fifth version) (Table 1) or by the investigator[7](s).

[7]Considering the low compliance with guidelines in real-world clinical practice, it is possible that there may be insufficient information from medical record to support the definition of clinical response according to the guideline (Table 1). Therefore, investigator's professional judgment could be used to define the clinical response. The subgroup analysis by the methods of clinical response definition (guideline vs. investigator's professional judgment) will be conducted depending on data availability. (see 7.7.2.1)

See Table 1 for the definitions for clinical response from the 2017 Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the fifth version). The Chinese guidelines are consistent with the 2008 EORTC/MSG guidelines.

Table 1 Clinical Response Definitions from the 2017 Chinese guidelines for the diagisnos and treatment of invasive fungal disease in patients with hematological disorders and cancers (the fifth version).

Outcome, Response	Criteria
Success	
Complete response	Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease [*Aspergillus spp*], resolution of radiological lesion(s), and documented clearance of infected sites that are accessible to repeated sampling.
Partial response	Survival within the prespecified period of observation, improvement in attributable symptoms and signs of disease [*Aspergillus spp*], improvement of radiological lesion(s)[a], and evidence of clearance of infected sites that are accessible to repeated sampling. In the case of radiological stabilization[b], resolution of all attributable symptoms and signs of fungal disease; or where biopsy of an infected site shows no evidence of hyphae; or where culture is negative.

Outcome, Response	Criteria
Failure	
Stable response	Survival within the prespecified period of observation and minor or no improvement in fungal disease; or persistent isolation of *Aspergillus spp* or histological present in infected sites.
Progression of fungal disease	Worsening of clinical symptoms and signs of disease [*Aspergillus spp*] plus new sites of disease or radiological worsening; or persistent isolation of *Aspergillus spp* from infected sites.
Death	All-cause death during the prespecified period of evaluation, regardless of attribution.

[a] improvement of radiological lesions is defined as at least 25% reduction in diameter of radiological lesion.
[b] radiological stabilization is defined as 0%-25% reduction in the diameter of the lesion.
Link: http://pubmed.ncbi.nlm.nih.gov/28592049/

Assessment for clinical response will occur at the end of treatment.

- For first line treatment of IA:

  The duration of treatment range from 42 days to 84 days. Patients may continue therapy beyond 12 weeks however clinical response will be assessed at 12 weeks (84 days) for such patients).

- For salvage treatment of IA:

  The duration of treatment range from 7 days to 84 days. Patients may continue therapy beyond 12 weeks however clinical response will be assessed at 12 weeks (84 days) for such patients).

Missing or 'unable to determine' treatment responses at assessment timepoint will be excluded.

7.3.2.2.2 Demographic and Clinical Characteristics

In support of the secondary objectives, we will report the following patient demographic, and clinical characteristics in the study population. Pending data availability, related variables may be adjusted and will be finalized in the case report form.

Demographics at Baseline

- Year and month of birth
- Age
- Gender

- Height and weight
- Smoking
- Alcohol use
- Geographic region (e.g., rural/urban, eastern/middle/western)
- Type of medical insurance
- Insurance coverage for posaconazole (injection and/or tablet formulations)

Clinical Characteristics

- Baseline disease(s)
- Infection history
- Treatment history
- Risk factor(s) related to treatment outcome, e.g. Allogeneic hematopoietic stem cell transplant (HSCT); Relapsed leukemia, undergoing salvage chemotherapy; Liver transplant recipients; all forms of immunocompromise (HIV infection; any solid organ transplantation; high dose corticosteroid therapy such as for chronic pulmonary or autoimmune diseases), etc

Examination

- Relevant examinations information for the diagnosis of proven, probable, possible IA and the treatment outcome assessment (e.g. galactomannan [GM] test, histopathology, cytopathological examination, needle biopsy record, imaging examination, bronchoscopy examination, antigen detection, etc.）

Diagnosis History

- IA diagnosis type (proven, probable, possible)
- IA infection site(s)
- Date of diagnosis
- Death date

7.3.2.2.3 Treatment Patterns

In support of the secondary objectives, we will report the following treatment patterns in the study population. Pending data availability, related variables may be adjusted and will be finalized in the case report form.

- First line/Salvage treatment
- Posaconazole regimen (dosage, duration)
- Combination therapy situation (list what agent(s) used, AmphoB, echinocandins, etc)
- Treatment related outcome (survival, death, complete response, partial response, stable response, progression of fungal disease)

Discontinuation of posaconazole Treatment (if applicable)

- Posaconazole discontinuation (yes/no)
- Stop date of posaconazole (date when previously dispensed medications were expected to be finished or documented by the clinician in medical records)

When a patient was considered to have discontinued posaconazole treatment, the below categories will be classified as the reason for discontinuation, if applicable, and the classification will be based on the descrition of the treating physician:

- Resistance (lack of response/persistent IA or progression of IA)
- Intolerance (patients discontinued because of toxicity related to Posaconazole; record clinical description/diagnosis once happens)
- Drug-drug interactions (e.g., potential interations, describe the product(s) and rationale to discontinue POSA therapy; actual interactions, describe products impacted and any associated AE)
- Financial (e.g., insurance coverage)
- Others (cannot be free text)
- Not documented

7.3.3 Covariates

Demographic and clinical characteristics will be collected at baseline in the study population if data is available (see 7.3.2.2.2).

7.4 Data Sources

Relevant patient-level information will be collected from multiple information systems, including EMR,paper medical records, Hospital Information System (HIS), Laboratory Information System (LIS), and routine patient management material from clinicians in selected hospitals. Medical records from other hospitals can be collected as needed The databases contain both inpatient and outpatient data.

For patient with retrospective data collection missing with dead or alive status in medical record, a follow up to confirm the dead or alive status through day 42 is required. Death certificate information or the follow-up contact/report/record by investigator would be the data sources.

All data will be collected with the use of a standardized case report form.

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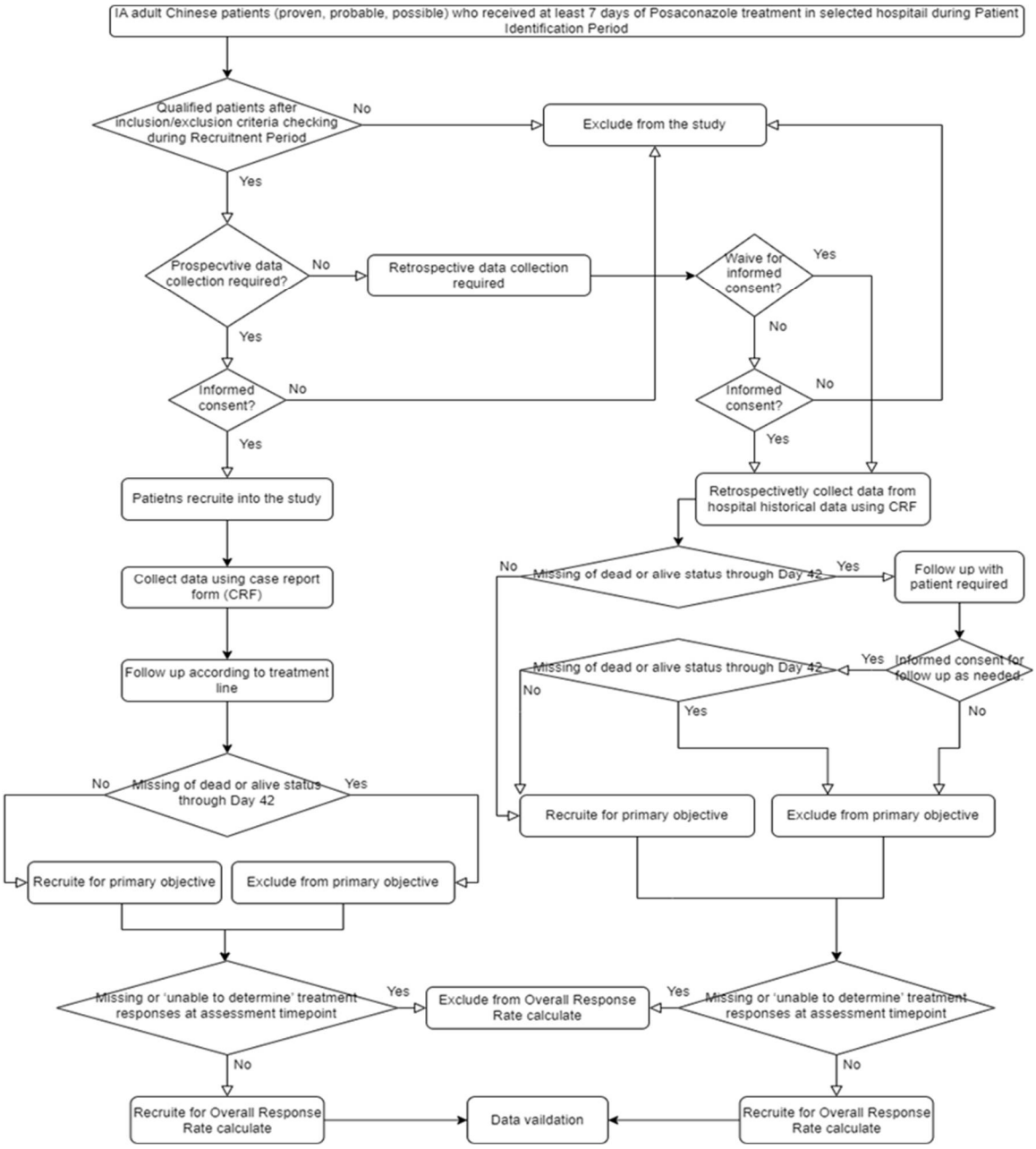
REVOPS ID NO: NIS102646 EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08047.004	CORE DRC APPROVAL DATE: 18-SEP-2024

7.4.1 Study Procedures

This study administered in a non-interventional setting. The study protocol will be submitted for approval by the institutional review board (IRB)/ethics review committee (ERC). Figure 2 shows the procedures of eligible patients enrollment.

Figure 2 Procedures of Eligible Patients Enrollment



Given that the study design involves prospective and retrospective data collection, the participating practitioner will obtain informed consent from patients included in prosepective data collection and submit the study to the IRB/ERC to let IRB/ERC determine whether the patients including in retrospective data collection qualifies to waive for informed consent. While doing retrospective data collection, if a follow up is need for patients to collect dead or alive status through Day 42, the informed consent should be obtained.

7.5 Study Size

All eligible IA patients will be identified and recruited from the March 2022 to Dec 2024.

55-70 cases with posaconazole treatment are expecting to be enrolled during the recruitment period for primary and secondary objectives (30-40 cases for primary objective). The estimation of sample size is based on market supply estimation and the RCT enrollment experience. The final sample size will depend on the number of patients eligible for the study in the study period. No hypothesis test and power calculation in this study. The total sample size in the final study report may be less. See Table 2, assuming 15%-50% of all-cause mortality observed through Day 42 for primary objective, the half-width of 95% confidence interval (CI) will range from 12.1%-18.7%.

Table 2 Two-Sided 95% Confidence Intervals for All-cause Mortality

Estimated number for primary objective participants	Number of Death (%)	Two-Sided 95% Confidence Interval [a]	Half-width of 95% Confidence Interval
N=30	4.5 (15.0)	(4.7, 32.7)	14
	6 (20.0)	(7.7, 38.6)	15.4
	9(30.0)	(14.7, 49.4)	17.3
	12 (40.0)	(22.7, 59.4)	18.4
	15 (50.0)	(31.3,68.7)	18.7
N=40	6 (15.0)	(5.7, 29.8)	12.1
	8(20.0)	(9.1, 35.6)	13.3
	12(30.0)	(16.6, 46.5)	15
	16 (40.0)	(24.9, 56.7)	15.9
	20 (50.0)	(33.8, 66.2)	16.2

[a] Based on the two-sided exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).

7.6 Data Management

All data collected for the study should be recorded accurately, promptly, and legibly. For primary data collection, the investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. For data not obtained from a primary source (i.e., secondary data, such as claims and electronic health records), the investigator is responsible

for reviewing data quality and relevance to the best of the investigator's knowledge. By signing this protocol either electronically or written, the investigator confirms that the quality and relevance of data has been assessed to meet the minimum requirements for all study objectives.

If this study has been outsourced, the institutional policies of the supplier should be followed for development of data management plans. However, the supplier should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

Data Management Software and Hardware:

Electronic Data Capture (EDC) System will be used in this study to collect and clean clinical data.

Type	Software System & Version
Clinical Database	Oracle® Clinical RDC Onsite 4.6.2
Data Entry	Oracle® Clinical RDC Onsite 4.6.2
Data Validation	Oracle® Clinical RDC Onsite 4.6.2
Medical Coding	Coding out of system: Programming

Statistical analysis is performed using SAS (version 9.4 or above) software.

Description of Data Preparation and Methods for Data Retrieval and Collection:

A case report form will be used for data collection. All data management activities including data capture, data storage, data cleaning, data security, and system backup processes will be undertaken by qualified personnel and will follow all procedures detailed in a separate "Data Management Plan".

7.7 Programming Quality

Not applicable.

7.8 Data Analysis

A descriptive analysis of the distribution of values abstracted for each variable will be provided. For the continuous variables we are interested, the values of mean/median, standard deviation (SD), min/max, interquartile range (IQR, including the first quartile [Q1] and third quartile [Q3]) will be calculated; the frequency and percentages will be calculated for these categorical variables. All analyses will be carried out using all available data. A participant with missing data on one variable will be used only in calculations that do not involve that variable.

All analyses will use SAS (SAS Institute Inc., Cary, North Carolina). Detailed statistical analysis plan (SAP) and corresponding mock-up tables/figures/listings will be described separately prior to the commencement of any analyses.

All analysis detailed will be described in a separate "Statistical Analysis Plan". Key points are listed below.

7.8.1 Primary Objective

The primary objective is to assess the all-cause mortality of using posaconazole for proven, probable, possible IA patients. The all-cause mortality will be calculated with 95% CI.

Total all-cause mortality=number of total IA patients who die through Day 42/number of all IA patients (proven, probable, possible) included in the study with dead or alive status reported x 100%.

All-cause mortality by treatment line=number of IA patients by treatment line who die through Day 42/number of IA patients by treatment line (proven, probable, possible) included in the study with dead or alive status reported x 100%.

The analysis will be stratified by method of data collection: prospective vs. retrospective.

The following subgroupanalysis may be conducted depending on data availability:

1. Treatment duration (e.g. group by median treatment duration, etc);

2. Patients who only receive Posaconazole injection vs patients who receive Posaconazole injection then Posaconazole tablet;

3. Risk factors for mortality and poor outcome (Allogeneic hematopoietic stem cell transplant (HSCT); Relapsed leukemia, undergoing salvage chemotherapy; Liver transplant recipients)

4. IA at sites: Pulmonary IA vs others (sinus/upper respiratory involvement or disseminated disease to other organs).

The following sensitivity analysis may be conducted depending on data availability:

Merge analysis of data from both prospective and retrospective collection.

7.8.2 Secondary Objectives

7.8.2.1 Overall response rates of posaconazole injection and/or tablet by treatment line at the end of posaconazole treatment

The secondary objective is to assess the overall response rates of using posaconazole for proven or probable or possible IA patients by treatment line. The Numerator is the success response of posaconazole which include survival followed by either complete response (CR) or partial response (PR) definition by treatment line (first line or salvage). The overall response rates at the end of posaconazole treatment will be described by percent with 95% CI in the patients with proven or probable or possible IA patients by treatment line.

Overall response rates (ORRs)=(number of patients with CR or PR) by treatment line (first line or salvage treatment)/ number of IA patients included in the study with available evidence on treatment response at the end of treatment by treatment line (first line or salvage treatment) x 100%.

The analysis will be stratified by method of data collection: prospective vs. retrospective.

The following subgroup analysis may be conducted depending on data availability:

1. Treatment duration;

2. Patients who only receive posaconazole injection vs patients who receive posaconazole injection then posaconazole tablet;

3. Risk factors for mortality and poor outcome (Allogeneic hematopoietic stem cell transplant (HSCT); Relapsed leukemia, undergoing salvage chemotherapy; Liver transplant recipients; HSCT+Hematologic Malignancy vs. all other immunocompromised vs. No recorded risk factor (if any));

4. IA at sites: Pulmonary IA vs others (sinus/upper respiratory involvement or disseminated disease to other organs);

5. Methods of clinical response definition: guideline vs. investigator judgment.

The following sensitivity analysis may be conducted depending on data availability:

Merge analysis of data from both prospective and retrospective collection.

7.8.2.2 Baseline Demographic and Clinical Characteristics by treatment line

The variables list in Section 7.3.2.2.2 Demographic and Clinical Characteristics will be described among patients in the study population overall, and separately by treatment line.

7.8.2.3 Treatment Patterns by treatment line

The variables list in Section 7.3.2.2.3 Treatment Patterns will be described among patients in the study population overall, and separately patients by treatment line.

For discontinuation characteristics, frequency, proportion of patients with discontinuation, and time taken from the initiation to discontinuation will be reported. The reason for discontinuation will be classified and reported.

7.9 Quality Control

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), Good Pharmacovigilance Practices (GVP) and all applicable, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP and GVP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

For retrospective data, the data will be assessed in terms of the integrity and completeness.The data will be collected and entered into EDC by trained study personnel, will be reviewed for compliance with medical record writing specifications and with reasonable ranges of clinical variables by investigators. All data will be monitored by assigned qualified study research associates by source data verification, For data with logical errors, abnormal values or missing values, the investigator will be consulted on the possible causes of low data integrity and an effective data management plan will be proposed.

7.10 Limitations of the Research Methods

As this is an observational study, potential bias cannot be ruled out. 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 available and its interpretation. Potential sources of bias and limitations as well as strategies to minimize these are discussed further below.

First, cases from the potential leading site or potential sub sites may be sicker as these potential sites are the top-level hospitals in China. Patient with sicker situation in China

prefer top-level hospitals. Sicker cases will lead to lower ORR and higher ACM which may not reflect the real value of posaconazole. (Admission rate bias) To mitigate this bais, the following action will be implemented. The study design to assess the study outcomes (see 7.3.2) by different treatment lines (first line and salvage treatment) to differentiate patients' disease conditions. Patient characteristics by treatment line are also described as secondary endpoint.

Second, survivor cases from retrospective data collection are easier to be reached to sign the ICF in the recruitment period, at the same time, cases from retrospective data collection or prospective data collection may be lost to follow-up without clear alive or dead status or response data. These situations will lead to underestimate or overestimate the ACM/ORR. (Immortal time bias/ No-respondent bias/Survivor bias) To mitigate this bias, study design to contact not only the case himself/herself from retrospective data collection, but also their relatives to follow up with missing dead or alive status. And cases from prospective data collection will be closed monitor to make sure the alive or dead status and response data are recorded.

Third, for cases from retrospective data collection, some historical clinical data may be missing. (Missing clinical data bias) The missing data may be correlated with the outcome (e.g., perhaps more clinical data is included for more severe cases that require more frequent monitoring, which would lead to underrepresentation of less severe cases that are more likely to survive) such that estimates could be biased. Case with missing critical data, for example, missing withdead or alive status at day 42/ information of treatment responsed after the end of treatment, will be excluded from the ACM and ORR calculation, so the sample size will be smaller than estimation. CCI [redacted] this may impact on the patient number received posaconazole injection and/or tablet. To ensure the completeness of clinical data, cases without treatment response or classification of proven, probable, possible will require doctor’s judgement about whether the treatment response and classification can be defined by the other examination/test reports previously to minimum the missing data rate.

Fourth, the selected hospitals or patients will not be randomly selected and may not be a representative sample of the whole posaconazole injection and/or tablet formulations.The hospital selection will based on the operation difficulty, potential number of IA patients and potential use of posaconazole injection and/or tablet formulations. This study aim to select hospital with more potential IA patients and use of posaconazole injection and/or tablet formulations to present the representativeness.

7.11 Other Aspects

Not applicable.

8 PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study, the study protocol and informed consent will be submitted for review and approval by an IRB/ERC prior to study execution. The privacy of all participants will be well protected, personal identification data will be de-identified at the time of analysis, including but not limited to name, ID, etc.

All demographic and diagnosis information for each eligible patients, as well as laboratory information are generated during the routine clinical practice and before the conduct of the retrospective chart review process. The information will be tracked, collected, stored and used by selected hospitals or the study staff of the retrospective study and will not be provided to entities outside the study.

8.1 Informed Consent

For retrospective data collection, the study will be submitted to the IRB/ERC to let IRB/ERC determine whether the study qualifies for the waiver of informed consent. In the situation where informed consent could not be waived, consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

For prospective data collection, consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

Introduction

This is a non-interventional study being conducted within routine medical practice, which includes primary data collection and use of secondary data collected from healthcare professionals for other purposes. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol.

9.1 Adverse Event and Product Quality Complaint Reporting

9.1.1 Investigator Responsibility

Primary Data Collection (follow up activities for dead or alive status for patients with retrospective data collection missing with dead or alive status in medical record): if adverse events (AEs) or product quality complaints (PQCs) are identified following use of Noxafil, or any other Sponsor product, then the AE* and/or PQC must be reported according to Table 3. The investigator must evaluate each SAE and NSAR for causality and record causality on the report form for each SAE and NSAR reported.

Secondary chart review: Although adverse events (AEs) and product quality complaints (PQCs) are not actively solicited in this study, there are certain circumstances in which individual AEs and/or PQCs will be reported. For example, during review of medical records or physician notes (paper or electronic), to collect data as required by the protocol, if a notation of an AE* or PQC to Noxafil or any other Sponsor's product is identified, the AE/PQC must be reported according to Table 3.

*For the purposes of this protocol, the term "AE" collectively refers to the following reportable events (refer to section 9.2 for definitions):

- Serious adverse events (SAEs), including death due to any cause (primary data collection)
- Serious adverse reactions (SARs), including death (secondary chart review)
- Non-serious adverse reactions (NSARs)
- Special situations

If any health outcomes are described in section 7.3.2, they must be assessed for AE reportability according to Table 3 (refer to section 7.3.2 for more information).

AEs, PQCs, and AEs that occur in combination with PQCs, or spontaneously reported events, should all be captured using the AE/PQC report form for each patient and reported according to Table 3.

Table 3 AE and PQC Reporting Timeframes and Process for Investigators

AEs AND PQCs	**INVESTIGATOR TIMEFRAMES Investigator to Sponsor [1], [2]**
SAE regardless of causality (primary data collection) SAR (secondary data collection) Serious Special Situation, regardless of causality	24 hours from receipt
NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt
PQC with or without an AE (SAE/SAR/NSAR/Special situation)	24 hours from receipt
Follow-up to any AE/PQC-submit using above timeframes	
BD-Business Day; CD-Calendar Day	
Non-Sponsor Product: If the investigator elects to submit AEs/PQCs for **non-Sponsor products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.	
[1] Investigator to Sponsor: AEs and PQCs for Sponsor study product and *other* Sponsor products are submitted to the Sponsor for reporting to worldwide regulatory agencies as appropriate. **[2] Investigator to Study Lead:** Study Lead ensures AEs for Sponsor study product are entered into study database (or equivalent repository) for tabulation in study report	
Submitting AEs and PQCs to China PV: All AEs and PQCs must be submitted to China PV FAX +86-10-58609044 or mailbox <drugsafetychina@merck.com> (via secure email) in Chinese/English using the AE/PQC reporting form.	

9.1.2 Study Report

The final study report, and any planned interim analysis, will include a summary of all reported AEs and special situations collected for Noxafil and will be provided to regulatory agencies by the Sponsor as required.

9.1.3 Periodic Safety Update Reports

Any relevant safety information will be summarized and the sponsor will include in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

9.2 DEFINITIONS

9.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered Sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

9.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

9.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

9.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 9.2.3.

9.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure

- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect

9.2.6 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

9.2.7 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

9.2.8 Sponsor's Product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

9.2.9 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form for each reported event in relationship to a Sponsor's product.

Primary Data Collection

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

Secondary Data Collection

Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as NSAR/SARs. During review of secondary data, causality should never be assigned retrospectively.

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9.3 AE/PQC Reconciliation

Reconciliation will be performed between the safety database and study data to ensure all reportable AEs and PQCs were reported and received. Starting from when the first patient is enrolled through the end of data collection, all AEs and PQCs will be reconciled on a periodic basis.

9.4 Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory agencies, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

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10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The primary results of this research study will be externally disseminated in a manuscript submitted to a peer-reviewed, scientific journal, abstract/presentation at a scientific conference or symposium, or results posted on the the EU PAS Register. Any publication related to the study will need to be reviewed/approved by the Sponsor prior to submitting results externally. Any publication resulting from this work will adhere to the procedures and pre-specified analysis plans within this protocol.

11 REFERENCES

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[Chinese Invasive Fungal Infection Working Group 2017]	Chinese Invasive Fungal Infection Working Group. [The Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the fifth revision)]. Chin J Intern Med. 2017 Jun;56(6):453-9. Chinese.	[05G2Z2]
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[Wang, W., et al 2011]	Wang W, Zhao CY, Zhou JY, Wang YD, Shen C, Zhou DF, et al. Invasive pulmonary aspergillosis in patients with HBV-related liver failure. Eur J Clin Microbiol Infect Dis. 2011;30:661-7.	[089T44]
[Yuan, X. U., et al 2018]	Yuan XU, Min C, Wan-qing L. [Epidemiology of invasive aspergillosis in China]. Chin J Mycol. 2018;13(1):57-60. Chinese.	[089SXF]

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[Zhou, L. H., et al 2020]	Zhou LH, Jiang YK, Li RY, Huang LP, Yip CW, Denning DW, et al. Risk-based estimate of human fungal disease burden, China. Emerg Infect Dis. 2020 Sep;26(9):2137-47.	[089STY]

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12 ANNEXES

Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1.	<No>	<Date>	ER212-PV001 Adverse Event and Product Quality Complaint Reporting Form

PRODUCT: MK5592	PROTOCOL/AMENDMENT VERSION NO.: 2
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Annex 2 ENCePP Checklist for Study Protocols (Revision 4)

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Post Marketing Surveillance of Effectiveness (All-Cause Mortality) of Posaconazole Injection and Tablet Treatment of Invasive Aspergillosis in Chinese patients

EU PAS Register® number:
Study reference number (if applicable): MK5592

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☐	☒	☐	2
1.1.4 Interim report(s)	☐	☒	☐	2
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	4
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

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Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	5
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9

Comments:

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Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	7.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	7.2.5
	4.2.2 Age and sex	☒	☐	☐	7.2.1
	4.2.3 Country of origin	☒	☐	☐	7.2.1
	4.2.4 Disease/indication	☒	☐	☐	7.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	7.2.5
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2.1, 7.4.1

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	7.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	7.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	7.3.3

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.9

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	7.7

Comments:

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Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	7.3.3
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
	9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

9.3 and 9.4 will be described in DMP.

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	7.5
10.3	Are descriptive analyses included?	☒	☐	☐	7.7
10.4	Are stratified analyses included?	☒	☐	☐	7.7
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	7.3
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	7.7

Comments:

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Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8
11.2 Are methods of quality assurance described?	☒	☐	☐	7.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	7.9
12.1.2 Information bias?	☒	☐	☐	7.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	8.1
13.3 Have data protection requirements been described?	☒	☐	☐	8

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3

Comments:

It is an original version.

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Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 CCI [redacted]	☒	☐	☐	5.1
15.2 Are plans described for disseminating study results externally, including publication?	☐	☒	☐	

Comments:

No plan for publication.

Name of the main author of the protocol: PPD

Date: 26/April /2023

Signature: _____

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Annex 3 Administrative and Regulatory Details

Confidentiality:

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence if applicable such information will be divulged to Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel (if applicable), may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. By signing

this protocol, the investigator expressly consents to these uses and disclosures. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. The investigator is hereby notified that the collection, processing and sharing of their personal data with respect to adverse event reports to the Sponsor and regulatory agencies occurs on the basis of performance of a legal obligation, and the investigator expressly consents to these uses and disclosures when reporting such events to other investigators.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

Administrative:

Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, such as ENCePP. Merck, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated studies. Information posted will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this study or its results to the Clinical Trials Data Bank.

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REVOPS ID NO: NIS102646 EPIDEMIOLOGY NO.(PE STUDIES ONLY): EP08047.004	CORE DRC APPROVAL DATE: 18-SEP-2024

Annex 4 Qualified Person for PharmacoVigilance (QPPV)

Peter De Veene
Global Qualified Person for Pharmacovigilance (GQPPV)
EU/UK QPPV
PPD

MSD Europe Belgium SRL
Boulevard du Souverain, 25
1170 Watermael-Boitsfort
Bruxelles, Belgique

Deputy QPPV:
PPD

GQPPV Office Physician:
PPD

Emergency/Out of Hours: As above or via PPD

Dear Sir/Madam,

Re: Global, EU/UK QPPV Signature Page for PASS

INN:
Product: NOXAFIL™ (MK5592)
Protocol No: MK5592-141
Epidemiology No: EP08047.004
Protocol Date: 18 September, 2024
MAH: Merck Sharp & Dohme LLC

In line with the Guideline on Good Pharmacovigilance Practice (GVP), Module VIII - Post-Authorization Safety Studies (PASS) and according to MSD internal SOPs, this study has been reviewed and approved by the Global Qualified Person for the Pharmacovigilance (GQPPV), EU/UK QPPV.

Yours faithfully PPD

Dr Peter De Veene
Associate Vice President, PPD

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Annex 5 Criteria for Diagnosis of Invasive Aspergillosis

In order to determine if a subject meets the 2020 EORTC/MSGERC or 2021 EORTC/MSGERC-ICU* consensus criteria for proven, probable, or possible invasive aspergillosis, use the criteria below.

* This criterion comes from the 2021 EORTC/MSGERC-ICU consensus criteria.

- Link for 2020 EORTC/MSGERC consensus criteria: https://pubmed.ncbi.nlm.nih.gov/31802125/

- Link for 2021 EORTC/MSGERC-ICU consensus criteria: https://pubmed.ncbi.nlm.nih.gov/33709127/

A subject can be diagnosed as having	**if they have:**
PROVEN Invasive Aspergillosis	One of the required criteria
PROBABLE Invasive Aspergillosis	One host factor AND One clinical feature AND One mycologic evidence
POSSIBLE Invasive Aspergillosis	One host factor AND One clinical features

Criteria for <u>Proven</u> Invasive Aspergillosis
- Tissue histopathologic, cytopathologic[a], or direct microscopic examination of a needle aspiration or biopsy specimen showing hyphal forms with evidence of associated tissue damage (either microscopically or as an infiltrate or lesion by imaging) OR - Recovery of Aspergillus species by culture from a sample obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site OR - Amplification of Aspergillus DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue
[a]Tissue and cells submitted for histopathology or cytopathology should be stained by Grocott-Gomori methenamine silver stain or by periodic acid Schiff stain to facilitate inspection of fungal structures. Where possible, wet mounts of specimens from foci related to invasive fungal infectious disease should be stained with a fluorescent dye (e.g., calcofluor or Blankophor).

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Criteria for Probable and Possible Invasive Aspergillosis
Host Factors[a]

- Recent history of neutropenia (0.5 x 109 neutrophils/L [<500 neutrophils/mm3] for >10 days) temporally related to the onset of invasive fungal disease

OR

- *Qualitative or quantitative neutrophil abnormality (inherited neutrophil deficiency, absolute neutrophil count of ≤500 cells/mm3)
- Hematologic malignancy[a]
- Receipt of an allogeneic stem cell transplan
- Receipt of solid organ transplant
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days

OR

- *Glucocorticoid treatment with prednisone equivalent of 20 mg or more per day
- Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 days
- Treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib
- Inherited severe immunodeficiency (such as chronic granulomatous di-sease, STAT 3 deficiency, or severe combined immunodeficiency)
- Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids
- *Chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis)
- *Decompensated cirrhosis
- *Human immunodeficiency virus infection
- *Severe influenza (or other severe viral pneumonia, such as coronavirus disease 2019 [COVID-19])

[a]Hematologic malignancy refers to active malignancy, in receipt of treatment for this ma-lignancy, and those in remission in the recent past. These patients would comprise largely acute leukemias and lymphomas, as well as multiple myeloma, whereas patients with aplastic anemia represent a more heterogeneous group of individuals and are not included.

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Criteria for Probable and Possible Invasive Aspergillosis Clinical Feature
Pulmonary aspergillosis - The presence of 1 of the following 4 patterns on CT: • Dense, well-circumscribed lesions(s) with or without a halo sign • Air crescent sign • Cavity • Wedge-shaped and segmental or lobar consolidation *Other pulmonary mold diseases* - As for pulmonary aspergillosis but also including a reverse halo sign *Tracheobronchitis* - Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis *Sino-nasal disease* - Acute localized pain (including pain radiating to the eye) - Nasal ulcer with black eschar - Extension from the paranasal sinus across bony barriers, including into the orbit *Central nervous system infection* - 1 of the following 2 signs: • Focal lesions on imaging • Meningeal enhancement on magnetic resonance imaging or CT

Criteria for Probable and Possible Invasive Aspergillosis Mycological Evidence
Galactomannan antigen - Antigen detected in plasma, serum, BAL, or CSF - Any 1 of the following: • Single serum or plasma: ≥1.0 • BAL fluid: ≥1.0 • Single serum or plasma: ≥0.7 and BAL fluid ≥0.8 • CSF: ≥1.0 *Aspergillus PCR* - Any 1 of the following: • Plasma, serum, or whole blood 2 or more consecutive PCR tests positive • BAL fluid 2 or more duplicate PCR tests positive • At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid - Aspergillus species recovered by culture from sputum, BAL, bronchial brush, or aspirate - *Cytology, direct microscopy, and/or culture indicating presence of Aspergillus spp. in a lower respiratory tract specimen - *Galactomannan antigen index >0.5 in plasma/serum and/or galactomannan antigen >0.8 in BALF

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13 SIGNATURES

13.1 Sponsor's Representative

PRINTED NAME	PPD
TITLE	Sr. Scientist, Biostatistics and Research Decision Sciences (BARDS)-Epidemiology, MSD R&D (China) Co., Ltd
SIGNATURE	
DATE SIGNED	

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13.2 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other project plans and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and the Use and Disclosure of Personal Data notice provided to me, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

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13.3 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and in order to perform any agreement between myself and the Sponsor, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	