PASS INFORMATION

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Joint PASS	No
Research question and objectives	To assess the effectiveness of posaconazole in Chinese adult patients with invasive aspergillosis who have received at least 7 days of posaconazole injection and/or tablet treatment.
Country(-ies) of study	China
Author	PPD

	PPD
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1 ABSTRACT

Title

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

Sponsor Final Repository (REDS) Date

08-Jul-2025

Author

PPD

Keywords

NOXAFIL®, Posaconazole Enteric-coated Tablets, Posaconazole Injection, Invasive Aspergillosis, Non-Interventional Study

Rationale and background

Posaconazole injection and enteric-coated tablets were approved by the National Medical Products Administration (NMPA) for the treatment of invasive aspergillosis (IA) in adult patients on 29 Mar 2022. The Center for Drug Evaluation (CDE) required the continued observation of the effectiveness of the treatment of IA in adults in a larger population after the product launch. This study was conducted to fulfill the post-marketing commitment.

IA is a serious fungal infection with a mortality rate of 39%-100%; therefore, a reduction in all-cause mortality (ACM) among treated patients is a critical measure of real-world effectiveness. ACM was also a clinical endpoint in the Phase 3 trial (MK-5592-069; NCT01782131) that supported the marketing approval for this indication. This study primarily focused on the assessment of the real-world effectiveness of posaconazole injection and tablets by evaluating ACM in Chinese adult patients with IA.

Research question and objectives

Primary objective:

- 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：

- 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.
- 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.
- 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 was a multicenter non-interventional study involving both prospective and retrospective data collection from medical charts in 9 hospitals using a case report form (CRF) during the study period.

Setting

Data for this study was collected prospectively and/or retrospectively from 9 tertiary Grade A hospitals where posaconazole injection and/or tablets were available during the study period (29 Mar 2022 to 24 Jan 2025). The patient identification period was from 29 Mar 2022 to 3 Jan 2025 (last patient in), with follow-up until 24 Jan 2025 (last patient last visit). Retrospective data was collected from 29 Mar 2022 to 21 Sep 2023, and prospective data from 22 Sep 2023 to 24 Jan 2025. Key information collected included study-related demographics, clinical characteristics (including medical history and diagnosis history), treatment information (including regimens and discontinuation), and outcomes (including all-cause mortality and clinical response assessments).

Subjects and study size, including dropouts

The Overall Study Population consisted of Chinese adult IA patients who had received at least 7 days of posaconazole injection and/or tablets at the 9 study sites. The sample size of the study depended on the number of eligible patients identified during the patient identification period. It was expected that 55 to 70 patients would be enrolled to meet the primary and secondary objectives, including 30-40 cases for the primary objective. Assuming an ACM rate of 15%-50% observed through Day 42 for the primary objective, the half-width of the 95% confidence interval (CI) was estimated to range from 12.1%-18.7%.

Variables and data sources

Variables

- Exposure: Posaconazole injection and/or tablet treatment.
- Primary outcome: All-cause mortality through Day 42 following the initiation of posaconazole injection and/or tablet treatment.
- Secondary outcome: Clinical response at the end of posaconazole treatment (prior to or on Day 84 following the initiation of posaconazole injection and/or tablet treatment).
- Other variables: Patient demographics, clinical characteristics, and posaconazole treatment patterns.

Data sources

Relevant patient-level information was collected from multiple information systems, including Electronic Medical Records (EMR), paper medical records, Hospital Information System (HIS), and Laboratory Information System (LIS) in selected hospitals. Death certificate information was collected for patients with retrospective data collection who had missing vital status in their medical records. Data was collected using a standardized CRF.

Results

Patient disposition

Of the 1,834 patients identified from 29 Mar 2022 to 3 Jan 2025 and screened for eligibility, a total of 56 patients were enrolled. After excluding 7 patients with important protocol deviations (PDs), 49 IA patients who had received at least 7 days of posaconazole injection and/or tablet treatment and met the eligibility criteria were included in the Overall Study Population, which consisted of 27 (55.1%) first-line treatment patients and 22 (44.9%) salvage treatment patients.

Demographic and clinical characteristics

The overall median age at the index date (the date of the first administration of posaconazole injection or tablet) was 56.0 years (interquartile range [IQR]: 41.0, 69.0), and the majority were male (67.3%, 33/49). Most patients (71.4%, 35/49) had a possible diagnosis of IA, followed by probable diagnosis (26.5%, 13/49) and proven diagnosis (2.0%, 1/49). Based on investigator assessment, nearly 80% (39/49) of the patients had risk factors for poor outcomes due to IA at the index date, including relapsed leukemia undergoing salvage chemotherapy (48.7%, 19/39), allogeneic hematopoietic stem cell transplant (HSCT; 7.7%, 3/39), and other immunocompromised conditions (71.8%, 28/39).

All-cause mortality (ACM) through Day 42

The primary analysis of ACM included 48 patients from the Overall Study Population, excluding one patient due to missing Day 42 vital status following the initiation of posaconazole treatment. Two of the patients had a death record through Day 42, corresponding to an overall ACM rate of 4.2% (95% CI: 0.5%, 14.3%).

Overall response rate (ORR) by treatment line

Among the 27 first-line treatment patients in the Overall Study Population, 6 met the criteria for first-line ORR analysis, which required receiving posaconazole treatment for at least 42 days. Of these 6 patients, 4 achieved success at the end of treatment or Day 84 post-treatment initiation, including 1 complete response (CR) and 3 partial responses (PRs). The first-line ORR was 66.7% (95% CI: 22.3%, 95.7%).

All 22 salvage treatment patients in the Overall Study Population met the criteria for salvage ORR analysis, which required receiving posaconazole treatment for at least 7 days. A total of 19 patients achieved success at the end of treatment or Day 84 post-treatment initiation, including 4 CRs and 15 PRs. The salvage ORR was 86.4% (95% CI: 65.1%, 97.1%).

Posaconazole treatment patterns

For the 27 first-line treatment patients in the Overall Study Population, the median posaconazole treatment duration was 16.0 days (IQR: 8.0, 37.0), with a median cumulative dosage of 5,400.0 mg (IQR: 2,400.0, 11,100.0). The most common medication administration type was tablets only (N=25, 92.6%), and the majority received posaconazole as monotherapy (N=22, 81.5%).

For the 22 salvage treatment patients in the Overall Study Population, the median posaconazole treatment duration was 25.5 days (IQR: 13.0, 31.0), with a median cumulative dosage of 7,650.0 mg (IQR: 3,900.0, 9,300.0). The most common medication administration type was tablets only (N=16, 72.7%), and most patients received posaconazole as monotherapy (N=18, 81.8%).

In this study, adverse events (AEs) and product quality complaints (PQCs) were not actively solicited. Only one special situation (pre-approval off-label use) met the reporting criteria specified in the protocol and was reported. No other AEs or PQCs were identified during the chart review.

Discussion

This is the first non-interventional study of posaconazole injection and tablets in China. The primary outcome, the 42-day ACM rate for posaconazole treatment in IA patients, was 4.2% (95% CI: 0.5%, 14.3%) in this study, which is consistent with the result in the CCI [redacted] global trial population (42-day ACM rate of 15.3%) of the pivotal clinical trial (MK-5592-069; NCT01782131). Additionally, the key secondary outcomes, the first-line ORR and salvage ORR, were 66.7% (95% CI: 22.3%, 95.7%) and 86.4% (95% CI: 65.1%, 97.1%), respectively, demonstrating favorable treatment outcomes.

Published real-world studies on posaconazole treatment for IA are extremely limited, and no relevant studies have been found in the Chinese population. Only a few studies have provided some reference results on the ACM rate and ORR in patients treated with posaconazole for invasive fungal diseases (IFDs) [Ref. 5.4: 08VW2S], [Ref. 5.4: 08VWQ5], [Ref. 5.4: 08VWQ9], [Ref. 5.4: 08VWQB]. Specifically, the ACM rate reported in these published studies ranged from 4.2% to 11.1%, and the ORR, regardless of the line of treatment, ranged from 50.0% to 59.3%. The results of this study, as stated above, are consistent with the findings from those published studies.

Caution should be exercised when interpreting the results from this study, as the sample size was relatively small, and the study sites were not randomly selected. Nevertheless, this study included 9 hospitals from various regions across China and assessed all eligible patients during the study period under real-world clinical settings. The included patients were typical of patients who receive treatment for IA in real-world settings. A standardized CRF and uniform criteria for IA diagnosis and clinical response assessments were employed to collect data, ensuring data integrity and quality. Given the rarity of the condition, these efforts increased the sample size and population representativeness, thereby strengthening the robustness and reliability of the findings. Consequently, the potential limitations should have minimal impact on the effectiveness evaluation and the generalizability of the findings.

Overall, this is the first post-marketing non-interventional study conducted in China assessing the effectiveness of posaconazole injection and tablets for IA in Chinese adult patients. The results demonstrate high effectiveness for both first-line and salvage treatment.

Marketing Authorisation Holder(s)

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Names and affiliations of principal investigators

Prof. Si Zhou Feng, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

2 LIST OF ABBREVIATIONS

ACM	All-Cause Mortality
AE	Adverse Event
CDE	Center for Drug Evaluation
CI	Confidence Interval
cm	Centimeter(s)
CR	Complete Response
CRF	Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
EORTC/MSGERC	European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium
EC	Ethics Committee
GM	Galactomannan
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B Virus
HGRAC	Human Genetic Resource Administration of China
HIS	Hospital Information System
HSCT	Hematopoietic Stem Cell Transplant
IA	Invasive Aspergillosis
ICF	Informed Consent Form
ICU	Intensive Care Unit
IDL	Imported Drug License
IFD	Invasive Fungal Disease
IFI	Invasive Fungal Infections
IPA	Invasive Pulmonary Aspergillosis
IQR	Interquartile Range
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram(s)

LIS	Laboratory Information System
LOT	Line of Treatment
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
NMPA	National Medical Products Administration
NSAR	Non-Serious Adverse Reaction
ORR	Overall Response Rate
PD	Protocol Deviation
PI	Principal Investigator
PQC	Product Quality Complaint
PR	Partial Response
PT	Preferred Term
Q1	The First Quartile
Q3	The Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SQI	Significant Quality Issue
TFL	Tables, Figures, and Listings
WHODD	World Health Organization Drug Dictionary

3 INVESTIGATORS

Principal investigator	Prof. Si Zhou Feng, 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	PPD

4 OTHER RESPONSIBLE PARTIES

Shared Responsibilities	Contact Person
Not applicable	

5 MILESTONES

Milestone	Planned date	Actual date	Comments
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	22-Sep-2023	NA
End of data collection	Jan 2025 (planned date of last patient last visit)	24-Jan-2025	NA
Registration in the HMA-EMA Catalogue of RWD Studies	Within 35 days of protocol finalization in Regulatory Enterprise Document Source (REDS)	18-Jan-2024	After protocol finalization, the Study Lead notified CDD&T to request assistance with EU PAS registration. Initially, CDD&T believed that PAES did not need to be registered in EU PAS. Based on previous study experience, the Study Lead and the Study Manager internally discussed and concluded that PAES requires EU PAS registration. The Study Lead communicated this to CDD&T, who verified and confirmed it afterwards. This process caused a delay of the registration.
First approval by IEC/IRB	NA	29-Jun-2023	NA
Last approval by IEC/IRB	NA	09-Feb-2024	NA
Final report of study results	Jun 2025	08-Jul-2025	NA

6 RATIONALE AND BACKGROUND

Posaconazole[1], a triazole antifungal agent, is indicated for the treatment of the following invasive fungal infections (IFI) worldwide in patients with disease that is refractory to, or in patients who are intolerant of other alternative therapies: aspergillosis, candidiasis, fusariosis, zygomycosis, cryptococcosis, chromoblastomycosis, mycetoma, and coccidioidomycosis.

In China, posaconazole injection (for intravenous [IV] use) and enteric-coated tablets (for oral use) were approved on 30 Jan 2021 and 7 Dec 2018, respectively, for the prophylaxis of invasive *Aspergillus* and *Candida* infections. Later, posaconazole injection and tablets were approved for the treatment of invasive aspergillosis (IA) in adults on 29 Mar 2022.

The estimated prevalence of IA in China was approximately 1.17 million cases in 2020 [Ref. 5.4: 089STY]. The incidence rate of IA has been rising, with conservative estimates indicating around 160,000 cases per year in 2016 [Ref. 5.4: 089SXF]. There are very few publications reporting the mortality of IA in the Chinese population, and existing literature is outdated. A review published in 2012 summarized that the global mortality rate of IA ranged from 30% to 95% [Ref. 5.4: 089SYX]. In China, a single-site study reported a mortality rate of 39% among non-neutropenic patients with proven or probable invasive pulmonary aspergillosis (IPA) [Ref. 5.4: 089T3B], and another single-site study reported a mortality rate of 100% among patients with a probable IPA diagnosis admitted with hepatitis B virus (HBV)-related liver failure [Ref. 5.4: 089T44]. IA patients with underlying disease without timely treatment have an extremely high fatality rate.

Therefore, reducing mortality among patients with IA is a measure of the real-world effectiveness of antifungal treatment. All-cause mortality (ACM) was also a clinical endpoint in the Phase 3 trial (MK-5592-069; NCT01782131) comparing posaconazole to voriconazole for the treatment of IA.

Rationale

The new injection and tablet formulations of posaconazole were able to achieve a higher exposure target with reduced variability compared to the posaconazole oral suspension. Posaconazole injection and enteric-coated tablets were approved by the National Medical Products Administration (NMPA) for the treatment of IA in adult patients on 29 Mar 2022. The Imported Drug License (IDL) of NOXAFIL® included a requirement to collect more effectiveness data in the Chinese patient population after the product launch. To fulfill the Center for Drug Evaluation (CDE) request to “continue observing the safety and effectiveness of the treatment of IA in adults in a larger population,” the sponsor proposed conducting a multicenter observational study to prospectively and retrospectively collect effectiveness information from Chinese adult IA patients treated with posaconazole injection and/or tablets.

The advantage of this observational study is that it can be conducted without any intervention, thereby providing information on patients receiving posaconazole that better reflects real-world clinical practice. Currently, there is no database in China that can be directly used to

[1] The posaconazole mentioned in this report refers to the posaconazole injection manufactured by FAREVA Mirabel and/or posaconazole enteric-coated tablets manufactured by N.V. Organon, under the brand ‘NOXAFIL’.

assess the effectiveness of posaconazole. This study, utilizing medical records from multiple centers as the primary data source, is the most feasible research method.

Based on the evaluation of the number of IA patients at potential research sites, the extensiveness of prophylactic use, and the enrollment difficulty and speed in clinical trials, the number of IA patients treated with posaconazole observed in this study might be limited. Hence, this study proposed a combination of prospective and retrospective study designs.

7 RESEARCH QUESTION AND OBJECTIVES

The aim of this study was to assess the ACM rate in Chinese adult patients with IA receiving treatment with posaconazole injection and/or tablets by a non-interventional study involving both prospective and retrospective data collection from study sites using a standardized case report form (CRF) during the study period.

7.1 Primary objective

1. To assess ACM 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.

7.2 Secondary objectives

1. To assess the overall response rate (ORR; 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[2] and maximum treatment duration 12 weeks [84 days]) in Chinese adult IA patients.
2. To assess the ORR (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[2] 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.
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.

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

[3] Complete response (CR) and partial response (PR) followed the definition of the Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the fifth version) [Ref. 5.4: 05G2Z2].

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

8 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
None				

9 RESEARCH METHODS

9.1 Study design

The study did not involve any interventional measures, such as receiving posaconazole injection and/or tablet or laboratory tests for IA diagnosis. All patients had previously received posaconazole injection and/or tablets in the course of routine clinical practice.

This was a multicenter non-interventional study involving prospective and retrospective data collection from medical charts in 9 tertiary Grade A hospitals using a CRF during the study period (29 Mar 2022 to 24 Jan 2025).

Chinese adult IA patients (≥18 years old) who had been treated with posaconazole for at least 7 days[2] in accordance with NMPA's approved product information were potential subjects for the study.

After confirming study eligibility, the following assessments were conducted:

- Patients who had continued posaconazole treatment for 7 to 42 days and had dead or alive status available through day 42 were evaluated for the primary objective.
- Patients who had continued posaconazole as first-line treatment for 42 to 84 days and had treatment response data available (success or failure at the end of treatment or at a maximum duration of 84 days) were evaluated for secondary objectives.
- Patients who had continued posaconazole as salvage treatment for 7 to 84 days and had treatment response data available (success or failure at the end of treatment or at a maximum duration of 84 days) were evaluated for secondary objectives.
- The demographics, clinical characteristics, and treatment patterns were described in this study.

Information was collected using a CRF during the study period (29 Mar 2022 to 24 Jan 2025), including but not limited to outpatient or inpatient medical records, lab reports, prescription records, etc., by qualified investigators.

9.2 Setting

9.2.1 Study sites

Hospitals where posaconazole injection and/or tablets were available and had the most patients using these products during the study period were considered for inclusion. Site selection was based on the availability of posaconazole injection and/or tablets, the number of potentially eligible patients, the principal investigator's (PI) willingness to participate, the completeness of medical records regarding key study information, and the feasibility assessment from an operational perspective.

A total of 9 sites were included in the study, including 1 leading site and 8 sub-sites:

Leading site:

1. Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

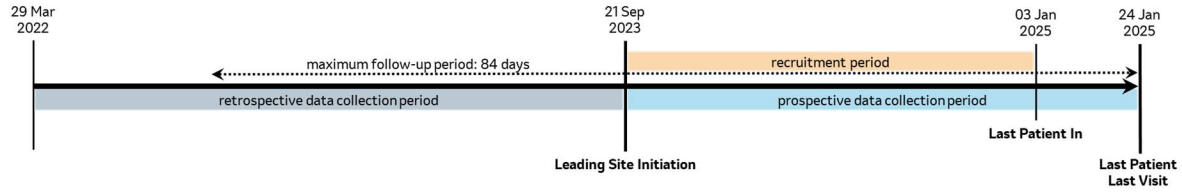
Sub-sites:

1. The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi Province, China
2. Taizhou Hospital of Zhejiang Province, Taizhou, Zhejiang Province, China
3. Sun Yat-sen Memorial Hospital, The Second Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong Province, China
4. Tianjin First Central Hospital, Tianjin, China
5. Xiangya Hospital of Central South University, Changsha, Hunan Province, China
6. West China Hospital of Sichuan University, Chengdu, Sichuan Province, China
7. Ningbo No. 2 Hospital, Ningbo, Zhejiang Province, China
8. Taizhou Central Hospital, Taizhou, Zhejiang, China
9.

9.2.2 Study period

Patients were identified during the patient identification period from 29 Mar 2022 (the date posaconazole injection and tablet formulations were approved by NMPA for the treatment of IA in adult patients in China) to 3 Jan 2025 (last patient in) and were enrolled or recruited during the recruitment period from 22 Sep 2023 to 3 Jan 2025. Data were collected retrospectively from 29 Mar 2022 to 21 Sep 2023 and prospectively from 22 Sep 2023 to 24 Jan 2025 (last patient last visit; Figure 9-1).

Figure 9-1 Study period



The index date was defined as the date of the first administration of posaconazole injection or tablet. Patients receiving first-line treatment were followed for a minimum of 42 days and a maximum of 84 days starting from the index date. Patients receiving salvage treatment were followed for a minimum of 7 days and a maximum of 84 days starting from the index date.

9.3 Subjects

The Overall Study Population consisted of adult Chinese patients with IA (proven, probable, possible[5]) who had received at least 7 days[2] of posaconazole (injection and/or tablet formulations) treatment, either as monotherapy or combination therapy[6], from 29 Mar 2022 to 3 Jan 2025 (last patient in).

[5] Followed the definition of the 2020 EORTC/MSGERC [Ref. 5.4: 080C85] or 2021 EORTC/MSGERC-ICU consensus criteria [Ref. 5.4: 08VW2Q].

[6] Combination therapy was defined as the use of posaconazole (injection and/or tablet formulations) with any other antifungal medications with activity against aspergillosis. Medications used in combination therapy were recorded.

9.3.1 Inclusion/Exclusion criteria for subjects receiving first-line treatment

Inclusion criteria:

- Chinese and resident in China;
- At least 18 years of age on the day of initiating posaconazole treatment;
- Diagnosed with proven, probable, or possible IA per the 2020 European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) [Ref. 5.4: 080C85] or the 2021 EORTC/MSGERC-intensive care unit (ICU) criteria [Ref. 5.4: 08VW2Q];
- Had received less than 7 days of other antifungal therapy with activity against aspergillosis (amphotericin, voriconazole, isavuconazole, or itraconazole) for the treatment of the current episode of IA.

Exclusion criteria:

- Unable to provide written informed consent if ethics committee (EC) requires;
- Participating in any interventional clinical trial;
- Pregnancy or breastfeeding during treatment with posaconazole;
- Prior enrollment in the study (each subject could only be enrolled once);
- History or known Aspergillus infection with a strain that is azole-resistant;
- Known or history of efficacy failure of posaconazole to treat a prior or current episode of IA.

9.3.2 Inclusion/Exclusion criteria for subjects receiving salvage treatment

Inclusion criteria:

- Chinese and resident in China;
- At least 18 years of age on the day of initiating posaconazole treatment;
- Diagnosed with probable, proven, or possible IA per the 2020 EORTC/MSGERC [Ref. 5.4: 080C85] or the 2021 EORTC/MSGERC-ICU criteria [Ref. 5.4: 08VW2Q];
- Had a diagnosis of IA with disease that is refractory to amphotericin B, voriconazole, itraconazole, isavuconazole, or other antifungal medications with activity against Aspergillus. Refractoriness was defined as progression of infection or failure to improve after receiving 7 or more days of these medicinal products for the treatment of the current episode of infection;
- OR
- Had a diagnosis of IA in patients who have shown intolerance to amphotericin B, voriconazole, itraconazole, isavuconazole, or other antifungal medications with activity against Aspergillus after receiving 1 or more days of any of these medicinal products given for the treatment of the current episode of infection.

Exclusion criteria:

- Unable to provide written informed consent if EC requires;
- Participating in any interventional clinical trial;
- Pregnancy or breastfeeding during treatment with posaconazole;
- Prior enrollment in the study (each subject could only be enrolled once);

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

9.4 Variables

9.4.1 Exposure

The exposure of interest was posaconazole injection and/or tablets administered in a non-interventional setting. The study included patients who had received posaconazole injection and/or tablets in routine clinical practice.

9.4.2 Outcome

9.4.2.1 Primary outcome

The primary outcome was ACM through Day 42 post-treatment initiation in the Overall Study Population (Section 9.3). Death was defined as a patient having a recorded death in their medical history or having a death certificate by Day 42. Patients with missing or 'unable to determine' vital status through Day 42 were excluded from the analysis.

9.4.2.2 Secondary outcomes

9.4.2.2.1 Clinical response

The key secondary outcome was the clinical response at the end of posaconazole treatment or Day 84 post-treatment initiation (whichever came first), assessed separately in first-line treatment patients and salvage treatment patients in the Overall Study Population (Section 9.3). Clinical response was defined based on the Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the fifth version) [Ref. 5.4: 05G2Z2] or by the investigators' professional assessments[7]. Patients with missing or 'unable to determine' clinical response at the assessment timepoint were excluded from the respective analysis.

For first-line treatment patients, clinical response was assessed only in those who received at least 42 days[2] of posaconazole treatment. For salvage treatment patients, clinical response was assessed in those who received at least 7 days[2] of posaconazole treatment, i.e., all salvage treatment patients in the study population.

9.4.2.2.2 Demographic and clinical characteristics

In support of the secondary objectives, the study reported the following demographic and clinical characteristics in the study population:

[7] Considering the low compliance with guidelines in real-world clinical practice, it was possible that there might be insufficient information from medical records to support the definition of clinical response according to the guideline. Therefore, investigators' professional assessments were used to supplement the definition of clinical response. The subgroup analysis by the method of clinical response definition was conducted depending on data availability.

Baseline demographic and clinical characteristics

- Age at index date (years)
- Sex
- Height (cm)
- Weight (kg)
- Smoking status
- Alcohol use
- Geographic region
- Type of medical insurance
- Posaconazole insurance coverage at hospital
- IA diagnosis type
- Invasive pulmonary aspergillosis at baseline
- Patients with ≥1 of each type of examination for IA diagnosis at baseline
- Risk factors for poor outcomes due to IA at baseline

Medical history and treatment history

- Clinical comorbidities: Collected from 90 days prior to the index date to the end of follow-up
- Surgical treatments: Collected from any time prior to the index date to the end of follow-up
- History of other antifungal therapy at baseline: Collected within any time prior to the index date
- History of other medications at baseline: Collected within 90 days prior to the index date
- Concomitant medications during follow-up: Collected during the follow-up period on or after the index date

9.4.2.2.3 Posaconazole treatment patterns

In support of the secondary objectives, the study reported the following posaconazole treatment patterns collected during the follow-up period in the study population:

Posaconazole treatment regimen

- Treatment duration (days)
- Cumulative dosage (mg)
- Medication administration type (injection only, tablets only, injection followed by tablets, or tablets followed by injection)
- Treatment modality and the specific agent(s) in combination therapy

Posaconazole treatment discontinuation

- Patients with ≥1 treatment discontinuation
- Reason for first treatment discontinuation
- Time to first treatment discontinuation (days)

9.4.3 Covariates

Please refer to Section 9.4.2.2.2 for the study covariates.

9.5 Data sources and measurement

Relevant patient-level information was collected from multiple information systems, including but not limited to electronic medical records (EMR), paper medical records, hospital information systems (HIS), laboratory information systems (LIS), and routine patient management materials provided by clinicians at the study sites. Both inpatient and outpatient data were included. All data were collected using a standardized CRF.

For patients with retrospective data collection who had missing vital status in their medical records, a follow-up was required to confirm their vital status by Day 42. Data sources for this confirmation included death certificate information or follow-up contacts, reports, or records by the investigators.

9.5.1 Study Procedures

This study did not involve the active administration of posaconazole injection or tablets. The study protocol was reviewed and approved by the Institutional Review Board (IRB)/EC and the Human Genetic Resources Administration of China (HGRAC) for International Cooperation Studies.

An exemption from obtaining written informed consent under certain conditions was authorized at all study sites for patients with only retrospective data collection. For patients involved in prospective data collection, including those in retrospective data collection who required a prospective follow-up to confirm their vital status at Day 42, participating practitioners obtained their written informed consent and submitted it to the IRB/EC.

Medical chart reviews were initiated at the sites on 22 Sep 2023 and concluded on 24 Jan 2025, last patient last visit. Using a standardized CRF, trained staff abstracted demographics, clinical characteristics, treatment patterns, and treatment outcomes from the medical charts.

9.6 Bias

As this was a non-interventional study, potential bias cannot be ruled out. Data collection reflected routine clinical practice rather than mandatory assessments at prespecified time points, which might have impacted the amount of data available and its interpretation. Potential sources of bias and limitations, as well as strategies to minimize them, are discussed further below.

First, cases from the study sites might be sicker, as these sites were the top-level hospitals in China. Patients in more severe conditions in China tend to prefer top-level hospitals. Sicker cases could lead to lower ORR and higher ACM, which might not reflect the true value of posaconazole treatment (admission rate bias). To mitigate this bias, the study was designed to assess the outcomes by treatment line (first-line treatment or salvage treatment) to differentiate patients' disease conditions. Patient characteristics by treatment line were also described as a secondary endpoint.

Second, survivor cases from retrospective data collection were easier to reach for signing the informed consent form (ICF) during the recruitment period. At the same time, cases from retrospective or prospective data collection might be lost to follow-up without clear alive or dead status or response data. These situations could lead to an underestimation or overestimation of ACM and/or ORR (immortal time bias/ no-respondent bias/survivor bias). To mitigate this bias, the study was designed to contact not only the patient themselves from retrospective data collection but also their relatives to follow up on the missing vital status. Additionally, cases from prospective data collection were closely monitored to ensure that vital status and response data were recorded.

Third, for cases from retrospective data collection, some historical clinical data might be missing (missing clinical data bias). The missing data might be correlated with the outcome (e.g., more clinical data might be included for more severe cases that require more frequent monitoring, leading to an underrepresentation of less severe cases that were more likely to survive), which could bias the estimates. Cases with missing critical data, such as missing vital status at Day 42 or information on treatment response after the end of treatment, would be excluded from the ACM and ORR calculations, respectively, resulting in a smaller sample size than estimated. Additionally, the planned date of study report submission in mid-2025 might impact the number of patients receiving posaconazole injection and/or tablets. To ensure the completeness of clinical data, cases without treatment response or classification of proven, probable, possible would require a doctor's assessment on whether the treatment response and classification could be defined by other examination/test reports to minimize the missing data rate.

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

9.7 Study size

As this was a non-interventional study, no hypothesis test or power calculation was conducted. All eligible patients were identified during the patient identification period and recruited during the recruitment period (Section 9.2.2). It was expected that 55-70 patients would be enrolled to meet the primary and secondary objectives, including 30-40 cases for the primary objective. The estimation of the sample size was based on market supply estimation and enrollment experience from the Phase 3 randomized controlled trial. Assuming an ACM rate of 15%-50% observed through Day 42 for the primary objective, the half-width of the 95% confidence interval (CI) was estimated to range from 12.1%-18.7% (Table 9-1).

Table 9-1 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 (13.3)	(3.8, 30.7)	13.5
	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).

9.8 Data transformation

Demographic and clinical characteristics (Section 9.4.2.2.2)

- Age at Index Date (years): Age at Index Date = (Index date – Date of birth) / 365.25.
- Geographic regions were categorized as:
  - North China (Beijing, Tianjin, Hebei, Shanxi, and Inner Mongolia)
  - Northeast China (Liaoning, Jilin, and Heilongjiang)
  - East China (Shanghai, Jiangsu, Zhejiang, Anhui, Fujian, Jiangxi, Shandong, and Taiwan)
  - Central South China (Henan, Hubei, and Hunan)
  - South China (Guangdong, Guangxi, Hainan, Hong Kong, and Macau)
  - Southwest China (Chongqing, Sichuan, Guizhou, Yunnan, and Xizang)
  - Northwest China (Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang)
- Clinical comorbidities and Surgical treatments were identified based on the Medical Dictionary of Regulatory Activities (MedDRA) and reported by System Organ Class (SOC) and/or preferred terms (PTs).
- History of other antifungal therapy at baseline, History of other medications at baseline, Concomitant medications, and antifungal medications in combination therapy were identified based on the World Health Organization Drug Dictionary (WHODD) and reported by Anatomical Therapeutic Chemical (ATC) and/or PTs.

Posaconazole treatment patterns (Section 9.4.2.2.3)

- Treatment duration (days): Treatment duration = End date of the last posaconazole administration – Index date + 1 (– any discontinuation period[s]).
- Medication administration types were categorized as:
  - Injection only
  - Tablets only
  - Injection followed by tablets
  - Tablets followed by injection
- Reason for first treatment discontinuation was categorized based on the treating physician's description for the patient who discontinued posaconazole treatment as:
  - Resistance
  - Intolerance
  - Drug-drug interaction
  - Financial reason
  - Other
  - Not documented
- Time to first treatment discontinuation (days): Time to first treatment discontinuation = Date of first treatment discontinuation – Index date.

9.8.1 Data management

All data collected for the study was recorded accurately, promptly, and legibly. For primary data collection, the investigator or qualified designee was 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 was responsible for reviewing data quality and relevance to the best of the investigator's knowledge. The investigator confirmed that the quality and relevance of data had been assessed to meet the minimum requirements for all study objectives.

The study had been outsourced, and the institutional policies of the supplier were followed for the development of data management plans. The supplier also ensured compliance with Good Pharmacoepidemiology Practice (GPP) and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the study.

An Electronic Data Capture (EDC) system, Oracle® Clinical RDC Onsite 4.6.2, was used to collect and clean clinical data. Statistical analysis was performed using SAS (version 9.4) software.

A CRF was used for data collection. All data management activities, including data capture, data storage, data cleaning, data security, and system backup processes, were undertaken by qualified personnel and followed all procedures detailed in a separate "Data Management Plan."

9.9 Statistical methods

9.9.1 Main summary measures

A descriptive analysis of the distribution of values abstracted for each variable was provided. For continuous variables of interest, the mean, median, standard deviation (SD), interquartile range (IQR, including the first quartile [Q1] and the third quartile [Q3]), and range (including the minimum and maximum) were calculated. For categorical variables, frequencies and percentages were calculated. All analyses were carried out using all available data. A participant with missing data on one variable was included only in calculations that did not involve that variable.

All analyses used SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina). A detailed statistical analysis plan (SAP) and corresponding mock-up tablets, figures, and listings (TFL) were developed and finalized prior to conducting any analyses. The plan was developed in accordance with GPP for conducting non-interventional studies.

9.9.2 Main statistical methods

9.9.2.1 Primary objective

The primary objective was to assess the ACM through Day 42 post-posaconazole treatment initiation for IA. The analysis was conducted in the overall ACM Rate Analysis Population, which consisted of patients from the Overall Study Population (Section 9.3) with available vital status record at Day 42, and separately for patients in retrospective data collection and patients in prospective data collection. The following ACM rates were calculated with a 95% CI:

- Overall ACM rate = number of overall IA patients who died through Day 42 / number of overall IA patients with available vital status record on Day 42 × 100%.
- ACM rate by treatment line = number of IA patients by treatment line who died through Day 42 / number of IA patients by treatment line with available vital status record on Day 42 × 100%.

Subgroup analysis was conducted in the overall ACM Rate Analysis Population based on the following potential factors, with only overall ACM rate calculated, depending on data availability. If the number of patients in any subgroup was <4 after grouping by a factor, subgroup analysis for that factor was not conducted:

1. Treatment duration (≥ median treatment duration, < median treatment duration).
2. Medication administration type (injection only, tablets only, injection and tablets).
3. Baseline IPA (infected, not infected, unable to determine).
4. Baseline risk factors for poor outcomes due to IA (with or without risk factors at baseline).

9.9.2.2 Secondary objectives

9.9.2.2.1 Overall response rate by treatment line

The secondary objective was to assess the ORR at the end of posaconazole treatment for IA by treatment line.

For first-line treatment, the analysis was conducted in the overall First-line ORR Analysis Population, which consisted of first-line treatment patients from the Overall Study Population (Section 9.3) who received at least 42 days[2] of treatment with available clinical response assessment at the end of treatment or on Day 84, whichever came first. The analysis was subsequently conducted separately for patients in retrospective data collection and for patients in prospective data collection.

Similarly, for salvage treatment, the analysis was conducted in the overall Salvage ORR Analysis Population, which consisted of salvage treatment patients from the Overall Study Population (Section 9.3) who received at least 7 days[2] of treatment with available clinical response assessment at the end of treatment or on Day 84, whichever came first. The analysis was subsequently conducted separately for patients in retrospective data collection and for patients in prospective data collection.

The following ORR was calculated with a 95% CI:

- ORR by treatment line = number of IA patients by treatment line with CR or PR at the end of treatment / number of IA patients by treatment line with available clinical response assessment at the end of treatment × 100%.

Subgroup analysis was conducted separately in the overall First-line ORR Analysis Population and overall Salvage ORR Analysis Population based on the following potential factors, depending on data availability. If the number of patients in any subgroup was less than 4 after grouping by a factor, subgroup analysis for that factor was not conducted:

1. Treatment duration (≥ median treatment duration, < median treatment duration).
2. Medication administration type (injection only, tablets only, injection and tablets).
3. Baseline IPA (infected, not infected, unable to determine).
4. Baseline risk factors for poor outcomes due to IA (with or without risk factors at baseline).
5. Method of clinical response assessment (only based on the guideline, based on investigators' professional assessment).

9.9.2.2.2 Demographic and clinical characteristics

Variables listed in Section 9.4.2.2.2 were described among all patients in the Overall Study Population (Section 9.3) and separately by patients receiving first-line treatment and patients receiving salvage treatment.

9.9.2.2.3 Posaconazole treatment patterns

Variables listed in Section 9.4.2.2.3 were described for all patients in the Overall Study Population (Section 9.3) and separately by patients receiving first-line treatment and patients receiving salvage treatment. Additionally, patient timelines were depicted separately for first-line treatment patients and salvage treatment patients. Key timepoints in the plots included IA diagnosis date, index date, treatment discontinuation date (if applicable), treatment end date, and date of death (if applicable).

9.9.3 Missing values

Any missing value was handled as a missing value, and no imputation was carried out. A participant with missing data on one variable was used only in calculations that did not involve that variable. This approach allows for analysis with larger sample sizes compared to using only complete datasets for all variables.

9.9.4 Sensitivity analyses

Please refer to Section 9.9.2.1 and Section 9.9.2.2 for analyses of primary and secondary objectives, respectively.

9.9.5 Amendments to the statistical analysis plan

Not applicable in this study.

9.10 Quality control

All parties agreed to following applicable standard operating procedures (SOPs). All parties also agreed to ensuring all existing and new study personnel were appropriately trained to ensure the study was conducted and data were generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), Good Pharmacovigilance Practices (GVP), and all applicable federal, 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 conducted routine or for-cause audits to ensure oversight and conduct of the study were completed in accordance with the protocol, quality standards (e.g. GPP and GVP), and applicable laws and regulations. There was no significant quality issue (SQI) identified during the conduct of the study. A SQI was 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 were expected to appropriately implement the action plan in a timely manner.

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

10 RESULTS

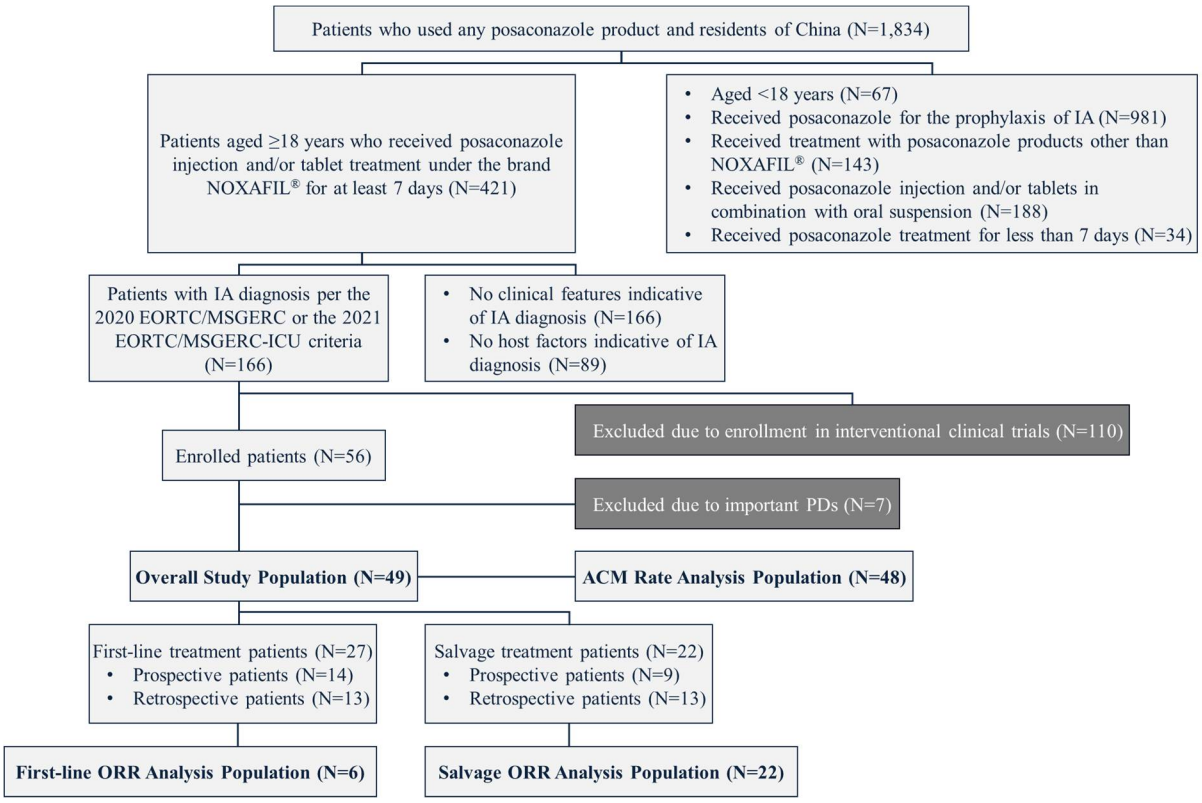
10.1 Participants

A total of 1,834 patients who used any posaconazole product from the 9 study sites were identified during the patient identification period (29 Mar 2022 to 3 Jan 2025) and screened for eligibility during the recruitment period (22 Sep 2023 to 3 Jan 2025). Of those, 56 (3.1%) IA patients who had received at least 7 days of posaconazole injection and/or tablets were enrolled (Figure 10-1).

A total of 49 patients comprised the Overall Study Population. Seven (12.5%) of the 56 enrolled patients were excluded from the Overall Study Population due to important protocol deviations (PDs), including 5 patients who lacked evidence for IA diagnosis, 1 patient who received posaconazole for prophylaxis, and 1 patient who received posaconazole treatment for less than 7 days. In addition, one of the 49 patients in the Overall Study Population had a non-important PD due to pre-approval off-label use of posaconazole treatment. This patient received posaconazole treatment for IA from 23 Dec 2021 to 28 Jan 2022, three months prior to the approval of posaconazole injection and enteric-coated tablets in China for the treatment of IA (29 Mar 2022). Protocol deviations are detailed in Annex 2 Listing 1.

Of the 49 patients in the Overall Study Population, 27 (55.1%) received posaconazole injection and/or tablets as first-line treatment and 22 (44.9%) as salvage treatment.

Figure 10-1 Patient disposition



Abbreviations: ACM, all-cause mortality; EORTC/MSGERC, European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium; IA, invasive aspergillosis; ICU, intensive care unit; N, number; ORR, overall response rate; PD, protocol deviation.
One patient was excluded from the ACM Rate Analysis Population due to missing Day 42 vital status following the initiation of posaconazole treatment.
Twenty-one patients were excluded from the First-line ORR Analysis Population due to receiving posaconazole injection and/or tablets for less than 42 days.

10.1.1 Protection of Human Subjects

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

All demographic and diagnosis information for each eligible patient, as well as laboratory information, were generated during routine clinical practice and before the conduct of the retrospective chart review process. The information was tracked, collected, stored, and used by selected hospitals or the study staff of the retrospective study and was provided to entities outside the study.

An exemption from obtaining written informed consent under certain conditions was authorized at all the 9 sites for patients with only retrospective data collection. Data from the other patients involved in prospective data collection, including those in retrospective data

collection who require a prospective follow-up to confirm their vital status at Day 42, were collected after obtaining their signed informed consent.

10.2 Descriptive data

10.2.1 Demographic and clinical characteristics

Demographic and clinical characteristics were summarized overall among all patients in the Overall Study Population (N=49), and separately among first-line treatment patients (N=27) and salvage treatment patients (N=22). Results were generally similar across patient groups (Table 10-1 and Table 10-2).

In the Overall Study Population, the median age at index date was 56.0 years (IQR: 41.0, 69.0), and the majority were male (N=33, 67.3%). The median height was 168.0 cm (IQR: 160.0, 173.0), and the median weight was 62.0 kg (IQR: 51.6, 68.0). More than half of the patients had no history of smoking (N=33, 67.3%) or alcohol use (N=39, 79.6%). Approximately half of the patients were from East China (N=23, 46.9%) and had medical insurance (N=23 [14+9], 46.9%). Posaconazole injection and tablets were included in the hospital listing where 63.3% (N=31) of the patients received care.

Most patients (N=35, 71.4%) had a possible diagnosis of IA, followed by probable diagnosis (N=13, 26.5%) and proven diagnosis (N=1, 2.0%). Sixteen (32.7%) patients had evidence of IPA at baseline, but for the other patients (N=33, 67.3%), it was undetermined. Imaging examination was the most common examination for IA diagnosis at baseline, conducted in 48 patients (98.0%); galactomannan (GM) tests were conducted in 3 patients (6.1%). Based on investigators' assessment, nearly 80% (N=39) of the patients had risk factors for poor outcomes due to IA at index date, including relapsed leukemia undergoing salvage chemotherapy (N=19, 48.7%), allogeneic hematopoietic stem cell transplant (HSCT; N=3, 7.7%), and other immunocompromised conditions (N=28, 71.8%).

Medical history, including clinical comorbidities, is detailed in Annex 2 Table 1.

Table 10-1 Baseline demographic characteristics

		Overall Study Population		
		All Patients (N=49)	**First-line Patients (N=27)**	**Salvage Patients (N=22)**
Age at index date[a], years	N (Nmiss)	49 (0)	27 (0)	22 (0)
	Mean (SD)	54.2 (17.12)	57.7 (18.09)	49.9 (15.13)
	Median	56.0	66.0	52.5
	Q1, Q3	41.0, 69.0	43.0, 70.0	38.0, 64.0
	Min, Max	20, 86	20, 86	21, 76
Sex, n (%)	Male	33 (67.3%)	17 (63.0%)	16 (72.7%)
	Female	16 (32.7%)	10 (37.0%)	6 (27.3%)
Height, cm	N (Nmiss)	48 (1)	26 (1)	22 (0)
	Mean (SD)	166.59 (7.967)	166.62 (8.891)	166.57 (6.925)
	Median	168.00	165.50	169.00
	Q1, Q3	160.00, 173.00	160.00, 174.00	160.00, 173.00
	Min, Max	150.0, 181.0	150.0, 181.0	152.0, 176.0

		Overall Study Population		
		All Patients (N=49)	**First-line Patients (N=27)**	**Salvage Patients (N=22)**
Weight, kg	N (Nmiss)	49 (0)	27 (0)	22 (0)
	Mean (SD)	59.63 (10.622)	58.54 (11.011)	60.98 (10.215)
	Median	62.00	58.00	63.55
	Q1, Q3	51.60, 68.00	51.00, 68.00	56.00, 68.00
	Min, Max	38.0, 78.0	40.0, 78.0	38.0, 77.0
Smoking status, n (%)	Never	33 (67.3%)	20 (74.1%)	13 (59.1%)
	Former	5 (10.2%)	3 (11.1%)	2 (9.1%)
	Current	5 (10.2%)	3 (11.1%)	2 (9.1%)
	Unknown	6 (12.2%)	1 (3.7%)	5 (22.7%)
Alcohol use, n (%)	Never	39 (79.6%)	23 (85.2%)	16 (72.7%)
	Former	2 (4.1%)	1 (3.7%)	1 (4.5%)
	Current	2 (4.1%)	2 (7.4%)	0
	Unknown	6 (12.2%)	1 (3.7%)	5 (22.7%)
Geographic region, n (%)	North China	6 (12.2%)	1 (3.7%)	5 (22.7%)
	Northeast China	3 (6.1%)	1 (3.7%)	2 (9.1%)
	East China	23 (46.9%)	16 (59.3%)	7 (31.8%)
	Central South China	6 (12.2%)	4 (14.8%)	2 (9.1%)
	Southwest China	2 (4.1%)	0	2 (9.1%)
	Northwest China	9 (18.4%)	5 (18.5%)	4 (18.2%)
Type of medical insurance, n (%)	Basic Medical Insurance for Urban Employees	14 (28.6%)	7 (25.9%)	7 (31.8%)
	Basic Medical Insurance for Urban and Rural Residents	9 (18.4%)	7 (25.9%)	2 (9.1%)
	None	7 (14.3%)	4 (14.8%)	3 (13.6%)
	Unknown	19 (38.8%)	9 (33.3%)	10 (45.5%)
Posaconazole hospital listing, n (%)	Yes	31 (63.3%)	14 (51.9%)	17 (77.3%)
	No	18 (36.7%)	13 (48.1%)	5 (22.7%)

Abbreviations: cm, centimeter(s); kg, kilogram(s); N, number; Nmiss, number of missing; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation.
[a] The index date for a patient was defined as the date of the first administration of posaconazole injection and/or tablet.

Table 10-2 Baseline clinical characteristics

		Overall Study Population		
		All Patients (N=49)	**First-line Patients (N=27)**	**Salvage Patients (N=22)**
IA diagnosis type, n (%)	Proven	1 (2.0%)	0	1 (4.5%)
	Probable	13 (26.5%)	4 (14.8%)	9 (40.9%)
	Possible	35 (71.4%)	23 (85.2%)	12 (54.5%)
Invasive pulmonary aspergillosis at baseline, n (%)	Yes	16 (32.7%)	8 (29.6%)	8 (36.4%)
	Unable to determine	33 (67.3%)	19 (70.4%)	14 (63.6%)
Patients with ≥1 of each type of examination for IA diagnosis at baseline, n (%)	**N of patients included**	**49**	**27**	**22**
	GM Tests	3 (6.1%)	0	3 (13.6%)
	Needle or Surgical Biopsies	2 (4.1%)	2 (7.4%)	0
	Imaging Examination	48 (98.0%)	26 (96.3%)	22 (100%)
	Other[a]	6 (12.2%)	1 (3.7%)	5 (22.7%)
Risk factors for poor outcomes due to IA at baseline, n (%)	**N of patients included**	**39**	**19**	**20**
	Allogeneic HSCT	3 (7.7%)	2 (10.5%)	1 (5.0%)
	Relapsed leukemia undergoing salvage chemotherapy	19 (48.7%)	10 (52.6%)	9 (45.0%)
	Other immunocompromised condition	28 (71.8%)	13 (68.4%)	15 (75.0%)

Abbreviations: GM, galactomannan; HSCT, hematopoietic stem cell transplant; IA, invasive aspergillosis; N, number.
[a] Included Alveolar Lavage Fluid Culture, Blood NGS Detection, Bronchoscopic Bronchoalveolar Lavage Fluid NGS, LGG Antibody to Aspergillus fumigatus, NGS, Sputum Culture, and Sputum DNA Test.

10.2.2 Posaconazole treatment patterns

Posaconazole treatment regimens and discontinuation were summarized overall among all patients in the Overall Study Population (N=49), and separately among first-line treatment patients (N=27) and salvage treatment patients (N=22). Slight differences were observed between first-line treatment patients and salvage treatment patients (Table 10-3 and Table 10-4).

Among the 27 patients who received posaconazole as first-line treatment, the median treatment duration was 16.0 days (IQR: 8.0, 37.0), and the median cumulative dosage was 5,400.0 mg (IQR: 2,400.0, 11,100.0). The vast majority (N=25, 92.6%) received posaconazole tablets only, and none of these patients used a combination of injection and tablets for treatment. Most patients (N=22, 81.5%) were treated with posaconazole as monotherapy, with amphotericin B formulations, caspofungin acetate, and micafungin being utilized for combination therapy in the remaining cases (N=5, 18.5%). Two patients (7.4%) experienced discontinuation during the course of treatment, although the reasons were not documented. The median time to the first treatment discontinuation was 10.5 days (IQR: 4.0, 17.0).

Among the 22 patients who received posaconazole as salvage treatment, the median treatment duration was longer at 25.5 days (IQR: 13.0, 31.0), and the median cumulative dosage was higher at 7,650.0 mg (IQR: 3,900.0, 9,300.0). Tablet-only administration remained the most common (N=16, 72.7%), and 4 patients (18.2%) received injection followed by tablets. The

majority (N=18, 81.8%) received posaconazole as monotherapy, with amphotericin B formulations and voriconazole being used for combination therapy in the remaining cases (N=4, 18.2%). Two patients (9.1%) experienced discontinuation during the course of treatment, with reasons not documented. The median time to the first treatment discontinuation was 14.5 days (IQR: 4.0, 25.0).

Additionally, prior to initiating posaconazole treatment, salvage treatment patients had been treated with the following antifungal therapies: voriconazole (N=16, 72.7%), amphotericin B formulations (cumulatively N=10, 45.5%), caspofungin formulations (cumulatively N=6, 27.3%), fluconazole (N=2, 9.1%), and itraconazole (N=1, 4.5%). Other treatment history, including surgical treatments, history of other medications at baseline, and concomitant medications during follow-up, is detailed in Annex 2 Table 2.

Furthermore, a detailed patient timeline, including IA diagnosis date, index date, treatment discontinuation date (if applicable), treatment end date, and date of death (if applicable), is presented for first-line treatment patients and salvage treatment patients in Annex 2 Figure 1 and Annex 2 Figure 2, respectively.

Table 10-3 Posaconazole treatment regimen

		Overall Study Population		
		All Patients (N=49)	**First-line Patients (N=27)**	**Salvage Patients (N=22)**
Treatment duration, days	N (Nmiss)	49 (0)	27 (0)	22 (0)
	Mean (SD)	26.8 (22.66)	24.6 (22.76)	29.5 (22.77)
	Median	20.0	16.0	25.5
	Q1, Q3	9.0, 31.0	8.0, 37.0	13.0, 31.0
	Min, Max	6, 84	6, 84	7, 84
Cumulative dosage, mg	N (Nmiss)	49 (0)	27 (0)	22 (0)
	Mean (SD)	8020.4(6652.00)	7474.1(6657.36)	8690.9(6738.94)
	Median	6000.0	5400.0	7650.0
	Q1, Q3	2700.0, 9600.0	2400.0, 11100.0	3900.0, 9300.0
	Min, Max	1800, 25200	1800, 25200	2100, 25200
Medication administration type, n (%)	Injection only	4 (8.2%)	2 (7.4%)	2 (9.1%)
	Tablets only	41 (83.7%)	25 (92.6%)	16 (72.7%)
	Injection followed by tablets	4 (8.2%)	0	4 (18.2%)
Treatment modality, n (%)	Monotherapy	40 (81.6%)	22 (81.5%)	18 (81.8%)
	Combination therapy	9 (18.4%)	5 (18.5%)	4 (18.2%)
	AMPHOTERICIN B	3 (37.5%)	3 (60.0%)	0
	AMPHOTERICIN B CHOLESTERYL SULFATE COMPLEX	3 (37.5%)	2 (40.0%)	1 (33.3%)
	AMPHOTERICIN B, LIPOSOME	1 (12.5%)	1 (20.0%)	0
	CASPOFUNGIN ACETATE	2 (25.0%)	2 (40.0%)	0
	MICAFUNGIN	1 (12.5%)	1 (20.0%)	0
	VORICONAZOLE	2 (25.0%)	0	2 (66.7%)

Abbreviations: mg, milligram(s); N, number; Nmiss, number of missing; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation

Table 10-4 Posaconazole treatment discontinuation

		Overall Study Population		
		All Patients (N=49)	**First-line Patients (N=27)**	**Salvage Patients (N=22)**
Patients with ≥1 treatment discontinuation, n (%)	Yes	4 (8.2%)	2 (7.4%)	2 (9.1%)
	No	45 (91.8%)	25 (92.6%)	20 (90.9%)
Reason for first treatment discontinuation, n (%)	Not Documented	4 (100%)	2 (100%)	2 (100%)
Time to first treatment discontinuation, days	N (Nmiss)	4 (45)	2 (25)	2 (20)
	Mean (SD)	12.5 (10.34)	14.5 (14.85)	10.5 (9.19)
	Median	10.5	14.5	10.5
	Q1, Q3	4.0, 21.0	4.0, 25.0	4.0, 17.0
	Min, Max	4, 25	4, 25	4, 17

Abbreviations: N, number; Nmiss, number of missing; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation.

10.3 Analysis population

10.3.1 ACM Rate Analysis Population

A total of 48 patients from the Overall Study Population were included in the ACM Rate Analysis Population, excluding one patient due to missing Day 42 vital status following the initiation of posaconazole treatment. This population included 26 patients (54.2%) who received posaconazole as first-line treatment and 22 (45.8%) as salvage treatment. Additionally, 23 patients (47.9%) were in prospective data collection, and 25 patients (52.1%) were in retrospective data collection (Table 10-5).

10.3.2 First-line ORR Analysis Population

Six of the 27 first-line treatment patients in the Overall Study Population were included in the First-line ORR Analysis Population, excluding 21 patients who received posaconazole injection and/or tablets for less than 42 days. Among them, 2 patients (33.3%) were in prospective data collection, and 4 patients (66.7%) were in retrospective data collection (Table 10-6).

10.3.3 Salvage ORR Analysis Population

All 22 salvage treatment patients in the Overall Study Population were included in the Salvage ORR Analysis Population. Among them, 9 patients (40.9%) were in prospective data collection, and 13 patients (59.1%) were in retrospective data collection (Table 10-7).

10.4 Main results

10.4.1 Primary outcome: ACM through Day 42

For the 48 patients included in the ACM Rate Analysis Population, 2 patients had a recorded death through Day 42 post-posaconazole treatment initiation. The overall ACM rate was 4.2% (95% CI: 0.5%, 14.3%). Both patients received posaconazole as first-line treatment,

corresponding to a first-line ACM rate of 7.7% (95% CI: 0.9%, 25.1%) and a salvage ACM rate of 0.0% (95% CI: 0.0%, 15.4%).

Detailed results, including ACM rate of patients separately in prospective and retrospective data collection, are presented in Table 10-5.

Table 10-5 ACM through Day 42, overall analysis

	ACM Rate Analysis Population					
	All Patients (N=48)		Prospective Patients (N=23)		Retrospective Patients (N=25)	
	First-line (N=26)	Salvage (N=22)	First-line (N=14)	Salvage (N=9)	First-line (N=12)	Salvage (N=13)
N of Overall death	2		0		2	
Overall ACM Rate (95% CI[a])	4.2% (0.5%, 14.3%)		0.0% (0.0%, 14.8%)		8.0% (1.0%, 26.0%)	
N of Death by LOT	2	0	0	0	2	0
ACM Rate by LOT (95% CI[a])	7.7% (0.9%, 25.1%)	0.0% (0.0%, 15.4%)	0.0% (0.0%, 23.2%)	0.0% (0.0%, 33.6%)	16.7% (2.1%, 48.4%)	0.0% (0.0%, 24.7%)

Abbreviations: ACM, all-cause mortality; CI, confidence interval; LOT, line of treatment; N, number.
[a] Calculated using the Clopper-Pearson method.

10.4.2 Secondary outcome: ORR for first-line treatment

For the 6 patients included in the First-line ORR Analysis Population, 4 patients (1 CR and 3 PRs) achieved success at the end of treatment or Day 84 post-treatment initiation, corresponding to a first-line ORR of 66.7% (95% CI: 22.3%, 95.7%).

The first-line ORR was 50.0% (95% CI: 1.3%, 98.7%) among patients in prospective data collection and 75.0% (95% CI: 19.4%, 99.4%) among patients in retrospective data collection (Table 10-6).

Table 10-6 ORR for first-line treatment, overall analysis

	First-line ORR Analysis Population		
	All Patients (N=6)	Prospective Patients (N=2)	Retrospective Patients (N=4)
ORR (95%CI[a])	**66.7% (22.3%, 95.7%)**	**50.0% (1.3%, 98.7%)**	**75.0% (19.4%, 99.4%)**
N of Success	4	1	3
N of Complete response	1	0	1
N of Partial response	3	1	2
N of Failure	2	1	1
N of Stable response	1	0	1
N of Progression of fungal disease	0	0	0
N of Death	1	1	0

Abbreviations: CI, confidence interval; N, number; ORR, overall response rate.
[a] Calculated using the Clopper-Pearson method.

10.4.3 Secondary outcome: ORR for salvage treatment

For the 22 patients included in the Salvage ORR Analysis Population, 19 patients (4 CRs and 15 PRs) achieved success at the end of treatment or on Day 84 post-treatment initiation, corresponding to a salvage ORR of 86.4% (95% CI: 65.1%, 97.1%).

The salvage ORR was 77.8% (95% CI: 40.0%, 97.2%) among patients in prospective data collection and 92.3% (95% CI: 64.0%, 99.8%) among patients in retrospective data collection (Table 10-7).

Table 10-7 ORR for salvage treatment, overall analysis

	Salvage ORR Analysis Population		
	All Patients (N=22)	**Prospective Patients (N=9)**	**Retrospective Patients (N=13)**
ORR (95%CI[a])	**86.4% (65.1%, 97.1%)**	**77.8% (40.0%, 97.2%)**	**92.3% (64.0%, 99.8%)**
N of Success	19	7	12
N of Complete response	4	3	1
N of Partial response	15	4	11
N of Failure	3	2	1
N of Stable response	3	2	1
N of Progression of fungal disease	0	0	0
N of Death	0	0	0

Abbreviations: CI, confidence interval; N, number; ORR, overall response rate.
[a] Calculated using the Clopper-Pearson method.

10.5 Other analyses

10.5.1 Subgroup analysis of ACM through Day 42 in ACM Rate Analysis Population

The subgroup analysis of ACM through Day 42 was conducted based on several factors, including treatment duration, medication administration type, baseline IPA, and baseline risk factors for poor outcomes due to IA, among all 48 patients included in the ACM Rate Analysis Population (Table 10-8). Details of the deceased patients in the ACM Rate Analysis Population are presented in Annex 2 Listing 2.

Subgroup by treatment duration

The two deceased patients received posaconazole treatment for less than the median treatment duration of 20.0 days among the Overall Study Population (Section 10.2.2), corresponding to an ACM rate of 8.7% (95% CI: 1.1%, 28.0%) in the subgroup with treatment duration < median treatment duration (N=23). The ACM rate in the other subgroup with treatment duration ≥ median treatment duration (N=25) was 0.0% (95% CI: 0.0%, 13.7%).

Subgroup by medication administration type

The two deceased patients received posaconazole tablets only, corresponding to an ACM rate of 5.0% (95% CI: 0.6%, 16.9%) in the subgroup of tablets only (N=40). The ACM rate in the subgroup of injection only (N=4) and the subgroup of injection and tablets (N=4) were both 0.0% (95% CI: 0.0%, 60.2%).

Subgroup by baseline IPA

One of the deceased patients had evidence of IPA at baseline, corresponding to an ACM rate in the IPA subgroup (N=15) of 6.7% (95% CI: 0.2%, 31.9%). The other deceased patient did not have evidence of IPA at baseline and was categorized into the 'unable to determine' subgroup (N=33), with a corresponding ACM rate of 3.0% (95% CI: 0.1%, 15.8%).

Subgroup by baseline risk factors for poor outcomes due to IA

Both of the deceased patients had risk factors for poor outcomes due to IA at baseline, corresponding to an ACM rate in the subgroup with risk factors (N=39) of 5.1% (95% CI: 0.6%, 17.3%). The ACM rate in the other subgroup without risk factors (N=9) was 0.0% (95% CI: 0.0%, 33.6%).

Table 10-8 ACM through Day 42, subgroup analysis

	ACM Rate Analysis Population (N=48)
Subgroup by treatment duration	
Treatment duration ≥ median[a]	
N of patients included	25 (52.1%)
N of death	0
ACM Rate (95% CI)	0.0% (0.0%, 13.7%)
Treatment duration < median[a]	
N of patients included	23 (47.9%)
N of death	2
ACM Rate (95% CI)	8.7% (1.1%, 28.0%)
Subgroup by medication administration type	
Injection only	
N of patients included	4 (8.3%)
N of death	0
ACM Rate (95% CI)	0.0% (0.0%, 60.2%)
Tablets only	
N of patients included	40 (83.3%)
N of death	2
ACM Rate (95% CI)	5.0% (0.6%, 16.9%)
Injection and tablets	
N of patients included	4 (8.3%)
N of death	0
ACM Rate (95% CI)	0.0% (0.0%, 60.2%)
Subgroup by baseline invasive pulmonary aspergillosis	
Infected	
N of patients included	15 (31.3%)
N of death	1
ACM Rate (95% CI)	6.7% (0.2%, 31.9%)
Unable to determine	
N of patients included	33 (68.8%)
N of death	1
ACM Rate (95% CI)	3.0% (0.1%, 15.8%)

	ACM Rate Analysis Population (N=48)
Subgroup by baseline risk factors for poor outcomes due to IA[b]	
With risk factors at baseline	
N of patients included	39 (81.3%)
N of death	2
ACM Rate (95% CI)	5.1% (0.6%, 17.3%)
Without risk factors at baseline	
N of patients included	9 (18.8%)
N of death	0
ACM Rate (95% CI)	0.0% (0.0%, 33.6%)

Abbreviations: ACM, all-cause mortality; CI, confidence interval; HSCT, hematopoietic stem cell transplant; N, number.
All 95% confidence intervals were calculated using the Clopper-Pearson method.
[a] The median posaconazole treatment duration among all patients in the Overall Study Population was 20.0 days (Table 10-3).
[b] The risk factors for poor outcomes due to IA at baseline included allogeneic HSCT, relapsed leukemia undergoing salvage chemotherapy, and other immunocompromised conditions (Table 10-2).

10.5.2 Subgroup analysis of ORR in First-line ORR Analysis Population

Due to the limited number of patients in the First-line ORR Analysis Population, none of the subgroup factors met the criteria for analysis, which required at least 4 patients per subgroup to ensure the statistical validity and reliability of the results. Therefore, no subgroup analysis was conducted for ORR for first-line treatment. Details of the six patients included in the First-line ORR Analysis Population are presented in Annex 2 Listing 3.

10.5.3 Subgroup analysis of ORR in Salvage ORR Analysis Population

The subgroup analysis of ORR for salvage treatment was conducted based on treatment duration, baseline IPA, and method of clinical response assessment, among all 22 patients included in the Salvage ORR Analysis Population (Table 10-9). Medication administration type and baseline risk factors for poor outcomes due to IA did not meet the criteria for subgroup analysis, which required at least 4 patients in each subgroup to ensure the statistical validity and reliability of the results. Therefore, subgroup analysis was not conducted for these two factors. Details of all patients in the Salvage ORR Analysis Population are presented in Annex 2 Listing 4.

Subgroup by treatment duration

Among the 22 patients included in the Salvage ORR Analysis Population, 11 received posaconazole treatment for more than the median treatment duration of 25.5 days among the salvage treatment patients in the Overall Study Population (Section 10.2.2). Of those, 9 patients achieved success (1 CR and 8 PRs) at the end of treatment or Day 84 post-treatment initiation, corresponding to an ORR of 81.8% (95% CI: 48.2%, 97.7%). For the other 11 patients who received posaconazole treatment for less than the median treatment duration, 10 patients achieved success (3 CRs and 7 PRs), corresponding to an ORR of 90.9% (95% CI: 58.7%, 99.8%).

Subgroup by baseline IPA

Eight of the 22 patients had evidence of IPA at baseline, and all of them achieved success (2 CRs and 6 PRs) at the end of treatment or Day 84 post-treatment initiation, corresponding to

an ORR of 100.0% (95% CI: 63.1%, 100.0%). For the other 14 patients categorized into the 'unable to determine' subgroup, 11 of them achieved success (2 CRs and 9 PRs), corresponding to an ORR of 78.6% (95% CI: 49.2%, 95.3%).

Subgroup by method of clinical response assessment

Five of the 22 patients had their clinical response assessed only based on the guideline, and all of them achieved success (1 CR and 4 PRs) at the end of treatment or Day 84 post-treatment initiation, corresponding to an ORR of 100.0% (95% CI: 47.8%, 100.0%). The other 17 patients had their clinical response assessed based on the investigators' professional assessment, and 14 of them achieved success (3 CRs and 11 PRs), corresponding to an ORR of 82.4% (95% CI: 56.6%, 96.2%).

Table 10-9 ORR for salvage treatment, subgroup analysis

	Salvage ORR Analysis Population (N=22)
Subgroup by treatment duration	
Treatment duration ≥ median[a]	
N of patients included	11 (50.0%)
ORR (95%CI)	81.8% (48.2%, 97.7%)
N of Success	9
N of Complete response	1
N of Partial response	8
N of Failure	2
N of Stable response	2
N of Progression of fungal disease	0
N of Death	0
Treatment duration < median[a]	
N of patients included	11 (50.0%)
ORR (95%CI)	90.9% (58.7%, 99.8%)
N of Success	10
N of Complete response	3
N of Partial response	7
N of Failure	1
N of Stable response	1
N of Progression of fungal disease	0
N of Death	0
Subgroup by baseline invasive pulmonary aspergillosis	
Infected	
N of patients included	8 (36.4%)
ORR (95%CI)	100.0% (63.1%, 100.0%)
N of Success	8
N of Complete response	2
N of Partial response	6
N of Failure	0
N of Stable response	0
N of Progression of fungal disease	0
N of Death	0
Unable to determine	
N of patients included	14 (63.6%)
ORR (95%CI)	78.6% (49.2%, 95.3%)
N of Success	11
N of Complete response	2

	Salvage ORR Analysis Population (N=22)
N of Partial response	9
N of Failure	3
N of Stable response	3
N of Progression of fungal disease	0
N of Death	0
Subgroup by method of clinical response assessment	
Only based on the guideline[c]	
N of patients included	5 (22.7%)
ORR (95%CI)	100.0% (47.8%, 100.0%)
N of Success	5
N of Complete response	1
N of Partial response	4
N of Failure	0
N of Stable response	0
N of Progression of fungal disease	0
N of Death	0
Based on investigators' professional assessment	
N of patients included	17 (77.3%)
ORR (95%CI)	82.4% (56.6%, 96.2%)
N of Success	14
N of Complete response	3
N of Partial response	11
N of Failure	3
N of Stable response	3
N of Progression of fungal disease	0
N of Death	0

Abbreviations: CI, confidence interval; N, number; ORR, overall response rate.
All 95% confidence intervals were calculated using the Clopper-Pearson method.
[a] The median treatment duration among the salvage patients in the Overall Study Population was 25.5 days (Table 10-3).

10.6 Adverse events/adverse reactions

As defined in the study protocol, this study was designed to be a non-interventional study conducted within routine medical practice, including primary data collection (follow-up activities for vital status for patients with retrospective data collection missing the vital status in medical records) and the use of secondary data previously collected by healthcare professionals for other purposes.

For the purposes of this protocol, the term "adverse event (AE)" collectively referred to the following reportable events:

- Serious AEs (SAEs) regardless of causality in primary data collection, including death due to any cause;
- Serious adverse reactions (SARs) in secondary chart review, including death;
- Non-serious adverse reactions (NSARs); and
- Special situations regardless of seriousness or causality.

Health outcomes (Section 9.4.2) were required to be assessed for AE reportability as described above. If AEs or product quality complaints (PQCs) were identified following the use of

posaconazole injection, posaconazole enteric-coated tablets, or any other Sponsor's products, the AE and/or PQC was required to be reported according to the protocol.

For primary data collection, the assessment of causality for each AE was to be determined by an investigator who was a qualified healthcare professional according to his/her best clinical judgment.

For 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 were required to be reported as NSAR/SARs. During the review of secondary data, causality should never be assigned retrospectively.

As a result of this study, no AEs or PQCs were reported from primary data collection.

Only one special situation (pre-approval off-label use) was reported during secondary data collection by chart review, where a patient received posaconazole treatment for IA from 23 Dec 2021 to 28 Jan 2022, three months prior to the approval of posaconazole injection and enteric-coated tablets in China for the treatment of IA (29 Mar 2022; Annex 2 Listing 1). No other reportable AEs or PQCs were identified during secondary data collection by chart review.

11 DISCUSSION

11.1 Key results

This multi-center, prospective and retrospective non-interventional study evaluated the effectiveness of posaconazole injection and posaconazole enteric-coated tablets in Chinese adult patients with IA, using ACM through Day 42 post-treatment initiation as the primary outcome. Among all included patients, the ACM rate at Day 42 was 4.2% (95% CI: 0.5%, 14.3%). Specifically, the ACM rate was 7.7% (95% CI: 0.9%, 25.1%) for first-line treatment patients and 0.0% (95% CI: 0.0, 15.4%) for salvage treatment patients. Subgroup analysis based on underlying medical conditions at index date revealed that the ACM rate at Day 42 was 5.1% (95% CI: 0.6%, 17.3%) among patients with risk factors for poor outcomes due to IA, whereas it was 0.0% (95% CI: 0.0%, 33.6%) among patients without risk factors. Additionally, when analyzing patients based on treatment duration, those whose treatment duration was less than the median treatment duration of 20 days in the Overall Study Population had an ACM rate at Day 42 of 8.7% (95% CI: 1.1%, 28.0%), compared to 0.0% (95% CI: 0.0%, 13.7%) for those whose treatment duration exceeded the median duration.

The effectiveness of posaconazole injection and tablets was evaluated using clinical response at the earlier of the end of treatment or Day 84 post-treatment initiation as a secondary outcome, separately in patients who received at least 42 days of first-line treatment and at least 7 days of salvage treatment. Results showed that the ORR at the end of treatment was 66.7% (95% CI: 22.3%, 95.7%) for first-line treatment patients and 86.4% (95% CI: 65.1%, 97.1%) for salvage treatment patients. Additionally, among salvage treatment patients, those whose treatment duration was less than the median treatment duration of 25.5 days had an ORR of 90.9% (95% CI: 58.7%, 99.8%), compared to 81.8% (95% CI: 48.2%, 97.7%) for those whose treatment duration exceeded the median duration.

11.2 Limitations

Due to the non-interventional design, data were collected from routine clinical practice which depended on the prescribing practices of physicians and patient adherence. This may have led to heterogeneity in treatment, thereby affecting the evaluation of outcomes. Unlike clinical trials that use medication diaries to monitor and ensure patient adherence and data integrity, this study relied solely on patient compliance with prescriptions. Patients might have forgotten or failed to take their medication as prescribed, or delayed refills, and these instances may not have been recorded in medical records, leading to the mistaken assumption of continuous medications use. Additionally, even in a non-interventional setting, patients whose data were collected prospectively might have received more frequent monitoring and reminders from their healthcare providers to take medication on time compared to those whose data were collected retrospectively. This increased interaction in the prospective group could lead to better adherence. To analyze the impact and support the interpretation of the study results, the following study design was employed. Patients' treatment patterns, including treatment discontinuations, were summarized, and timelines were plotted for each patient. The analysis of treatment outcomes, including 42-day ACM and clinical response at the end of treatment, was supplementally conducted separately for patients with prospective data collection and patients with retrospective data collection.

In addition, the inherent variability in definitions used by different hospitals and physicians, including those for IA diagnosis and clinical response assessment, is a key limitation of multi-center non-interventional studies. Despite the existence of guidelines, adherence to these guidelines in routine clinical practice may be suboptimal. However, relying solely on guidelines as the standard may result in a significantly smaller sample size than anticipated due to insufficient information in medical records, thereby affecting the reliability of the results. To address this issue, this study used guidelines as the primary standard for definitions, supplemented by the professional assessment of the investigators. This approach aimed to maintain data integrity without losing sample size. Furthermore, subgroup analyses based on different definitions of clinical response, comparing those strictly adhering to guidelines with those incorporating investigators' professional assessment, were designed to assess the impact of these variations.

The resulting sample size of this study was relatively small, especially in the First-line ORR Analysis Population, and the study sites were not randomly selected. The impact of insurance coverage on the sample size could not be assessed due to privacy regulations at the study sites, which restricted direct access to patient reimbursement data for posaconazole. Therefore, no further analysis was conducted on this matter, and this factor did not influence the effectiveness evaluation. Nevertheless, this study included nine tertiary Grade A hospitals from various regions across China and assessed all eligible patients during the study period under real-world settings. A standard CRF and uniform criteria for IA diagnosis and response assessments were employed to collect data, ensuring data consistency and quality. Given the rarity of the condition, these efforts maximized the sample size and increased population representativeness, thereby strengthening the robustness and reliability of the findings.

Consequently, the potential limitations should have minimal impact on the effectiveness evaluation and the generalizability of the findings.

11.3 Interpretation

Clinical trials remain the gold standard for evaluating the safety and efficacy of drugs during development and approval. However, the strict enforcement of inclusion and exclusion criteria can lead to selection bias, resulting in a highly selective study population. In contrast, real-world studies collect data from broader populations treated in various clinical settings outside the scope of tightly controlled RCTs. Therefore, it is crucial to conduct post-marketing studies and collect real-world data, especially for participant groups not well-represented in the respective RCTs. In this study, with inclusion and exclusion criteria consistent with the approved labels, posaconazole injection and tablets have been shown to be an effective treatment for IA patients in real-world clinical settings in China.

Among IA patients who received posaconazole injections and/or tablets for at least seven days, the ACM rate at Day 42 post-treatment initiation was 4.2%. This result is consistent with the point estimates from CCI [redacted] the point estimates from the overall analysis in the global population (42-day ACM rate of 15.3%; MK-5592-069; NCT01782131). Notably, both deceased patients had risk factors for poor outcomes due to IA at baseline, with one patient having high-risk conditions of relapsed leukemia undergoing salvage chemotherapy. However, the inherent limitations of real-world studies, such as variability in adherence, differences in

administration practices, and potential data quality issues, make it inappropriate to directly compare these results to those of RCTs.

Published real-world studies on posaconazole treatment for IA, especially regarding the injection formulation and its use as first-line treatment, are extremely limited, and no relevant studies have been found in the Chinese population. Only a few studies have provided some reference results on the ACM rate and ORR in patients treated with posaconazole for IFDs [Ref. 5.4: 08VW2S], [Ref. 5.4: 08VWQ5], [Ref. 5.4: 08VWQ9], [Ref. 5.4: 08VWQB], and this study shows similar results to those findings. The 42-day ACM rate of 4.2% observed in this study aligns with the reported range of 4.2% to 11.1% in prior real-world studies [Ref. 5.4: 08VW2S], [Ref. 5.4: 08VWQ5], [Ref. 5.4: 08VWQ9]. Additionally, the first-line ORR of 66.7% and salvage ORR of 86.4% in this study demonstrate favorable treatment outcomes, as indicated by the published ORR ranges of 54.2% to 59.3% for unspecified treatment [Ref. 5.4: 08VW2S], [Ref. 5.4: 08VWQ5], [Ref. 5.4: 08VWQB] and 50.0% to 53.1% for salvage treatment [Ref. 5.4: 08VWQ9], [Ref. 5.4: 08VWQB]. However, it is important to exercise caution when referencing published studies due to variations in studied indications, treatment formulations, and treatment patterns.

11.4 Generalisability

This is the first post-marketing non-interventional study conducted in China to evaluate the effectiveness of posaconazole injection and tablets in Chinese adult patients with IA. The study design combined prospective and retrospective chart review, with inclusion and exclusion criteria broader than those of clinical trials, consistent with the population specified in the Chinese label. All Chinese adult IA patients from the selected sites who received at least 7 days of posaconazole treatment and met the eligibility criteria from the time posaconazole injection and tablets were approved in China (Mar 2022) until Jan 2025 were included in the study. This approach not only captured a broader range of patient data and more accurately reflected real-world practice but also ensured that the results are applicable to the actual patient population using posaconazole.

To meet the target sample size, hospitals with a higher number of potential IA patients and greater use of posaconazole injection and tablets were selected, but the study sites could not be selected randomly which resulted in the study population may not fully represent the overall population of Chinese patients using posaconazole injection and tablets. Ultimately, the study was conducted in nine tertiary Grade A hospitals located across various regions of China. Despite regional differences, all clinicians routinely manage IA patients in clinical practice, and most patients have access to information, education, and services that benefit adherence. Therefore, these differences are unlikely to significantly affect the generalizability of the study results in other regions.

12 OTHER INFORMATION

Not applicable in this study.

13 CONCLUSION

Overall, this is the first post-marketing non-interventional study conducted in China assessing the effectiveness of posaconazole injection and tablets for proven, probable, and possible IA in Chinese adult patients. The results demonstrate high effectiveness for both first-line and salvage treatment.

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