NON-INTERVENTIONAL STUDY PROTOCOL

Study Title:	A Multi-country, Non-interventional, Retrospective Drug Utilization Study in Haematological Malignancy Patients Treated for Probable or Proven Invasive Aspergillosis
Short Title:	AmBiVor
Marketing Authorisation Holder:	Belgium: Gilead Sciences Ireland UC Carrigtwohill County Cork, T45 DP77 Ireland France: Gilead Sciences 65, Quai Georges Gorse 92100 Boulogne-Billancourt France Germany: Gilead Sciences GmbH Fraunhoferstraβe 17 82152 Martinsried Germany Spain: Gilead Sciences, S.L. Via de los Poblados, 3 ef 7/8 plte 6ª – Pque Empresarial Cristalia Madrid 28033 Spain United Kingdom: Gilead Sciences International Ltd, Granta Park, Abington, Cambridge, CB21 6GT UK

EU PAS Register No:	Registration will be performed prior to the start of data collection
Clinical Trials.gov Identifier:	Study not registered
Indication:	Fungal infection. Treatment of proven or probable invasive aspergillosis
Active substance:	ATC Code J02AA01 Liposomal amphotericin B
Medicinal Product:	AmBisome liposomal amphotericin B 50 mg, powder for dispersion for infusion
Product reference:	Belgium BE166257, France 562 408 2 or 34009 562 408, Germany 34231.00.00, Spain 61.117, UK 16807/0001
Joint PASS:	No
Research Question and Objectives:	To evaluate the drug utilization in haematological malignancy patients treated for probable or proven invasive aspergillosis and to generate real-world evidence on current treatment patterns/sequences, treatment outcomes, and adverse events of special interest. CCI [redacted]
Countries of study:	Belgium, France, Germany, Spain, United Kingdom
Protocol ID:	GS-EU-131-6385
Protocol Version / Date:	Original / PPD
Author / Contact Information:	Name: PPD Telephone: PPD

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AIC	Akaike information criterion
ALL	acute lymphoblastic leukaemia
Allo-HSCT	allogeneic haematopoietic stem cell transplantation
ALP	alkaline phosphatase
ALT	alanine transaminase
AML	acute myeloid leukemia
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
CI	confidence interval
CRF	case report form
CRO	contract research organization
eCRF	electronic case report form
ECIL	European Conference on Infections in Leukemia
ECMM-ERS	European Confederation of Medical Mycology and the European Respiratory Society
EDC	electronic data capture
EMA	European Medicines Agency
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU	European Union
FDA	(United States) Food and Drug Administration
GEE	generalized estimating equations
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GSI	Gilead Sciences, Inc.
GVHD	graft-versus-host disease
GVP	European Medicines Agency Guidelines on Good Pharmacovigilance Practices
HMA	Heads of Medicines Agencies
HR	hazard ratio
HSCT	haematopoietic stem cell transplantation
IA	invasive aspergillosis
ICF	informed consent form
IDSA	Infectious Diseases Society of America
IEC	independent ethics committee
IFI	invasive fungal infection
IPTW	inverse probability treatment weighting
IV	intravenous
LFT	Liver Function Tests

MAH	marketing authorisation holder
MDS	myelodysplastic syndromes
NIS	non-interventional study
OS	overall survival
PAS	post-authorisation study
PS	propensity score
RWD	real-world data
RWE	real-world evidence
SAP	Statistical Analysis Plan
SD	standard deviation
QIC	Quasi-likelihood under the Independence model Criterion
TTE	time to event
UK	United Kingdom

PROTOCOL SYNOPSIS

Gilead Sciences Inc.
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Foster City, CA 94404
USA

Study Title:	A Multi-country, Non-interventional, Retrospective Drug Utilization Study in Haematological Malignancy Patients Treated for Probable or Proven Invasive Aspergillosis
Short Title:	AmBiVor
EU PAS Register No: **ClinicalTrials.gov Identifier:**	Registration will be performed prior to the start of data collection. Study will not be registered.
Study Sites Planned:	Approximately 16 sites in Belgium, France, Germany, Spain, and United Kingdom
Rationale and Background:	Opportunistic invasive fungal infections are a major cause of morbidity and mortality in haematology patients with invasive aspergillosis (IA) being a particular problem despite the widespread use of mould-active prophylaxis in vulnerable populations. International clinical guidelines (see Section 1.2) recommend voriconazole and isavuconazole as the first-line treatment of IA, with amphotericin B and its various lipid-formulations being recommended as an alternative. This is based partly on the result of the study conducted by Herbrecht et al. {Herbrecht 2002}, which compared conventional amphotericin B to voriconazole and concluded that voriconazole resulted in improved survival with decreased adverse events (AEs) compared with conventional amphotericin B. Due to the lack of real world data (RWD) in the targeted treatment setting, the current study will generate evidence associated to the characterization of AmBisome®- and voriconazole treated patients, including effectiveness and adverse events of special interest (AESIs). The study will be based on existing (retrospective) data of high-risk haematological malignancy patients defined as adult patients who have undergone haematopoietic stem cell transplantation (HSCT) or patients with acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), or acute lymphoblastic leukaemia (ALL).

Research Question and Objectives:	Primary objectives: • To describe demographic, clinical and treatment patterns/sequences in haematologic malignancy patients treated either with AmBisome or voriconazole as primary treatment for the index proven or probable IA (according to {De Pauw 2008}) Secondary objectives: • To determine 42-day overall survival (OS) in haematological malignancy patients with IA treated either with AmBisome or voriconazole as primary treatment • To estimate the percentage AmBisome- and voriconazole-treated patients that experience AESIs, in particular nephrotoxicity and hepatotoxicity, and any AEs leading to treatment discontinuation or modification • Estimate the time to first nephrotoxicity and/or hepatotoxicity during the follow-up period (in patients without kidney or liver deficiency at index date) CCI [redacted]
Study Design:	This is a real-world, non-interventional, multi-country, retrospective chart review study using patient medical record data collected from approximately 16 hospitals in 5 European countries (Belgium, France, Germany, Spain, and United Kingdom [UK]). High-risk haematological malignancy patients (HSCT, AML, MDS, and ALL) with a diagnosis of documented probable or proven IA, who initiated primary treatment of AmBisome or voriconazole between 01 January 2014 and 31 December 2019, will be included in the study. All treatments must have been prescribed in accordance with local routine clinical practice. There will be no additional samples, visits, diagnostic, or monitoring procedures required in the study.

Study Size:	The primary objective of the study is the characterization of AmBisome- and voriconazole-treated high-risk haematological malignancy patients with respect to their demographics, clinical characteristics, and treatment patterns. Approximately 200 patients will be included in each arm. This sample size is considered sufficient to estimate all binary and continuous outcomes with high precision. With respect to secondary objectives associated with effectiveness (42-day OS as binary outcome) and safety (percentage of patients with AESIs), a sample size of 200 patients will yield a 95% CI with a half-width of 6.9% for an expected proportion of 50% (worst-case scenario).
Study Population:	The study population will consist of adult high-risk haematological malignancy patients (HSCT, AML, MDS, and ALL) who received at least 1 dose of AmBisome or voriconazole as primary treatment for probable or proven IA, at any time from 1 January 2014 to 31 December 2019.
Main Eligibility Criteria:	**Inclusion criteria** • Adult patients (age ≥ 18 years) with haematologic malignancies who have undergone allogeneic HSCT or patients with AML, MDS, or ALL • Patients with proven or probable IA according to {De Pauw 2008}, for whom the treating physician initiated treatment with either AmBisome or voriconazole • Patients who received at least 1 dose of AmBisome or voriconazole as primary treatment for probable or proven IA at any time from 01 January 2014 to 31 December 2019 (Primary antifungal therapy is defined as the first antifungal treatment that was administered for at least 5 consecutive days) **Exclusion criteria** • Patients who were treated with AmBisome or voriconazole as part of a clinical trial during the observational period • Patients treated jointly with any combination of AmBisome or voriconazole, and/or other mould-active azoles and/or echinocandins in primary setting

Study Period/Follow-up	Clinical data will be extracted from the start of AmBisome or voriconazole treatment, until the end of follow-up period, defined as death, lost to follow-up, or 84 (±7) days after start of primary therapy (inclusive), whichever came the earliest. Primary antifungal therapy is defined as the first antifungal treatment that was administered for at least 5 consecutive days. Treatment variables will be followed as long as patients were treated for the index probable/proven IA. If IA resolution is recorded, then treatment follow-up only aims to establish if secondary prophylaxis was required.
Variables:	Each patient's data will be pseudonymized and collected from the start of AmBisome or voriconazole treatment for the index proven or probable IA. Available routine clinical data will be extracted until the end of follow-up period. **Baseline (defined as start of AmBisome or voriconazole as primary treatment for the index proven or probable IA):** • Demographics, clinical variables (see Table 2), and treatment patterns **Follow-up period:** • IA treatment and outcome variables **Safety information:** • Any AEs that led to AmBisome or voriconazole dose modification or discontinuation, as well as AESIs (nephrotoxicity, hepatotoxicity) (safety events will be only collected for primary therapies)
Data Sources:	Data will be collected from approximately 16 participating sites across Belgium, France, Germany, Spain, and the UK. The primary data source will be the patient's medical records. Review of electronic or paper medical records, data identification, abstraction, and data transcription will be performed by trained site personnel. All data will be pseudonymized and collected for patients meeting all eligibility criteria. Each patient will be identified by a unique electronic case report form generated patient identifier.

Data Analysis:	**Descriptive Analysis** Descriptive statistics will be tabulated for the demographic and clinical characteristics and outcome variables. In all cases, point estimates as well as the corresponding two-sided 95% CIs will be presented. No missing value imputation will be performed. **Treatment Sequence Analysis** Treatment sequence will be visualized through Sankey diagrams. **Time-to-event Analysis** The secondary objective is to estimate the 42-day OS of patients treated with AmBisome and of patients treated with voriconazole. OS and time to first nephrotoxicity and hepatotoxicity will be described using Kaplan-Meier methods and reported using descriptive statistics with 95% CIs and survival curves. **Regression Analysis** *Unadjusted*: The OS will be compared between AmBisome and voriconazole cohorts with a univariate Cox proportional hazards model. The associated hazard ratio (HR) with 95% CI and *P* values will be reported. Proportionality assumptions and log-linearity will be assessed before application. *Adjusted*: Multivariable modeling (ie, Cox proportional hazards model) will also be conducted to determine risk factors associated to OS. Relevant confounders will be identified through literature research and expert consultation. Furthermore, propensity scores will be combined with regression adjustment to improve the estimation efficiency. **Sensitivity Analysis** The regression analysis proposed for OS on Day 42, it will be repeated at Day 84, to assess robustness of the results.

PLANNED MILESTONES

Table 1. Planned Milestones

Milestone	Planned Date
Registration in the EU PAS Register (if applicable)	Q2 2023
Start of data collection	Q3 2023
End of data collection	Q1 2024
Final Report of Study Results	Q3 2024

1. INTRODUCTION

1.1. Background

Opportunistic fungal infections are a major cause of morbidity and mortality in haematological malignancy patients. Antifungal agents are used both as prophylaxis and treatment in these patients. The population at risk comprises patients with prolonged neutropenia, allogeneic stem cell transplant (haematopoietic stem cell transplantation [allo-HSCT]), corticosteroid use, solid organ transplant, and various inherited or primary immunodeficiency conditions. The most frequent pathogens are *Candida* spp., however, invasive aspergillosis (IA) is also important in these patients, especially as it is often difficult to diagnose and is associated with significant mortality despite the use of mould-active prophylaxis in these high-risk haematology populations. Azole antifungals are effective in decreasing invasive fungal infections (IFIs), but in the context of high background rates of resistance or due to factors connected with the drug such as intolerance, adverse side effects, poor absorption, or other unfavourable pharmacokinetics considerations, these drugs may fail and result in breakthrough IFIs.

1.2. Rationale for the Study

AmBisome® is a polyene antifungal agent with a broad spectrum of activity against yeasts and moulds that was first approved in Ireland in 1990 and is currently approved in 69 countries, The efficacy of AmBisome has been established in a number of clinical trials {Cornely 2007, Hamill 2010, Kuse 2007, Lanternier 2015, Ringden 1991, Walsh 1999, Walsh 2002, Walsh 2004, Wingard 2000} for the treatment of invasive fungal disease, including IA, as empirical therapy for fever of unknown origin in neutropenic patients and for the treatment of visceral leishmaniasis, cryptococcal disease and histoplasma.

Voriconazole is recommended as primary treatment for IA in guidelines such as the ones from the Infectious Diseases Society of America (IDSA) {Patterson 2016}, the European Conference on Infections in Leukemia (ECIL) {Tissot 2017}, and the joint guidelines from the European Society of Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology and the European Respiratory Society (ESCMID-ECMM-ERS) {Ullmann 2018}, with lipid derivatives of amphotericin B such as AmBisome being recommended as an alternative treatment.

Voriconazole has been studied against conventional amphotericin B for the targeted treatment of IA in a trial conducted by Herbrecht {Herbrecht 2002}. In most of the patients, the underlying condition was allo-HSCT, acute leukemia, or other haematologic diseases. This study concluded that voriconazole led to better responses and improved survival, and resulted in fewer adverse events (AEs) than the standard approach of initial therapy with conventional amphotericin B. The data from this trial have contributed to the perception that other intravenous (IV) formulations of amphotericin have comparable efficacy with conventional amphotericin B. Since there has been no head-to-head trial comparing AmBisome with voriconazole, its position in the various guidelines has remained unchanged. However, the scientific conclusions made by Herbrecht et al. {Herbrecht 2002} contradict other published evidence. For example, a Cochrane

review {Jorgensen 2014} concluded that liposomal amphotericin B is significantly more effective than voriconazole for empiric therapy of IFI in neutropenic cancer patients. The fungicidal nature of AmBisome compared with the fungistatic nature of voriconazole could translate into a more rapid treatment response in immunosuppressed patients, who rely upon a functioning immune system to clear the infection, which could shorten the length of hospital stay and possibly improve the survival rate at 42 days, which is the standard time adopted in antifungal treatment trials.

There are no head-to-head trials comparing liposomal amphotericin B with voriconazole for targeted treatment of IA and as per our knowledge there has been no recent and direct evaluation of the treatments being used in clinical practice for IA. There is therefore a need to generate real-world evidence (RWE) of IA treatments in Europe (AmBisome and voriconazole) associated with current treatment patterns (including treatment sequencing, duration of treatment), treatment outcomes (overall survival [OS]), and adverse events of special interest (AESIs) (ie, nephrotoxicity and/or hepatotoxicity).

2. RESEARCH QUESTIONS AND OBJECTIVES

The primary objective of this study is as follows:

- To describe demographic, clinical, and treatment patterns/sequences in haematologic malignancy patients treated either with AmBisome or voriconazole as primary treatment for the index proven or probable IA (according to {De Pauw 2008})

The secondary objectives of this study are as follows:

- To determine 42-day overall survival (OS) in haematological malignancy patients with IA treated either with AmBisome or voriconazole as primary treatment (Day 42 is selected as per FDA requirement for antifungal studies. As per the Neofytos et al. {Roth 2022}, the longer the follow-up the greater the likelihood of incorrectly classifying drugs used as treatment when in fact they were used as secondary prophylaxis. Additionally the longer the follow up period the more likely patients may die due to underlying morbidity than invasive fungal infection thus confounding results. Patients who have undergone HSCT or have GVHD are immunocompromised so when the IA is resolved the clinical guidelines {Patterson 2016} recommend that the patient should be put on secondary prophylaxis to prevent any new invasive fungal infection from happening)

- To estimate the percentage of AmBisome- and voriconazole-treated patients that experience AESIs, in particular nephrotoxicity and hepatotoxicity, and any AEs leading to treatment discontinuation or modification

- Estimate the time to first nephrotoxicity and/or hepatotoxicity during the follow-up period (in patients without kidney or liver deficiency at index date)

CCI [redacted]

[redacted]

3. RESEARCH METHODS

3.1. Study Design

This is a real-world, non-interventional, multi-country, retrospective chart review study using patient medical record data collected from approximately 16 hospitals in 5 European countries (Belgium, France, Germany, Spain, and the United Kingdom [UK]). Haematological malignancy patients (HSCT, acute myeloid leukemia [AML], myelodysplastic syndromes [MDS] and acute lymphoblastic leukaemia [ALL]) with a diagnosis of documented probable or proven IA and who received at least 1 dose of AmBisome or voriconazole as primary treatment from 01 January 2014 to 31 December 2019, will be included in the study.

Index date (Baseline): Defined as the date of the first dose of AmBisome or voriconazole as primary treatment for a first event (index event) of probable or proven IA during the index period. Primary antifungal therapy is defined as the first antifungal treatment that was administered for at least 5 consecutive days

Index period: The patients fulfilling the inclusion criteria will be identified during the period 01 January 2014 to 31 December 2019, inclusive

Study period: The period between 01 January 2013 and 07 April 2020 to allow 12 months pre-index and 3 months (84 days ± 7-days) post-index period.

3.2. Setting

All treatments must have been prescribed according to local treatment guidelines and/or routine or standard clinical practice. There will be no additional samples, visits, diagnostic, or monitoring procedures required in the study.

Data will be pseudonymized and retrospectively collected from medical records of patients meeting all inclusion/exclusion criteria.

3.2.1. Inclusion Criteria

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

- Adult patients (age ≥ 18 years) who have undergone allogeneic HSCT or patients with AML, MDS, or ALL
- Patients with proven or probable IA according to {De Pauw 2008}, for whom the treating physician initiated treatment with either AmBisome or voriconazole
- Patients who received at least 1 dose of AmBisome or voriconazole as primary treatment for probable or proven IA at any time from 01 January 2014 to 31 December 2019 (Primary antifungal therapy is defined as the first antifungal treatment that was administered for at least 5 consecutive days)

3.2.2. Exclusion Criteria

Patients who meet *any* of the following criteria will be excluded from the study:

- Patients who were treated with AmBisome or voriconazole as part of a clinical trial during the observational period
- Patients treated jointly with any combination of AmBisome and voriconazole, and/or other mould-active azoles and/or echinocandins in primary setting

3.3. Variables

This is a non-interventional retrospective chart review study. Only data available from routine medical practice will be collected retrospectively for this study. The primary data source will be the patient's medical records. Each patient's data will be pseudonymized and collected from the start of AmBisome or voriconazole treatment for proven or probable IA until the end of the follow-up period, defined as death, lost to follow-up, or 84 (±7) days after start of primary therapy (inclusive), whichever came the earliest.

More details on how comorbidities are identified, attribution of nephrotoxic or hepatotoxic concomitant medication or other drugs leading to AEs, association of AEs with nephrotoxicity and hepatotoxicity will be provided in the Statistical Analysis Plan (SAP).

Because this is a study conducted in a real-world setting, patients might not have been assessed exactly on the proposed days. To address this limitation the following time windows will be used:

- For Day 42, the window of ±2 days will be used
- For Day 84, the window of ±7 days will be used

Should more than one measurement be available, the value closest to the day assessed will be considered. If two values are equally close, i.e., one value before and one value after, the first one is taken. In the case of no information available, then it will be set to missing.

Baseline (start of AmBisome or voriconazole as primary treatment for the index proven or probable IA):

- Demographic factors
  - — Year of birth
  - — Sex
- Weight

- IA diagnostic certainty, according to the site criteria:
  - Confirm if proven or probable
  - Date of diagnosis, if applicable
  - Data on site of infection, including cerebral, sinus, lung, cardiac manifestation (e.g., endocarditis), gastrointestinal disease, other (specified)
- Any prophylaxis with antifungals immediately prior (up to one week) to the start of primary treatment for proven or probable IA
  - Type of treatment
  - Dose
  - Duration
- Comorbidities diagnosed within 1 year prior to baseline, including:
  - Diabetes mellitus, other underlying immunosuppression, hepatic disease/injury, renal disease/injury
- Underlying haematology conditions diagnosed within 1 year prior to baseline, including:
  - AML, ALL, MDS, HSCT, other haematological conditions that led to the need for HSCT
- Serum creatinine (closest available value prior to baseline but within 3-months from index date (baseline) {National Institute of Health 2012})
- Liver Function Tests (LFT), including (closest available value prior to baseline but within 3-months from index date (baseline) {National Institute of Health 2012}):
  - Alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), serum bilirubin and total protein
- Neutropenia (closest available value prior to baseline but within 3-months from index date (baseline) {National Institute of Health 2012})
  - Neutropenia (defined as < 500 neutrophils/µL) at onset of treatment for probable or proven IA
  - Neutropenia duration (days)
  - Depth of neutropenia (neutrophil count)

- Relevant nephrotoxic or hepatotoxic concomitant medication or other drugs that may cause significant interactions resulting in AEs:
  - Drug name, dose, regimen, start/end date, indication
  - Agents such as antibiotics (aminoglycosides, amoxicillin, ciprofloxacin, co-trimoxazole, isoniazid, vancomycin, polymixins), allopurinol, amiodarone, antineoplastic agents (antimetabolites, cisplatin, tyrosine kinase inhibitors), cidofovir, foscarnet, IV pentamidine, ganciclovir, highly active antiretroviral therapy, ciclosporin, tacrolimus, chronic daily nonsteroidal anti-inflammatory drugs, paracetamol, anti-seizure medication (phenytoin, valproate), statins, tumor necrosis factor-alpha inhibitors

Follow-up period:

Treatment patterns/sequences will be described over 84 (±7) days follow-up period from baseline. Primary, second-line, and subsequent treatments will be collected.

- AmBisome or voriconazole as primary treatment
  - Start/end date
  - Dose and frequency at start of primary treatment
  - Route of administration
- Serum creatinine (the value closest to the day assessed will be considered)
- LFT, including: ALP, ALT, AST, serum bilirubin and total protein (the value closest to the day assessed will be considered)
- Neutropenia (the value closest to the day assessed will be considered)
  - Timing of neutrophil recovery following start of primary treatment (neutrophil count first value of at least three consecutives >500 neutrophils/μL)
- Any event of GVHD
- If AmBisome or voriconazole was discontinued and switched to second-line (not part of a clinical study) and subsequent therapy for the same index IA:
  - Drug name
  - Dose and frequency
  - Start/end date

— Reason for discontinuation

- Relevant nephrotoxic or hepatotoxic concomitant medication or other drugs that may cause significant interactions resulting in AEs:

  — Drug name

  — Dose

  — Regimen

  — Start/end date

  — Indication

  — Agents such as antibiotics (aminoglycosides, amoxicillin, ciprofloxacin, co-trimoxazole, isoniazid, vancomycin, polymixins), allopurinol, amiodarone, antineoplastic agents (antimetabolites, cisplatin, tyrosine kinase inhibitors), cidofovir, foscarnet, IV pentamidine, ganciclovir, highly active antiretroviral therapy, ciclosporin, tacrolimus, chronic daily nonsteroidal anti-inflammatory drugs, paracetamol, anti-seizure medication (phenytoin, valproate), statins, tumor necrosis factor-alpha inhibitors

- Resolution of the index IA (on Day 84 +/- 7-days), as determined by the treating physician or measured by discontinuation of antifungal treatment in a living patient where no other reason was stated

  — Date of resolution

- After the index IA resolution, secondary prophylaxis treatment

  — Drug name

  — Start/end date

- Record of death at Day 42 ± 2 days and at end of follow-up (Day 84 ±7)

  — Patient still alive (Yes/No)

  — Date of death

  — Reason for death (IA vs non-IA related)

In addition, the below safety information will be collected from the first dose of AmBisome or voriconazole until the end of primary therapy:

- Any AE that led to AmBisome or voriconazole dose modification (including treatment interruption and dose reduction) or discontinuation
- AEs associated with an event of special interest (AESIs)
  - — Nephrotoxicity, if this led to new renal replacement therapy, persistent renal dysfunction, or death
  - — Hepatotoxicity, if this led to hepatic failure, jaundice cholestatic, cholecystitis, or death

Table 2. Variable Table

Data to Be Provided if Available or Applicable	Baseline	Follow-up Period
IA diagnosis (confirm if proven or probable and date of diagnosis, if applicable)	X	X
Demographic factors at start of primary treatment (Year of birth and sex)	X	
Weight at start of primary treatment	X	
Any prophylaxis with antifungals immediately prior (up to one week) to the start of primary treatment for proven/probable IA	X	
Comorbidities (diagnosed within 1 year prior to baseline) (Diabetes mellitus, other underlying immunosuppression, hepatic disease/injury, renal disease/injury)	X	
Underlying haematology conditions (diagnosed within 1 year prior to baseline) (AML, ALL, MDS, HSCT, other haematological conditions that led to the need for HSCT)	X	
Serum creatinine	X	X
Liver function tests (alkaline phosphatase, alanine transaminase, aspartate transaminase, serum bilirubin and total protein)	X	X
Neutropenia	X	X[a]
Relevant nephrotoxic or hepatotoxic concomitant medication or other drugs that may cause significant interactions causing AEs	X	X
AmBisome or voriconazole treatment	X	X
AmBisome or voriconazole discontinuation and switch to second-line and/or subsequent therapy for index IA		X
Any event of GVHD		X
After IA resolution, secondary prophylaxis treatment		X
Record of death [b]		X
IA resolution		X
Safety information (***refer to Section 6***)	Safety information will be collected from the first dose of AmBisome or voriconazole until the end of therapy with AmBisome or voriconazole (safety events will be collected for primary therapies only)	

a Timing of neutrophil recovery following start of primary treatment (neutrophil count).
b Record of death at Day 42 ± 2 days and end of follow-up (Day 84 ±7).
AML = acute myeloid leukemia; ALL = acute lymphocytic leukemia; GVHD = graft-versus-host disease; HSCT = haematopoietic stem cell transplantation; IA = invasive aspergillosis; MDS = myelodysplastic syndromes

3.4. Data Sources

Data will be collected from approximately 16 participating sites across Belgium, France, Germany, Spain, and the UK. The primary data source will be the patient's medical records. Review of electronic or paper medical records, data identification, abstraction, and data transcription will be performed by trained site personnel.

Data collection will be performed by manual entry of data from the patient's medical file to a computer-based electronic case report form (eCRF). All data will be pseudonymized and collected for patients meeting all eligibility criteria. Each patient will be identified by a unique eCRF generated patient identifier.

3.5. Data Management

After finalization and approval of the protocol, an eCRF will be built in an electronic data capture (EDC) system to collect the data listed in the Variables section (Section 3.3). Personal identifying data such as names, health records, or social security identifiers will not be collected. Investigational site users will receive a unique username and password per user from the EDC system administrator following completion of the EDC system training. Completion of training and receipt of username/password will allow the site to enter data into the EDC system. Investigators will electronically sign the eCRF to confirm responsibility for data following completion of data entry and data quality activities. Study datasets will be stored on secure Gilead network drives with access restricted to authorised personnel only.

3.6. Study Size

The primary objective of the study is the characterization of AmBisome- and voriconazole-treated patients with respect to their demographics, clinical characteristics and treatment patterns. In total 400 subjects will be included across both cohorts, from approximately 16 sites in 5 European countries. Assuming that 200 patients are included in each arm, the sample size will yield sufficient precision to describe both the binary and continuous outcomes. More precisely, for binary outcomes and an expected proportion of 50% (worst case scenario), then a sample size of 200 patients will yield a 95% confidence interval (CI) with a half-width of 6.9%. Furthermore, for continuous outcomes and assuming standard deviation (SD) equal to 20, a sample size of 200 treated patients will yield a 95% CI with a half-width of approximately 2.8. With respect to secondary objectives associated with effectiveness (42-day OS as binary outcome) and safety (percentage of patients with AESIs), the worst-case scenario of $\pi = 0.50$ is considered (ie, the variance of the binomial distribution is at its maximum when the probabilities for success and failure are both 0.5). For an expected proportion of 50%, a sample size of 200 patients will yield a 95% CI with a half-width of 6.9%.

Table 3. Distance from the Expected Proportion to the Limit for a Two-sided 95% Confidence Interval

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Expected proportion (π)	0.200	0.300	0.400	0.500
Precision	0.055	0.064	0.068	0.069
Sample size	200	200	200	200

3.7. Data Analysis

3.7.1. Primary Analysis

Descriptive statistics will be tabulated for the demographic and clinical characteristics and outcome variables. In all cases, point estimates as well as the corresponding two-sided 95% CIs will be presented. No missing value imputation will be performed.

3.7.1.1. Continuous and categorical variables

Continuous variables will be summarized by providing the number of observations, means and SDs, percentiles (25%, 50%, and 75%), and minimum and maximum values, as well as two-sided 95% CIs of the mean. Categorical variables will be summarized by providing counts and proportions, with missing data considered as a separate category. Furthermore, two-sided 95% CIs will be derived for all proportions.

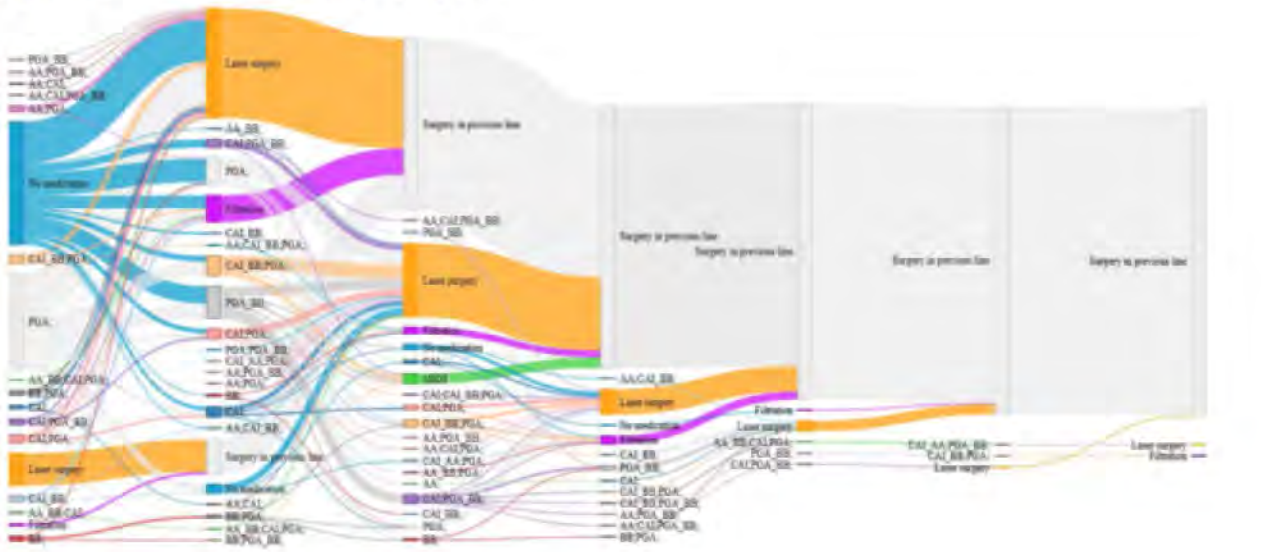
3.7.1.2. Treatment patterns

The following items will be described for each study cohort: treatment sequencing, dosing, duration of treatment, and reason for treatment switch/discontinuation.

3.7.1.3. Treatment sequencing

The use of antifungal treatments for IA will be described from the baseline date to the end of follow-up. Primary antifungal therapy is defined as the first antifungal treatment that was administered for at least 5 consecutive days. Second-line and subsequent therapy is defined as any other therapy administered after primary antifungal therapy due to refractory, intolerance, or de-escalation. The flow of patients between treatments will be depicted using a Sankey diagram.

Figure 1. Sankey Diagram



The treatment and dose changes, including discontinuation (without switching), withdrawal, switch for another treatment, and addition of antifungal treatment, will be presented. The frequency of patients with discontinuation will be presented according to the reason for discontinuation.

In addition, in each cohort, the proportion of patients receiving a second-line treatment and/or subsequent treatment for IA will be described.

The time to event (TTE; the event being treatment discontinuation, withdrawal, switch, addition of antifungal treatment, dose change and receipt of second-line and/or subsequent treatment) will include the index date and event date; i.e., TTE equals (event date − index date) + 1. Calculation of TTE requires each patient to have either a date of event or a censor date, being death or end of follow--up. If no event is observed in the follow-up period, the TTE equals (end of follow-up period for the patient − index date) + 1. TTE will be described using Kaplan-Meier methods and reported using descriptive statistics with 95% CIs and survival curves.

3.7.1.4. Treatment duration

The total treatment duration as well as the duration of the primary treatment will be described in the cohorts during the follow up-period. Durations will also be assessed in subgroups in each cohort, according to treatment events: duration of treatment in patients who had a switch, dose changes, duration of treatment in patients who discontinued their treatment, and duration of treatment in patients without switch nor discontinuation.

3.7.2. Secondary Analyses

3.7.2.1. Estimation of overall survival (OS) in AmBisome and voriconazole cohorts

The 42-day OS will be estimated in AmBisome and voriconazole primary treatment cohorts, respectively. The median OS and 95% CI plus other quantiles of interest (ie, 25% and 75% quantiles) will be assessed. Results will be depicted graphically by Kaplan-Meier curves.

Overall survival is a derived outcome measure that characterizes the time interval from a given index date to death due to any cause for each patient in a study cohort. In the current study, OS will be defined by the time from the index date corresponding to the first AmBisome or voriconazole administration to death due to any cause. If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive (on or before the cutoff date, Day 42).

3.7.2.2. Estimation of time to first nephrotoxicity and hepatotoxicity in AmBisome and voriconazole cohorts

Patients with documented liver or kidney dysfunction up to three months before index date will be excluded from the time to nephrotoxicity and hepatotoxicity analysis {National Institute of Health 2012}.

Time to first nephrotoxicity and hepatotoxicity will be described using Kaplan-Meier methods and reported using descriptive statistics with 95% CI and survival curves. Time to nephrotoxicity and time to hepatotoxicity will be assessed separately.

The TTE (being first nephrotoxicity event in nephrotoxicity analysis; similarly for the hepatotoxicity event/analysis) will include the index date and event date; i.e., TTE equals (event date − index date) + 1.

Calculation of TTE requires each patient to have either a date of event (nephrotoxicity or hepatotoxicity) or a censor date, being death or end of follow-up.

If no event is observed in the follow-up period, the TTE equals (end of follow-up period for the patient − index date) + 1.

3.7.2.3. AESIs and AEs leading to treatment discontinuation and/or modification

A multivariable regression model (generalized estimating equations [GEE]) will be used to assess the predictive value of demographics and baseline clinical characteristics. The dependent variable will be AESIs (no/yes), and independent variables will include age (in years), gender, treatment (AmBisome vs voriconazole) and covariates defined in the SAP based on clinicians' input and after looking into the literature. The variables will enter the model one block at a time and model selection will be based on the quasi-likelihood under the independence model criterion (QIC).

A similar model will be fit for AEs that led to treatment discontinuation and/or modification.

3.7.2.4. Subgroup analysis

The analysis of OS on Day 42 will be repeated for the following subgroups:

- after excluding all patients who received fewer than 5 consequent doses of either AmBisome or voriconazole from the index date
- by disease stage or refractory stage

3.7.3. Other Analyses

3.7.3.1. Unadjusted comparison between AmBisome and voriconazole cohorts

A univariate Cox proportional hazards model will be used to compare 42-day OS between AmBisome and voriconazole cohorts. The associated hazard ratio (HR) with 95% CI and *P* values will be reported. Proportionality assumptions and log-linearity will be assessed before application.

3.7.3.2. Adjusted comparison between AmBisome and voriconazole cohorts

Multivariable modeling will also be conducted to determine risk factors associated with OS. These models will employ a large number of fixed baseline covariates. Along with input from clinicians, a comprehensive analysis of collinearity will be conducted to better understand potential confounding issues.

Given the expected large number of risk factors, variables will be entered into the models (eg, a Cox proportional hazards model) one block at a time, starting with demographics, etc. The variable selection/deletion process will be guided by statistical significance (*P* values), penalized likelihood (e.g., lasso), and the Akaike information criterion (AIC). After adding each block, a variable will be deleted if it is not nominally significant, yields a poor AIC value, or has a penalized likelihood estimate of zero. After the last block is entered, the final model will be fitted using the selected covariates.

The propensity score, defined as the conditional probability of exposure to either AmBisome or voriconazole given observed covariates, will be calculated for each patient. Propensity scores will be combined with regression adjustment to improve the estimation efficiency.

3.7.3.3. Sensitivity analyses

In order to assess robustness of OS results on Day 42, the univariate and multivariable regression analyses will be repeated with data up to Day 84.

3.7.3.4. Interim analyses

An interim analysis might be conducted in case of any delays in study initiation / completion, in order to meet timelines for abstract(s) submission to international congresses. More details will be provided at the SAP.

3.7.4. Missing Data

Missing data will not be imputed with the exception of dates used in time-to-event analyses (further details will be provided at the SAP). The number and proportion of patients with missing data will be reported for categorical and continuous variables, respectively. Patients with missing data will not be included in the denominator for ratio calculations including continuous variables. Only available data will be summarized.

3.7.5. Quality Control

To ensure the quality and integrity of the study results, the EDC system will include automatic data validation checks. Gilead and/or a contracted third-party vendor will perform data quality review in accordance with the study data quality and monitoring documents. In addition, monitors will engage sites about data quality and completeness via telephone calls and may perform onsite visits, as documented in the study monitoring plan. The investigator agrees to respond to the resulting queries in a timely manner to enable the collation of data.

3.8. Limitations of the Research Methods

This study reflects real-world clinical care. Therefore, several physicians at once might have been involved in treatment of a single patient over time. Furthermore, this observational study has characteristic disadvantages of retrospective studies, for example, selection bias, recall bias, and information bias.

A selection bias introduced by the choice of sites that contribute patient data cannot totally be avoided. Therefore, the results of this study may not be generalizable. Selection bias might also be associated with physicians and the way that patient records are selected. Therefore, every effort will be made to train physicians on how to capture patients across all years and all statuses (alive or dead). Finally, selection bias can be associated to the administration of AmBisome in sicker patients. Such a bias is controlled (to an extent) by adjusting the treatment effect for propensity scores.

Information bias can be prevented by using standard measurement instruments such as eCRF and appropriate training of personnel entering the data. Appropriate training of personnel entering data is also important to avoid missing values when checking the patients' medical records.

Adverse event reporting of established products might be underreported in real--world data (RWD) and depending on the size of the study.

The association between demographics and events (like death and/or AESIs) depends on the number of cases captured in the study. Since not all information is captured in RWE studies, some important predictors might be missed from the planned analyses.

Even with these limitations, it is important to note that this multi-country study will provide RWD as well as a description of clinical and treatment characteristics in these significantly immunocompromised patients.

Since the index period is overlapping with the conduct of voriconazole clinical studies, it might be the case that the more challenging cases are treated in real life and included in the current study, introducing a bias towards AmBisome cohort.

3.9. Other Aspects

This study will be conducted according to the Good Pharmacoepidemiology Practice (GPP) and in line with the relevant Modules of the Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP).

4. PROTECTION OF HUMAN SUBJECTS

4.1. Independent Ethics Committee (IEC) Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, informed consent form (ICF) if applicable (see Section 4.3), and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to an independent ethics committee (IEC). The investigator will not begin any study patient activities until approval from the IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IEC for any modifications made to the protocol or any accompanying material to be provided to the patient after initial IEC approval, except for those necessary to reduce immediate risk to patients.

4.2. Confidentiality

The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only a unique identifier (as allowed by local law) and a unique study identification code should be recorded on any study-related document.

The investigator agrees that all information received from Gilead, including but not limited to this protocol, CRFs, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

4.3. Informed Consent

No informed consent will be obtained unless specifically required by an appropriate ethics committee or required by country National Data Protection Laws for a participating site. All data used in this study will be pseudonymized and collected in an eCRF with a unique patient identifier for each patient by each participating site.

In case the IEC requires a written consent, the investigator is responsible for obtaining written informed consent from each patient participating in this study after adequate explanation of the aims, methods, objectives, prior to study participation and before performing any study-related activities.

The investigator must utilize the most current IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person

conducting the consent discussion, and by an impartial witness if required by IEC or local requirements.

5. RESPONSIBILITY AND STUDY CONDUCT

5.1. Protocol Modifications

The investigator must submit all protocol modifications to the IEC in accordance with local requirements and receive documented IEC approval before modifications can be implemented.

5.2. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRFs, IEC approvals (if applicable), health authority approval (if applicable), ICF (if applicable), staff curriculum vitae, and other appropriate documents and correspondence.

All non-interventional study documents will be retained per records retention schedule and local regulations. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

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5.3. Access to Information for Audit and Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the study. If the investigator is notified of an inspection by a regulatory authority, the investigator must notify Gilead immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

5.4. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

6. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

Based on current guidelines from the International Society for Pharmacoepidemiology and the EMA Guideline on Good Pharmacovigilance Practices (GVP) Module VIII, non-interventional studies such as the one described in this protocol conducted using patient medical record data are observational in nature, and individual patient data are pseudonymized. This non-interventional observational study is derived from secondary data i.e., previously collected for other purposes, therefore expedited collection and submission of suspected adverse reactions in the form of Individual Case Safety Reports is not required. Safety data of relevance to the purpose of the study will be provided in aggregated form with the final study report.

6.1. Definitions

6.1.1. Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Any medical condition or clinically significant laboratory abnormality with an onset date before treatment initiation. These are preexisting and should be documented on the medical history CRF (if applicable).

Pre-existing events or conditions that increase in severity or change in nature after treatment initiation will be considered AEs.

6.1.2. Adverse Events of Special Interest

An **adverse event of special interest** (serious or nonserious) is an AE for which it has been deemed important to obtain complete information.

6.2. Investigator Instructions for Collecting Safety Information

6.2.1. Safety Information to be Collected

Safety information will be collected:

- From the first dose of AmBisome or voriconazole
- Until the end of primary therapy with AmBisome or voriconazole

Safety information to be collected includes a description of the AE, start and stop dates, causality, and other relevant medical information, such as concomitant medication that is known to be nephrotoxic or hepatotoxic.

Safety events listed below will be collected in the eCRF but will not be reported to Gilead in an expedited fashion:

- Any AE that led to AmBisome or voriconazole dose modification or discontinuation
- AEs associated with an event of special interest (AESIs)
  - — Nephrotoxicity, if this led to new renal replacement therapy, death, or persistent renal dysfunction
  - — Hepatotoxicity, if this led to hepatic failure, jaundice cholestatic, cholecystitis, or death

6.3. Assessment of Causality for Study Drugs

The investigator or qualified subinvestigator is responsible for assessing the causal relationship to drug therapy for each event using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the drug.
- **Yes:** There is a reasonable possibility that the event may have been caused by the medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of collecting safety information.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

7.1. Study Report and Publications

The results of this study will be submitted for publication. Authorship of study manuscripts and presentations at scientific conferences will follow the guidelines established by the International Committee of Medical Journal Editors (https://www.icmje.org/).

Gilead will ensure that the final study report is submitted within 12 months from study completion unless otherwise required by local regulations.

8. REFERENCES

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9. APPENDICES

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
NA	NA	NA	NA

Appendix 2. Gilead Signature Page

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

A MULTI-COUNTRY, NON-INTERVENTIONAL, RETROSPECTIVE DRUG UTILIZATION STUDY IN HAEMATOLOGICAL MALIGNANCY PATIENTS TREATED FOR PROBABLE OR PROVEN INVASIVE ASPERGILLOSIS

PROTOCOL VERSION 1.0; DATE: 17-MAR-2023

This protocol has been approved by Gilead Sciences, Inc. The following signatures document this approval.

Please refer to the electronic signature page at the end of this document
Gilead Scientific Lead
PPD
PPD
PPD

Please refer to the electronic signature page at the end of this document
Signature

Please refer to the electronic signature page at the end of this document
Date

Appendix 3. Investigator Signature Page

Investigator Statement

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 4. Amendments and Updates

Table 4. Protocol Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
NA	NA	NA	NA	NA

Protocol modifications may only be made by Gilead Sciences, Inc.

Prot GS-EU-131-6385 Original

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Epidemiology eSigned	PPD PPD