NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	*GO-First:* Real-world treatment patterns and effectiveness outcomes associated with gemtuzumab ozogamicin (GO) in first-line Acute Myeloid Leukaemia (AML).
Protocol number	B1761038
Protocol version identifier	2.0
Date	19 October 2023
EU Post Authorisation Study (PAS) register number	EUPAS49268
Active substance	L01XC05
Medicinal product	Gemtuzumab ozogamicin (GO) [Mylotarg®]
Product reference	PF-05208747
Procedure number	Not applicable
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	How is GO being used in real world clinical practice of de novo intermediate/favourable risk AML patients and what are the outcomes? **Co-Primary objectives** • To describe the patient demographics and clinical characteristics of patients treated with GO in intermediate and favourable cytogenetic risk, de novo AML. • To describe GO treatment patterns in the study population, including the number of doses of GO and the timing of GO doses in first line (1L) treatment.

	Secondary objective
	• To describe first-line (1L) treatment effectiveness outcomes for the study population, including:
	  • Time-to-next treatment
	  • Survival (event-free survival [EFS], relapse-free survival [RFS], overall survival [OS])
	
	Exploratory objective:
	To describe minimal residual disease status (MRD) for the study population.

Country(-ies) of study	Austria Belgium Germany
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Marketing Authorization Holder(s)

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEM	Adverse Event Monitoring
AML	Acute Myeloid Leukaemia
BMI	Body Mass Index
CBF	Core Binding Factor
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CR	Complete Remission
CRp	Complete Remission with Incomplete Platelet Recovery
CRi	Complete Remission with Incomplete Haematologic Recovery
CRF	Case Report Form
eCRFs	Electronic Case Report Forms
ECOG	Eastern Cooperative Oncology Group
EDC	ElectronicData Capture
EFS	Event Free Survival
ELN	European Leukemia Net
EMA	European Medicines Agency
EMR	Electronic Medical Record
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
GDPR	General Data Protection Regulation
GO	Gemtuzumab Ozogamicin
GvHD	Graft vs Host Disease
HIPAA	Health Insurance Portability and Accountability Act of 1996
HITECH	Health Information Technology for Economic and Clinical Health Act
HTA	Health Technology Assessment
ICD-10	10th International Classification of Diseases, Tenth Revision, Clinical Modification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISCN	International System for Human Cytogenomic

Abbreviation	Definition
	Nomenclature
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LoT	Line of Therapy
MRD	Minimal Residual Disease
NIS	Non-Interventional Study
OS	Overall Survival
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
QC	Quality Control
RFS	Relapse-Free Survival
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SFTP	Secure File Transfer Protocol
UK	United Kingdom
VOD	Veno-Occlusive Disease
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: *GO-First:* Real-world treatment patterns and effectiveness outcomes associated with gemtuzumab ozogamicin (GO) in first-line AML.

Date: 19 October 2023, version 2.0; B1761038; Alexander Russell-Smith, Pfizer R&D UK Ltd.

Rationale and background: AML is a complex and rare cancer of the bone marrow caused by genetic alterations in stem cells. In 2013, it was estimated that the incidence of AML in Europe was 5.06 patients per 100,000 people. The survival outcomes of AML patients are poor and treatment choice is influenced by various clinical characteristics including: type of AML, white blood cell count, cytogenetic risk groups and molecular mutations. Gemtuzumab ozogamicin (GO) [Mylotarg®] is an antibody-drug conjugate used for the treatment of AML patients with myeloid cells that express the CD33 receptor. The ALFA-0701 multi-centre Phase 3 trial demonstrated an estimated median event-free survival (EFS) of 17.3 and 9.5 months for patients receiving GO and chemotherapy or chemotherapy alone respectively, and 27.5 and 21.8 months for overall survival (OS). The results from this trial ultimately led to the approval of GO in the US and European Union.[1] There is limited knowledge of its real-world use and outcomes of GO in 1L treatment with the recent licensed dosing. This study will investigate the treatment patterns and effectiveness outcomes of 1L GO use on de novo AML patients in real-word healthcare, specifically those in the favourable and intermediate risk groups. This will allow the assessment of whether GO prescription patterns are aligned with licensed dosing/guidelines.

Research question and objectives:

This study aims to answer the following research question:

How is GO being used in real world clinical practice of de novo intermediate/favourable risk AML patients and what are the outcomes?

Co-Primary objectives

- To describe the patient demographics and clinical characteristics of patients treated with GO in intermediate and favourable cytogenetic risk, de novo AML.
- To describe GO treatment patterns in the study population, including the number of doses of GO and the timing of GO doses in 1L treatment.

Secondary objective

- To describe 1L treatment effectiveness outcomes for the study population, including:
  - Time-to-next treatment
  - Survival (event-free survival [EFS], relapse-free survival [RFS], overall survival [OS])

Exploratory objective:

- To describe minimal residual disease status (MRD) for the study population.

Study Design: Retrospective medical chart data and retrospective registry data will be collected from 3 countries to address the study objectives. The chart review will be conducted across various sites in Belgium, Austria and Germany that have been previously identified as having high patient populations prescribed GO as 1L therapy for AML. Electronic case report forms (eCRFs) will be completed by clinicians and site staff at the site for all patients diagnosed with de novo AML between April 2018 and May 2023 (indexing period) that meet the inclusion/exclusion criteria outlined below. As well as chart review data, retrospective registry data from the Austrian Myeloid Registry will be extracted for de novo AML patients indexed in the same period as above. Baseline patient demographics and clinical characteristics will be evaluated at index. Treatment patterns and effectiveness outcomes will be described throughout the follow-up period. Patients will have a minimum follow-up of 3 months defined as patients with 3 months of data following the 1L treatment initiation.

Population: Patients aged 18 years and above with a diagnosis of de novo AML in the indexing period will be identified within the sites/datasets using the inclusion and exclusion criteria specified below. The indexing period should allow us to maximise the number of patients treated with GO at 1L that are eligible for inclusion in this study in all countries/sites where data will be collected, following European Medicines Agency (EMA) approval in April 2018. No formal sampling will be conducted in any country. Sites selected for a chart review methodology will complete data collection for all eligible patients and all data collected on eligible patients captured in secondary datasets will be extracted.

Variables: Baseline patient and clinical characteristics, treatment details and clinical outcomes will be assessed in order to address the research objectives.

Patient characteristics include socio-demographics, and clinical characteristics include comorbidities, cytogenetics, molecular details, performance status and various blood test results.

Treatment patterns will be assessed in the follow-up period and include pharmacological treatment details: regimen details, treatment setting and timings of treatments. The occurrence of stem cell transplants will also be recorded.

Clinical outcomes will be defined using data collected if available. Clinical outcomes to be assessed include treatment response, survival outcomes, time-to event(s), minimal residual disease (MRD) status and post-transplant events.

Data sources: Data will be collected/extracted from a combination of sites and a registry. The sources include: 1 site and 1 registry in Austria (Austrian Myeloid Registry); 3 sites in Belgium; 1 site in Germany.

Study size: This study is purely descriptive and there will be no limit on the sample size in terms of patients meeting the eligibility criteria. Based on initial feasibility assessments, approximately 230 patients are expected to be eligible for inclusion, however this number will vary once sites are finalised.

Data analysis: Frequencies and percentages will be reported for categorical variables, including the percentage of missing/unknown data, while counts, number of missing, means, medians, standard deviations (SDs), standard errors (SEs), first and third quartiles, minimum and maximum values will be reported for continuous numeric variables. Where applicable, all estimates will be described with accompanying 95% confidence intervals (CI). Time to event analyses will be conducted, with Kaplan-Meier (KM) curves and 95% CI estimated for KM curves outputted. Finally, Sankey diagrams will be generated to aid in interpretation of the analysis of treatment patterns.

Data analysis will be aligned with data extracted/collected from all data sets. Where specific variables or outcomes cannot be assessed/described subgroup analyses could be conducted for a subset of patients from certain data sources.

Milestones:

- Feasibility assessment: 31 July 2022
- Start of data collection (planned): 01 November 2023
- End of data collection (planned): 30 April 2024
- Registration in the EU PAS register: EUPAS49268
- Final study report (planned): 06 September 2024

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	27 September 2023	Administrative	Cover Page	Updated protocol date.	Protocol date changed to reflect when the updated protocol was finalized.
	27 September 2023	Administrative	Cover Page, 4 Abstract, and 8 Research Question and Objectives	Updated research question objectives section to include a research question.	Updated based on reviewer feedback.
	27 September 2023	Administrative	3 Responsible Parties	Removed study member Redacted and added member Redacted. Adjusted titles and affiliations for Redacted and Redacted to reflect current roles and for accuracy.	Change in Pfizer role titles and persons in roles.
				Removed study member Redacted and added member Redacted Updated Redacted current role.	Change in persons in Pfizer role.
				Updated spelling mistake in Redacted name.	Updated spelling mistake.
	27 September 2023	Administrative	4. Abstract	Subtitle updated to include the protocol finalization date and protocol version number.	Updated to reflect the template and the updated protocol finalization date.
				Reference added in the Rationale and Background section.	Updated based on reviewer feedback.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				Updated the Research Questions and Objectives section to align with the wording listed on the cover page of the protocol.	Updated based on reviewer feedback and for alignment with research question and objectives described on the protocol cover page.
				Changed text in the Study Design section to reflect registry data is retrospective.	Updated based on reviewer feedback
				Changed text in the Population section to clarify what the meaning of 'large population' of patients refers to.	Updated based on reviewer feedback
				Updated planned study dates with latest estimates. Index date also updated accordingly (Figure 9, 9.2 Setting, and Abstract).	Delays in study caused change to timelines.
	27 September 2023	Administrative	6. Milestones	Updated planned study dates with latest estimates. Index date also updated accordingly (Figure 9 and Abstract).	Delays in study caused change to timelines.
	27 September 2023	Administrative	7. Rationale and Background	Reference added in the Rationale and Background section.	Updated based on reviewer feedback.
	27 September 2023	Administrative	9. Research Methods, 9.4 Data Sources, and 9.5 Study Size	Cross-reference errors amended throughout.	Updated based on reviewer feedback.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
	27 September 2023	Administrative	9.2 Setting	Changed text to reflect the rationale for the study inclusion/exclusion criteria.	Updated based on reviewer feedback and to reflect the protocol template.
	27 September 2023	Administrative	9.3.3.1 Baseline patient characteristics	Changed text to clarify *biological* sex is captured in the CRF.	Updated based on reviewer feedback.
	27 September 2023	Administrative	9.3.3.2 Baseline clinical characteristics	Changed text to clarify *day, month, and year* are captured in the CRF.	Updated based on reviewer feedback.
				Changed text to detail the list of comorbidities captured in the CRF.	Updated based on reviewer feedback.
	27 September 2023	Administrative	9.4 Data Sources	Updated the formatting in one paragraph.	Updated based on reviewer feedback.
	27 September 2023	Administrative	9.6 Data Management	Changed text to reflect patient identification numbers will allow to data to be pseudonymized, rather than pseudo-anonymized.	Requested from UZ Leuven site in Belgium, after reviewing the protocol
				Changed text to amend a spelling mistake.	Spelling mistake updated.
				Changed text to clarify data harmonization will be detailed in the SAP.	Updated based on reviewer feedback.
	27 September 2023	Administrative	9.6.1 Case Report Forms (CRFs)	Changed text to reflect the protocol template.	Updated to reflect the protocol template.
	27 September	Administrative	9.6.2 Record Retention	Changed text to reflect	Updated to reflect the

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
	2023			the protocol template.	protocol template.
	27 September 2023	Administrative	9.7 Data Analysis	Changed text to signpost reviewers to the limitations section where bias is described.	Updated based on reviewer feedback and to reflect the protocol template.
				Changed text to amend the term 'extreme levels'.	Updated based on reviewer feedback.
	27 September 2023	Administrative	9.9 Limitations of the Research Methods	Changed text to amend the term 'significantly' and amended spelling errors in this section.	Updated based on reviewer feedback.
	27 September 2023	Administrative	10.1 Patient Information	Changed text to include both paper and electronic personal data will be stored at the study site.	Updated based on reviewer feedback.
	27 September 2023	Administrative	10.2 Patient Consent and 10.3 Patient Withdrawal	Changed to text to detail the patient consent requirement in Belgium.	Updated to reflect the protocol template.
	27 September 2023	Administrative	11. Management and Reporting of Adverse Events/Adverse Reactions	Change text to update spelling mistakes and add text from the Safety Reporting template.	Updated to amend spelling mistakes and to reflect the safety reporting template.
				Edited wording in paragraph describing the reporting of adverse events related to Pfizer products to clarify that within the protocol that the sites should report via the AE Form in the appendix directly to	Wording was repetitive and clarity was lacking on process for reporting safety.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				Pfizer Safety.	
				Removed text which was template instructions around modifications and deletions.	Template instructions were accidentally left in the protocol

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	31 July 2022
Registration in the EU PAS register	07 October 2022
Start of data collection (planned)	01 November 2024
End of data collection (planned)	30 April 2024
Final study report (planned)	06 September 2024

7. RATIONALE AND BACKGROUND

AML is a complex and rare cancer of the bone marrow caused by genetic alterations in stem cells.[2,3] These genetic alterations result in the accumulation of poorly differentiated myeloid cells which are important for innate immunity.[3,4] In 2013, it was estimated that the incidence of AML in Europe was 5.06 patients per 100,000 people.[5] AML is more common in men and its incidence increases with older age, with the median age of diagnosis being ~70 years old.[3,6] The survival outcomes of AML patients are poor. A population-based study in the UK estimated a 5-year overall survival (OS) of 12.9% for patients with AML. This was representative of both sexes combined, although evidence suggests survival outcomes to be worse in men.[5]

Suspected AML patients undergo genetic investigations to allow the classification of their cytogenetic and molecular characteristics, which helps guide treatment decisions and predict prognosis.[6] The European Leukemia Net (ELN) developed recommendations (2017) which categorizes AML patients into 3 risk groups based on their cytogenetic karyotype and molecular features: favourable, intermediate and adverse.[7] These risk groups predict the risk of disease relapse.

Treatment of AML may vary between patients depending on their clinical characteristics, some of which include: a diagnosis of acute promyelocytic leukaemia (APL), a diagnosis of core binding factor (CBF) AML, white blood cell count, sign of leucostasis, cytogenetic risk groups, molecular mutations, and fitness for intensive therapy. The European Society for Medical Oncology (ESMO) have developed various treatment eligibilities and guidelines for the treatment of patients with AML.[6] Types of drugs and regimens used for treatment of AML include chemotherapy and chemotherapy-free regimens.[8] Initial treatment of patients who are eligible for intensive therapy typically involves induction therapy which is used to attempt to achieve a response to treatment so a patient might be able to enter a state of complete remission (CR). Following response, consolidation therapy is often required with the aim of preventing disease relapse, as residual disease may remain after induction therapy.[6,9] In patients who are eligible to receive intensive therapy, a common chemotherapy regimen used for induction is the '3+7' or '7+3' regimen. This includes 3 days of anthracyclines (daunorubicin) administered intravenously and 7 days of continuous infusion of cytarabine.[8,9] Consolidation therapy often involves chemotherapy or allogeneic haematopoietic stem cell transplantation (allo-HSCT) depending on patient eligibility. For example, age helps determine eligibility as elderly patients often cannot tolerate such consolidation therapy.[9] In recent years, the US Food & Drug Administration (FDA) has approved the use of various regimens for the treatment of AML, including chemotherapy-free regimens, chemotherapy/non-chemotherapy drug combinations and hypomethylating chemotherapy.[8] These novel agents and regimens aim to improve the survival outcomes of AML patients of all risk profiles.

Gemtuzumab ozogamicin (GO) [Mylotarg®] is an antibody-drug conjugate used for the treatment of AML patients with myeloid cells that express the CD33 receptor.[10] The FDA approved GO for the treatment of newly diagnosed CD-33-positive AML in September 2017.[1] for use alone or in combination with chemotherapy, depending on the characteristics of the patient. In April 2018, GO received marketing authorisation from the EMA for the European Union, to be used in combination with daunorubicin and cytarabine chemotherapy.[11,12] The ALFA-0701 multicentre Phase 3 trial results demonstrated the effectiveness of GO, which ultimately led to its approval. Patients aged 50-70 years old with newly-diagnosed de novo AML were treated with GO in combination with daunorubicin and cytarabine chemotherapy. The trial demonstrated an estimated median event-free survival (EFS) of 17.3 and 9.5 months for patients receiving GO and chemotherapy or chemotherapy alone respectively and 27.5 and 21.8 months for overall survival (OS).[1]

Over the years GO has been studied in multiple different combination regimens and different dosing schemes.[12] There is limited knowledge of its real-world use and outcomes as first line treatment with the recent licensed dosing (ie, 3 doses during the induction cycle). Using results from a feasibility study conducted by Adelphi Real World (ARW) and contacts with data source custodians, evidence suggests that 1L treatment with GO has been used to treat AML patients in several countries. Pfizer would like to conduct a study investigating the treatment patterns and effectiveness outcomes of 1L GO use on de novo AML patients in real-word healthcare, specifically those in the favourable and intermediate risk groups. This will allow the assessment of whether GO prescription patterns are aligned with licensed dosing/guidelines and will provide novel insights into whether the observed real-world outcomes associated with these prescription patterns are effective. The study will use a combination of AML specific data sources and a retrospective medical chart review using a Case Report Form (CRF) to conduct a multi-country study with Belgium and Austria. Such data sources were identified during a feasibility assessment and were deemed to likely capture a sufficient sample size of patients (according to the eligibility criteria outlined in Section 9.2).

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

This study aims to answer the following research question:

How is GO being used in real world clinical practice of de novo intermediate/favourable risk AML patients and what are the outcomes?

Co-Primary objectives

- To describe the patient demographics and clinical characteristics of patients treated with GO in intermediate and favourable cytogenetic risk, de novo AML.
- To describe GO treatment patterns in the study population, including:
  - Combination chemotherapy regimen
  - GO use in induction and consolidation
  - Number of doses of GO
  - Timing of GO doses in 1L treatment
  - GO dosage

Secondary objective

- To describe 1L treatment effectiveness outcomes for the study population, including:
  - Time-to-next treatment
  - Survival (EFS, RFS, OS)

Exploratory objective

- To describe MRD (minimal residual disease) status for the study population.

9. RESEARCH METHODS

9.1. Study Design

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the countries where this non-interventional study is being conducted.

The following study has been designed to address the limited knowledge of real-world treatment patterns and effectiveness outcomes of GO treatment in AML, according to recent licensed dosing. As a result of the rarity of disease and limited patient numbers, a multi-country study has been designed, in order to gain sufficient sample size and also to assess the differences of treatment patterns in different countries. Data from the following countries will be sought:

- Austria
- Belgium
- Germany

All countries and data sources specified within the protocol are provisional and subject to final feasibility confirmation. The current selection of data sources is described below and in Section 9.4. They have been selected due to their associated sufficiently sized GO patient population and data availability, which was identified through previous feasibility work.

A combination study design approach of a retrospective cohort study and retrospective chart review will be employed to address the study objectives described in Section 8. The cohort study will be conducted using a disease-specific dataset in Austria. This source was identified during a previous feasibility assessment as a dataset with the required data variables. The chart review will be conducted across various sites in Austria, Belgium, and Germany. Belgium and Germany have a high patient population, but no appropriate dataset was identified, hence the combination approach. The Austrian site and dataset together, in addition to the site-reported data captured in Belgium and Germany will provide a substantial sample size to address the research objectives – see Section 9.2 for a detailed explanation of each data source.

The study aims to assess the treatment patterns of patients treated with GO and capture their demographics and clinical characteristics, as co-primary objectives. The study also aims to describe the clinical outcomes associated with these patients where feasible, looking at MRD as an exploratory finding. See Section 8 and Section 9.3 for a breakdown of the specific endpoints and variables of interest. Details of the study period are shown in Figure 1 and Section 9.2.

9.2. Setting

This study aims to look at de novo AML patients who have received GO as 1L therapy in Austria, Belgium and Germany. Some Austrian and all Belgian and German patients' data will be captured via chart review; the data sources and the method of data collection for the Austrian secondary dataset is outlined in Section 9.4. Potential sites participating in the retrospective chart review were invited to complete a short feasibility questionnaire prior to site selection. The feasibility questionnaire was used to confirm suitability of sites for inclusion, confirming study critical information such as GO patient caseload and data availability. Additionally, logistical information pertaining to site contracting and IRB processes will also be assessed. Following this, eCRFs will be completed by clinicians and site staff at the site for patients meeting the inclusion/exclusion criteria below.

Patients aged 18 years and above with a diagnosis of de novo AML between 01 April 2018 and 31 May 2023 (indexing period) will be identified within the sites/datasets using the inclusion and exclusion criteria specified below. The indexing period should allow for a large proportion of patients treated with GO in these countries/sites to be gathered, following EMA approval in April 2018. No formal sampling will be conducted in any country. Sites selected for a chart review methodology will complete data collection for all eligible patients and all data collected on eligible patients captured in secondary datasets will be extracted.

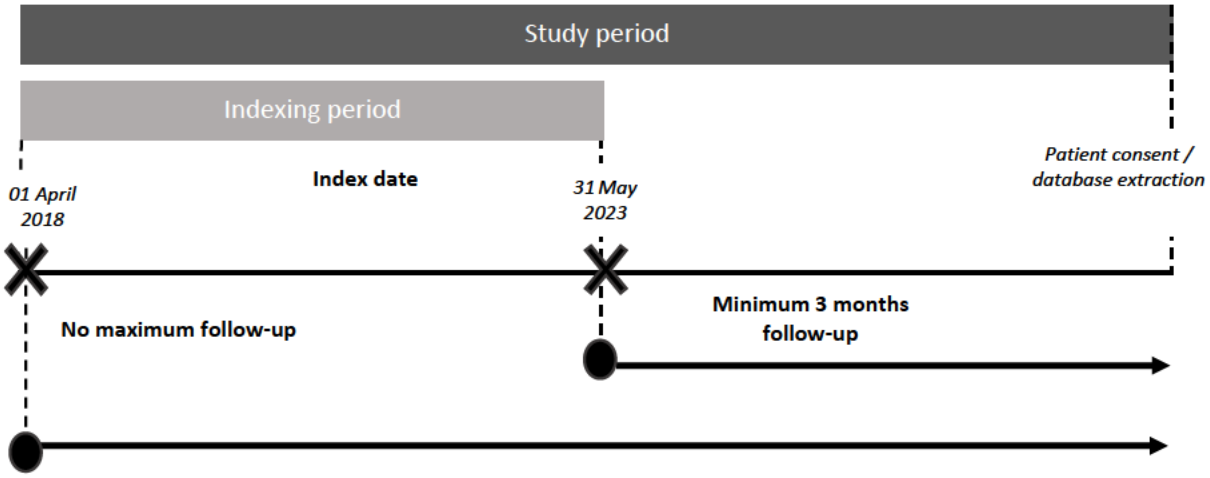
There are minimal inclusion/exclusion criteria (Section 9.2.1 and 9.2.2) in order to maximize the number of GO-treated patients eligible for this study. Inclusion criteria were designed to reflect the population GO is indicated for and to align with the phase III ALFA-0701 clinical trial[1] (inclusion criteria 1 – 4, exclusion criteria 1 - 2). Patients must have data available for a minimum of 3 months after initiation of GO-regimen to capture data relating to effectiveness outcomes (eg, time to next treatment, survival; inclusion criteria 5). If required by country IRB, patients (or a legally acceptable representative) will need to provide a personally signed and dated informed consent form for their data to be extracted from their medical records (inclusion criteria 6).

Each data source is likely to capture a large proportion of GO-treated patients in that country, hence their selection. The Austrian, Belgian and German centres have been selected as they meet the feasibility requirements (capture the relevant data variables) and due to the sample size of GO patients that they contain. The Austrian Myeloid Registry recruits data on patients with myeloid diseases from 15 Austrian centres (excluding the Medical University of Vienna) with an estimated enrollment of 3000 patients. The eligibility criteria below are largely based upon the recommend use of GO; ensuring that the overall patient sample gathered will be clinically representative of the GO treated population.

The initiation date of 1L treatment within the indexing period will be defined as the index date. De novo AML diagnosis will be captured within the screening questions of the eCRF and fully defined for each data source within the Statistical Analysis Plan (SAP). Baseline patient demographics and clinical characteristics will be evaluated at index. Treatment patterns and effectiveness outcomes will be described throughout the follow-up period. Patients will have a minimum follow-up of 3 months defined as patients with 3 months of data, following the 1L treatment initiation. This will allow for assessment of treatment patterns and early effectiveness outcomes. Follow-up will end with the following endpoints: death, loss of data (eg, transfer to a new hospital) or end of the study period. In order to maximise the follow-up data captured necessary to accurately assess survival outcomes (EFS, RFS and OS), follow-up will extend up until either the last data available for the patient (in Austrian, Belgium, and German sites), or the date of database extraction (in the Austrian Myeloid Registry). Patients who have limited follow-up data which is not sufficient for the assessment of OS and accurate EFS and RFS, will be right-censored for the purpose of survival outcome specific analysis. Patients who die within the 3-month follow-up period would be considered eligible for inclusion in order to evaluate EFS, RFS and OS outcomes.

Figure 1. Study Schematic

Study Schematic–eCRF and secondary data dataset design



9.2.1. Inclusion Criteria

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

1. Patient has a clinical diagnosis of **de novo** AML.
2. Patient is aged 18 years or older.
3. Patient has a cytogenetic risk stratification of 'favourable' or 'intermediate (classified according to the International System for Human Cytogeneic Nomenclature criteria.[13]

4. Patient has been treated with GO in a 1L induction setting in a combination chemotherapy treatment.

5. Patient has data points available for a minimum of 3 months data from the first GO- containing regimen (index). Patients who die within the 3 months are eligible for inclusion within the study.

6. *For patients from Austrian, Belgium, and German sites:* Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study. Note – may not be required and depends on individual country/site IRB guidance.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patient has been exposed to any other 'non-GO' treatment regimen prior to treatment with GO for their AML (except leukoreduction with and without hydroxyurea).

2. Patient has been treated with GO only as a consolidation therapy and not as induction.

9.3. Variables

This study will bring together different data sources that will be harmonised to have common variables and allow for analysis of one multi-country combined dataset. The variables below and the CRF were designed using knowledge of datasets known to collect data from medical records. All data variables present in the Austrian registry are not explicitly known but are likely to cover those listed below. The CRF captures all data variables of interest therefore allowing research objectives to be addressed. Final variables will be confirmed upon finalisation of the data sources within the SAP. Data sources have been selected following feasibility assessments, whereby the presence of the variables below will be assessed within the data captured.

9.3.1. Exposures

GO use

Patients have been treated with GO in a 1L chemotherapy regimen for AML. GO must be administered concomitantly with induction chemotherapy, ie, between the start and end date of a patient's 1L therapy regimen they have received GO and another chemotherapy drug between the indexing period outlined in Section 9.2.

9.3.2. Outcomes

9.3.2.1. Treatment Patterns

The treatment landscape for GO will be described for all de novo AML patients treated with the drug as a 1L therapy. The following will be assessed to describe the overall treatment pathway for each patient:

Pharmacological treatment

- **Lines of therapy (LoT)**: The number of LoT received by a patient from and including the index date, to the end of their observation period will be reported as a categorical (1, 2) numeric variable

- **Treatment regimen**: The number and percentage of patients receiving a given treatment regimen will be reported for each LoT, up to 2 LoT – defined as the combination of drugs (including GO)

- **Treatment setting pathway**: The treatment setting by regimen will be reported as a categorical variable using the following groups:

  - Induction, consolidation

  The number of patients receiving GO in induction **AND** consolidation (in succession) will also be reported.

- **Number of doses per regimen**: The number of doses of GO in the first-line treatment regimen, broken out by first-line induction and first-line consolidation. This will be reported as a categorical (1, 2, 3, 4+) numeric variable.

- **Dosing per administration**: Actual total dose (mg) administered for GO will be reported for the first-line treatment regimen, broken out by first-line induction and first-line consolidation. This will be reported as a categorical (1, 2, 3, 4+) numeric variable.

- **Time between dosing**: Time in days between the combined chemotherapy and GO initiation (and vice versa) and time in days between each GO dose will be reported as continuous numerical variables. *Subject to availability – as multiple doses of GO are captured as one regimen; this information may not be explicitly available.*

- **Cytogenetic complete response**: Recorded for each LoT as a categorical variable:

  - Yes, No, Not examined, Undisclosed

Stem cell transplants

- **Stem cell transplants:** The occurrence of a haematopoietic stem cell transplant (HPSCT) [allogeneic or autologous] will be reported as a binary categoric variable – 'Y' or 'N.' The type of transplant will not be reported.

The feasibility of capturing/defining these data points will be assessed upon communication with data custodians and sites. Details of variable definitions will be captured in the SAP.

9.3.2.2. Effectiveness Outcomes

- **Patient response to treatment regimen:** Response to each treatment regimen will be recorded as a categorical variable:

  - CR; CR with incomplete platelet recovery (CRp); CR with incomplete haematologic recovery (CRi); Partial Remission; Stable Disease; Progressive Disease; Uncertain Response; Other (before evaluation); Not evaluated/unknown

  The response to stem cell transplant for relevant patients will be reported separately, again as a categorical variable:

  - CR; CRp; CRi; Partial Remission; Stable Disease; Progressive Disease; Uncertain Response; Not evaluated/unknown

  The event of veno-occlusive disease (VOD) following stem cell transplant for relevant patients will be recorded as a binary 'Y' or 'N' variable, where available.

  The event of graft versus host disease (GvHD) following stem cell transplant for relevant patients will be recorded as a binary 'Y' or 'N' variable, where available.

- **Time to subsequent treatment:** Time in days between start of 1L induction treatment and the initiation of the next line of treatment will be reported as a continuous numerical variable.

- **MRD status:** Minimal residual disease status will be reported for each treatment regimen as a categorical variable:

  - Positive, negative, unknown

- **EFS:** Defined as the date of the start of induction treatment for de novo AML to relapse, death from any cause, or failure to achieve any of the following: CR; CRp; CRi

  - **RFS:** Defined as the date of the start of first line treatment for de novo AML, to relapse, will be reported as a separate outcome specifically.

- **OS:** Defined as the date of the start of first line treatment for de novo AML, to death from any cause.

Detailed methodology for identifying the effectiveness outcomes of interest will be built in collaboration with the Pfizer team and aligned as closely with ELN 2017 guidelines[7] were possible, whilst recognising the limitations associated with identifying complex outcomes using routinely collected real-world data. As such, sensitivity analyses will be applied where necessary, with full details to be documented in the SAP.

9.3.3. Covariates

9.3.3.1. Baseline Patient Characteristics

The following characteristics will be captured at baseline – the data point closest to the index date will be used:

- **Index date**: The month and year of the patient's index date (start of 1L treatment) will be identified and reported:
  - January, February, March, April, May, June, July, August, September, October, November, December
  - *2018, 2019, 2020, 2021, 2022*
- **Age:** Age (in years) as of index date will be reported as a numeric value and categorised as follows:
  - *≥18 years and <30 years, ≥30 years and <40 years, ≥40 years and <50 years, ≥50 years and <60 years, ≥60 years and<70 years, ≥70 years and <80 years, or ≥80 years*
- **Biological Sex:** *Male or female*; patients with sex stated as unknown will be classified as missing data for the purpose of this analysis.
- **Body Mass Index (BMI):** Weight in kilograms divided by height in meters squared, will be utilised as either a continuous variable or a categorical variable using the following categories: Underweight (Below 18.5), Normal (18.5 - 24.9), Overweight (25.0 - 29.9), Obese (30.0 – 34.9) and Morbidly obese (35.0 and greater). Most recent measurement prior to and including index date will be reported. If BMI is provided explicitly, patients will be categorised into these groups if and where appropriate.

9.3.3.2. Baseline Clinical Characteristics

- **Date of diagnosis:** day, month, and year of AML diagnosis will be captured.

- **Comorbidities**: The presence of specific comorbidities prior to the index date (ie, not constrained by the study period) will be reported for all patients based on the presence of diagnosis codes (ICD-10). The list of comorbidities captured are as follows:

    - *Myocardial infarction, congestive heart failure, peripheral vascular disease / peripheral arterial disease, stroke, dementia, chronic obstructive pulmonary disease (COPD), connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia, moderate-to-severe chronic kidney disease, solid tumour, lymphoma, aids, hepatitis B, hepatitis C, other, don't know, or no concomitant conditions*

- **Qual-Charlson Comorbidity Index:** The CCI prior to the index date will be calculated based on the presence of specific diagnosis (ICD-10) codes and scored using published weights for each condition included .[14]

- **ELN 2017 risk group:** The ELN risk group (*Favourable or Intermediate*) will be reported as a continuous categorical variable

- **ISCN karyotype**

- **Classical cytogenetics**: will be reported as a continuous categorical variable:

    - *Normal; Clonal changes; Non-clonal changes; Both Clonal and non-clonal changes; Unknown; No mitoses*

- **Number of metaphases analysed**: reported as a continuous numerical and categorical variable.

- **Number of abnormal metaphases:** reported as a continuous numerical and categorical variable.

- **Number of clonal changes:** reported as a continuous numerical and categorical variable.

- **Number of non-clonal changes**: reported as a continuous numerical and categorical variable.

- **WHO specific recurrent changes**: reported as a categorical variable

  - *Normal; t (8; 21) (q22; q22) AML1-ETO; inv (16) (p13; q22) CBFB- / MYH11; t (15; 17) (q22; q12) PML-RARA; t (1; 19) (q23; p13) E2A-PBX1; t (4; 11) (q21; q23) MLL-AF4; t (12; 21) (p13; q22) TEL-AML1; t (9; 22) (q34; q11) BCR-ABL; part (1) (p32; q32) SIL-TAL1 9; Not performed/unknown*

- **ECOG/WHO performance status**: the performance status at the time closest to index will be reported as a categorical variable:

  - *0 – Fully active, able to carry on all pre-disease performance without restriction;*

  - *1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work;*

  - *2 – Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours;*

  - *3 – Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours;*

  - *4 – Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair;*

- **Level of leucocytes [m/L]**: Captured at the time closest to index will be reported as a continuous numerical variable.

- **Level of thrombocytes [m/L]**: Captured at the time closest to index will be reported as a continuous numerical variable.

- **Level of lactate dehydrogenase (LDH) [U/L]**: Captured at the time closest to index will be reported as a continuous numerical variable.

- **Bone marrow blasts [%]:** Captured at the time closest to index will be reported as a continuous numerical variable.

- **Peripheral blood marrow blasts [%]**: Captured at the time closest to index will be reported as a continuous numerical variable.

Categories for variables will be further defined upon receipt of data within the SAP.

9.4. Data Sources

As indicated in Section 9.1, all countries and data sources specified below are provisional and subject to final feasibility confirmation.

The primary investigators for each country involved in this study are as follows (inclusion of each provisional site is dependent on contractual agreement):

- Austria – Prof. Wolfgang Sperr, Medical University of Vienna
- Austria – Prof. Richard Griel, Chariman of the Austrian Group of Medical Tumor Therapy (AGMT)
- Belgium – Dr Johan Maertens, UZ Leuven; Dr Dominik Selleslag, Az Sint Jan Brugge; Dr Tom Lodewyck, Az Sint Jan Brugge; Dr Ann De Becker, UZ Brussel
- Cologne – Prof. Dr Karl-Anton Kreuzer, University of Cologne

Austrian, Belgian, and German centres

For Austrian, Belgian, and German centres, an eCRF will be used by physicians at study sites to abstract data for patients who meet the eligibility criteria outlined in Section 9.2.1 and Section 9.2.2. Sites will be selected based on the results of a site feasibility assessment.

Each eligible site will be required to complete a short screener for each patient, before abstracting data from electronic medical records (EMR) into the eCRF, to confirm their eligibility for the retrospective chart review. Sites will be instructed to refer to the patient's complete EMR whilst completing the eCRF and not to answer any question from memory or that is not listed within the patients' EMR.

The data to be abstracted will include, but is not limited to, baseline demographics and clinical characteristics, treatment patterns and effectiveness outcomes as detailed in Section 9.3. Once the data are extracted, they will be stored in a secure study database. Further details around the data management can be found in Section 9.6.

Austrian Myeloid Registry

The Austrian Myeloid Registry aims to assess the treatment patterns, clinical outcomes and quality of life of patients with myeloid diseases from 15 Austrian sites.[15] Data will be extracted for patients who meet the eligibility criteria outlined in Section 9.2.1 and 9.2.2, resulting in an estimated 30 patients. The data to be abstracted or extracted will include but is not limited to baseline demographics and clinical characteristics, treatment patterns and effectiveness outcomes. Where required, treatment patterns and effectiveness outcomes will be defined using numerical and statistical methods. Initial feasibility investigations showed the registry extract data in a similar way to an eCRF and extract data from EMRs at multiple sites across Austria.

It is estimated that around 230 patients will be included across Austria, Belgium, and Germany; this comprises of 1 site plus 1 registry in Austria, 3 sites in Belgium and 1 site in Germany. However, the final number will vary from this estimate and that is permissible.

9.5. Study Size

This study is purely descriptive and there will be no limit on the sample size in terms of patients meeting the eligibility criteria in Section 9.2.1 and 9.2.2. Estimated sample sizes are presented below by county in Table 1. Sample sizes will be maximized where feasible and appropriate and will likely vary from the below estimates.

Table 1. Sample Size Estimations per Data Source

	Site name	Number of patients treated with GO
Austria	Medical University of Vienna	50
	Austrian Myeloid Registry	30
Belgium	UZ Leuven	50
	Az Sint Jan Brugge	42
	UZ Brussels	18
Germany	University of Cologne	40

9.6. Data Management

eCRF

Each patient enrolled into the study will have a unique identification number which will allow the study data to be pseudonymised. The linkage between the identification number and the patient will not be shared externally and sites will be required to permanently delete any linkage information following site close-out at the end of the study. In Germany, where subjects must be completely anonymised in order for their data to be processed without informed consent, these patients will not be assigned a unique identification number. Data will be abstracted by site staff from patient medical records and entered into an eCRF hosted on secure, password protected electronic data capture (EDC) software. The software has been certified as being compliant with the FDA's 21eCRF Part 11 regulation. Patient data will be entered into the eCRF identified only by the unique, anonymised identification number (except in Germany).

With the exception of Germany (where it will not be possible to identify patients' data after being entered), any inconsistencies noted in the eCRF data will be queried with the site using data clarification procedures. Automatic checks and prompts are also built into the EDC programme (eg, checks for out-of-range numeric values). Each individual eCRF will be further evaluated for logical consistency between study variables, potential outliers, and missing information. Sites will be queried for clarification via the EDC system if any such issues are identified. A full audit trail will be maintained against original data entries and, if

applicable, subsequent edits. Database lock will be issued when all queries have been resolved. Full details of the data management will be outlined in a data management plan.

Secondary datasets

For secondary data, anonymised data will be provided to the ARW Data and Analytics Team via an accredited Secure File Transfer System (SFTS) email and file encryption service or equivalent. Data will be securely stored on the central servers at ARW headquarters and access restricted to only the immediate project team.

Upon receipt of the data, ARW will assess the data quality and perform any required data cleaning and quality checking to address any erroneous or implausible observations in the data (which will be queried to resolution with the data custodians where appropriate). Quality checks will be logged, thus ensuring replicability and transparency of decisions for inclusion in external communications.

Inclusion and exclusion criteria (as per Section 9.2) will be applied to identify the target patient population and a flow diagram constructed to highlight patient attrition per selection criteria. Variables that require derivation from pre-existing data fields and code lists will be derived and data will be manipulated and transformed to construct a patient-level data frame on which all statistical analysis will be performed. All data manipulation, variable derivations and data analysis will be conducted in Stata v17.0 or the latest available version at time of data receipt (StataCorp, College Station, TX),[16] and logged in coding files within the study folder to ensure replicability. See Section 9.8 for quality control procedures.

All data collected for the study should be recorded accurately, promptly, and legibly. The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

Combined data

Where possible, variables across the eCRF and secondary datasets will be harmonized (as detailed in the SAP), as the initial feasibility investigations showed the registry extract data in a similar way to an eCRF this is believed to be possible for the majority of variables collected. If specific data variables must be requested from the Austrian Myeloid Registry, these will be aligned with the eCRF. Following alignment of common variables and cross-

referencing of eCRF responses, where possible, data from all sources will be combined in a single dataset – the method/process of this will be described in detail in the SAP.

9.6.1. Case Report Forms (CRFs)

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

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorised representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital's or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), original signed informed consent/assent documents (if applicable), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless ARW and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

All analyses will be conducted using Stata 17 software, version 17 or the latest available version (StataCorp, College Station, Texas).

The study is not intended to test hypotheses and is primarily descriptive in nature. Frequencies and percentages will be reported for categorical variables, including the percentage of missing/unknown data, while counts, number of missing, means, medians, SDs, SEs, first and third quartiles, minimum and maximum values will be reported for continuous numeric variables. Where applicable, all estimates will be described with accompanying 95% CIs. Time to event analyses will be conducted, with KM curves and 95% CI estimated for KM curves outputted. Finally, Sankey diagrams will be generated to aid in interpretation of the analysis of treatment patterns.

Where missing values are found in a particular variable, these will be reported either as an unknown categorical group or as the number of patients with a missing data point for continuous variables. In cases where there are large amounts of missing data or where the volume of missing data is differential between important clinical/prognostic groups, imputation may be used and reported in a sensitivity analysis with appropriate methods of imputation decided at analysis phase with the lead study analyst. The threshold of missing data which will require imputation and sensitivity analyses will be determined following initial review of the data.

Data analysis will be aligned with data extracted/collected from all data sets. Where specific variables or outcomes cannot be assessed/described subgroup analyses could be conducted for a subset of patients from certain data sources. Details of potential bias in this dataset are detailed in Section 9.9.

In the event of a data source being unable to provide data for ARW led analysis, variables and outcomes will be assessed using aggregated outputs.

9.8. Quality Control

For chart review:

Data from the eCRF will be stored in the study database. The database will be housed and managed by ARW during the study and analysis. Any data transfers to Pfizer will be carried out via a Secure File Transfer Protocol (SFTP) to ensure any international transfers are safeguarded. ARW's data server is based within the UK. Following completion of the study, the study database will be archived and subsequently permanently deleted, in accordance with ARW's and Pfizer's Master Services Agreement.

Version control will be used during the development of all data collection materials to ensure there is an auditable record of requested updates and changes is available.

For the chart review data collection in Austria and Belgium, each individual eCRF will be reviewed by 2 members of the project team to check for logical and medical consistency. Queries will be raised throughout the data management process and will only be closed following the satisfactory correction or explanation by each site. All queries will be logged within the EDC as part of the audit trail and will also be recorded within the data management plan. Following the review and sign-off of each eCRF by 2 members of the project team, the eCRF will be locked and will not be accessible for further data entry or changes. In Germany, where patient data must be completely anonymised (ie, no linkage document is permitted), all entered data will be reviewed, but data queries will be limited by the inability for sites to reidentify patients. As automated checks will be programmed into the eCRF, the impact on the completeness of the data in Germany is expected to be minimal.

When all checks have been completed to the satisfaction of the project manager, the database will be considered complete and the database will be locked. This formally announces that there is no intention to make any further changes to the data and that data analysis can proceed. A database lock declaration form will be completed by the project manager and the form will be kept in the study file. The locked database will be saved into a folder with restricted access. A copy of the locked database will be made available to the analyst.

Secondary data analysis:

For quality control purposes, documented evidence of correct interpretation of the study protocol will be achieved through development of a detailed SAP, reviewed, and approved by the Pfizer study team, and an extensive decision log maintained and updated by the ARW study team, which can be shared with Pfizer throughout the course of the study. Documented evidence of correct execution of the study protocol will be achieved through completion of ARW's internal quality control (QC) checklist (see ARW QC Checklist) by both the project analyst and an independent QC analyst, which, on completion, can be made available to the Pfizer study team on request. The independent QC analyst will be responsible for a detailed review of the project analyst's programming code and outputs prior to sign-off, ie, no code replication.

On production of study results, ARW will perform QC of the outputs including, but not limited to, logic checks on base sizes, missing values and totals, consistency of output across tables, extreme/unexpected values and results, typographical errors and interpretations (where applicable). Any issues identified during this process will be logged and resolved to completion with the appropriate analyst team. On receipt of any updated output, additional checks will be performed in accordance with the initial data check to ensure all issues have been adequately resolved and no further issues are identified. In the event that the original issues have not been resolved or further issues have been identified, the quality control process will be repeated.

9.9. Limitations of the Research Methods

Study design limitations:

- The overall sample size of patients (~230) may limit comparisons if subgroup numbers are low, such as ELN risk status (intermediate and favourable) and cytogenetic risk subgroups. However, the sample size is not substantially low in relation to the global population of interest. Furthermore, this is purely a descriptive study with no statistical comparisons and so the assessment of treatment patterns and effectiveness outcomes will not be affected by the small sample sizes.

- As this a multi-county multisource study, it is likely that there will differences in data variable availability. To mitigate this, the eCRF used for Austrian, Belgian, and German sites will be designed using knowledge of datasets known to collect data from medical records. When requesting data from the Austrian Myeloid Registry, variables will be requested in this same format where possible. Furthermore, during analysis where specific variables or outcomes cannot be assessed/described in one data source, subgroup analyses could be conducted for a subset of patients from certain data sources.

- GO-based treatment regimens and dosing schedules may differ through the different countries, adding to the complexity of the assessment of effectiveness outcomes. Subgroup analyses could be conducted for subsets of patients receiving the same or similar treatment regimens and or dosage schedules. Furthermore, dosing information per regimen may not be available in the data sources. For example, a total dose of GO may be provided, without numbers and/or timings. Nevertheless, number of doses is likely to be imputable due to prescribing guidelines and consistent quantities of GO supplied in vials (each dose). Timings of doses could be derived algorithmically, details of which would be provided in the SAP.

- The multiple cytogenetic risk groups included in the study cohorts, could similarly add complexity to the assessment of effectiveness outcomes. As a result, the analyses could include a stratification of risk group, subject to sample sizes.

- The minimum follow-up period has been set to 3 months. Consequently, for a large number of patients, OS and EFS maybe not assessable. These patients will be censored for such analyses.

Data source related limitations:

- For the chart review, selection bias may arise. Site participation is influenced by willingness to take part, and may be based on workload, levels of consulting patients during the data collection period, or familiarity with the research nature of the study. It should also be noted that the sites eligible for inclusion in the study are those with whom Pfizer have existing relationships with, and those ultimately selected for inclusion may be those deemed most suitable based on the feasibility assessment stage (ie, those sites with higher numbers of patients or who are most suited to executed non-interventional data collection studies) may be chosen over those considered to be less suitable. These factors introduce a bias whereby patients from non-participating sites are not represented in the results. Nonetheless, this method of site selection is the most practical approach for a non-interventional study such as this, whereby resources and timelines, to an extent, dictate the sites that can be considered eligible for inclusion.

- Further to the previous point, in the event that informed consent is required for patient participation, the patient sample may potentially be biased towards less severe patients who are capable and willing to provide consent to participate. To mitigate both of these selection biases, patient demographic and clinical characteristic data will be captured to allow for comparisons with published datasets to understand the generalizability of results. Additionally, should informed consent be required in Austria and/or Belgium and/or Germany, a legally acceptable representative would be permitted to provide informed consent on behalf of the patient should they be unable to consent, reducing the bias associated with the need to obtain patient consent. Based on initial information, informed consent is unlikely to be necessary to process pseudoanonymised data in Austria and Belgium, and is not required in Germany to process completely anonymised data. In order to avoid this limitation, efforts will be made to ensure a waiver for informed consent is provided by local IRBs.

- Missing data from the eCRF is an important limitation to consider in this study. Some variables that we intend to collect may not be present within a patient's medical record and so cannot be extracted during the eCRF. To address this limitation, the standardised eCRF will undergo a thorough review process prior to implementation which will help ensure that the content is appropriate for the listed research objectives and can reasonably be expected to be captured within patients' medical notes. Further, the eCRF will be designed in such a way that incomplete variables will be flagged and eCRFs will not be able to be locked until all variables have been completed. Where data is not available in Austria and Belgium, the sites will be asked to provide an explanation for the missing data, thus providing the opportunity to capture data not provided during initial data entry. In Germany, it is important to note the additional limitation that data will need to be completely anonymised, meaning a patient linkage file cannot be created and thus, it will not be possible to query patient data that requires identification through a linkage document.

- Secondary data often poses a limitation in regard to data lag. The Austrian Myeloid Registry may not have data for patients available to the present day – the data lag associated with this registry; however, is currently unknown but will be determined through custodian contact.

- Data access to registries is often complex, due to the application requirements, ethical approval processes and policies behind transfer of data; these complexities often cause long timelines receipt of aggregated data. ARW and Pfizer are currently in communication with data custodians to understand the feasibility of accessing the registry and ways of accessing registry data. If registry access is required, ARW will conduct the necessary processes to allow for efficient data access.

- The Austrian Myeloid Registry had reduced data collection in recent years due to the COVID-19 pandemic. Consequently, the current number of patients treated with GO with data available in the registry is relatively low. Nonetheless, data collection should increase in the coming months enabling more GO-treated patient data. The timeline for data collection should align with eCRF-based data collection for the Austrian, Belgian and German sites, as a result, data extraction and analysis should align with the both the registry and site-collected data.

- It is currently unknown whether de novo status will be explicitly indicated within the Austrian registry, this will be confirmed up contact with data custodians. It is likely that patients will enter the registry upon de novo diagnosis however. If de novo status is not explicitly captured, other variables/information will be considered to determine this. Furthermore, GO-based treatment regimens are expected to be used on only de novo patients.

- Information regarding MRD status may be missing across data sources. Current knowledge suggests that is captured in the Austrian Myeloid Registry. This may be seen in Austrian, Belgian, and German sites also. When MRD status is captured, it could be described for the relevant patients within a subgroup analysis.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. Alongside this, ARW will conduct the study in line with General Data Protection Regulation (GDPR), Health Insurance Portability and Accountability Act of 1996 (HIPAA) and Health Information Technology for Economic and Clinical Health Act (HITECH) regulations.

The personal data will be stored at the study site in encrypted electronic and paper form and will be password protected or secured in a locked room to ensure that only authorised study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, at no point will patient names be captured and stored within the study database. Instead, in Austria and Germany, each patient will be assigned a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. Investigators will be required to destroy this linkage document at the point of site close-out. In order to comply with local regulations in Germany, which states that pseudoanonymised data cannot be processed without patients' informed consent, all data captured in Germany will be completely anonymised, with no unique identifier assigned to patients, and no linkage document stored by the site in Germany. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the Adelphi-Pfizer Master Services Agreement and applicable privacy laws.

10.2. Patient Consent

Following IRB review in Belgium, an informed consent document must be signed by the patient (or patient's legal representative) to process pseudonymized data in Belgium. Patients (or a patient's legal representative) will be asked to sign the informed consent document through their/patient's physician. The informed consent document, version 3.0, 07 June 2023, was approved by the UZ Leuven ethics committee.

10.3. Patient Withdrawal

In Belgium, patients (or a patient's legal representative) will be asked to sign the informed consent document through their physician (see Section 10.2). After signing the informed consent document, a patient is not required to do anything further in the study. However, should a patient wish to withdraw from the study, the informed consent document details that a participant is free to stop participation at any time, with no consequence to their medical care.

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

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

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in:

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2016; 25:2-10.

- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making

- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS)

- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

- The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies

- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

- FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Structured Data Analysis:

- This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

Human Review of Unstructured Data:

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE. The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the NIS AEM Report Form included in Annex 3 (Appendix 2), and reported within 24 hours of awareness to Pfizer Safety.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- For exposure during pregnancy in studies of pregnant women, data on the exposure to GO during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed. Additionally, the onset/start dates and stop dates for "Illness," "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format."

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics."*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer. Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

- Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities (YRR) with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Findings generated from the analyses of the study data are intended to be developed into one or more publication(s).

Given the multiple data sources required for this study (as described in prior sections), it is anticipated that there may be a significant time delay between the completion of data collection across different countries. In order to allow for publication of the study results in 2023, there may therefore be a need to generate interim analyses and publications before the global dataset is available for analysis and reporting.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Study title: ***GO-First:*** Treatment patterns and effectiveness outcomes of gemtuzumab ozogamicin (GO) in AML patients.

EU PAS Register® number: EUPAS49268
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

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

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

Comments:

The dates for data collection and the final report are TBD. These dates are dependent on contracting timelines with sites.

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
	2.1.2 The objective(s) of the study?	☒	☐	☐	7
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is a descriptive study whereby no hypotheses are to be tested.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	6
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.2
	4.2.2 Age and sex	☒	☐	☐	8.2
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	8.2
	4.2.5 Duration of follow-up	☒	☐	☐	8.2

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8.2

Comments:

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Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.2 and 8.3.1
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	8.2
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

This is a secondary data including AML patients treated with Gemtuzumab ozogamicin (Mylotarg®), which is defined as the exposure. As this is a retrospective study, patients will have already received the drug and included based on this previous exposure. Patients must have received the drug during the index period and in an induction setting (see **Section 8.2**).

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

This is a purely descriptive study and outcomes assessed in this study will not be provided to HTA.

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☒	☐	
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	8.9
7.3	Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9

Comments:

This is a purely descriptive study with no hypothesis testing, so confounding has not been addressed by design

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.7 and 8.9

Comments:

Potential subgroup analyses are mentioned for where specific variables or outcomes cannot be assessed/described for all patients eg, MRD status.

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
	9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
	9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
	9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3	Is a coding system described for:				
	9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
	9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
	9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4	Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Exposure, outcomes, covariates, and other characteristics are described in **Section 8.3** of the protocol. This section captures the variables which will be captured/defined through the data provided by the sites submitted via the CRF and secondary data sources. The protocol itself does not indicate the exact variables which will be provided by the data sources themselves. These will be described in detail within the study Statistical Analysis Plan (SAP).

The coding system for any exposures, outcomes or covariates is not applicable to the secondary data source or the sites where a chart review will be used for data collection. There is no linkage that will be utilised.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.3, 8.7 and 8.9
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.3 and 8.7

Comments:

A potential stratification of risk group is stated in **Section 8.9**. Its inclusion will be defined in the SAP and is subject to sample size.

Sensitivity analyses are not described in detail but their potential for inclusion is described with rationale.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.8
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6 and 8.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Quality assurance methods are captured under the quality control section of the protocol (Section 8.8)

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	

Comments:

As this study is purely descriptive and does not involve any hypothesis testing, confounding has not been addressed by design.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	

Comments:

The ethical review procedure has not been carried out at this time.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☐	☒	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	

Comments:

The study data is not currently intended to be submitted to regulatory authorities.

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature:

ANNEX 3. ADDITIONAL INFORMATION

Appendix 1. ARW QC Checklist

Appendix 2. Adverse Event Reporting Form for Events not Previously Reported

Document Approval Record

Document Name:	B1761038 Non Interventional Study Protocol Amendment 1_Version 2.0_19 October 2023
Document Title:	B1761038 Non Interventional Study Protocol Amendment 1_Version 2.0_19 October 2023

Signed By:	Date(GMT)	Signing Capacity
Redacted	16-Nov-2023 12:03:39	Manager Approval
Redacted	16-Nov-2023 15:41:46	Final Approval