NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real-World Observational Study of Outcomes for Acute Myeloid Leukemia (AML) Patients Treated With Glasdegib or Venetoclax in US Community Oncology Practices
Protocol number	B1371039
Protocol version identifier	Final
Date	11 May 2020
EU Post Authorization Study (PAS) register number	Not yet registered
Active substance	glasdegib
Medicinal product	DAURISMO ™
Research question and objectives	Primary 1) Document and understand the demographic, clinical, and disease-related characteristics of AML patients who initiated treatment with a glasdegib (GLAS)-based regimen. 2) Assess treatment patterns of AML patients who initiated treatment with GLAS-based regimen (regimen, cycles, dose details, duration of therapy by line of therapy up to 2 lines). 3) Estimate the clinical outcomes of AML patients who initiated treatment with GLAS-based regimen. a. Transfusion independence (TI), disease response, event-free/relapse-free survival (EFS/RFS), and overall survival (OS) for AML patients treated with GLAS-based regimen. Secondary

	4) Document and understand the patient demographic, clinical, and disease-related characteristics of AML patients who initiated treatment with a venetoclax (VEN)-based regimen. 5) Assess treatment patterns of AML patients who initiated treatment with a VEN-based regimen (regimen, cycles, dose details, duration of therapy by line of therapy up to 2 lines). 6) Estimate the clinical outcomes of AML patients who initiated treatment with a VEN-based regimen. a. TI, disease response, EFS/RFS, and OS for AML patients treated with a VEN-based regimen. b. Treatment related toxicities and adverse events (AEs) related to AML patients who initiated treatment with VEN-based regimens (type of Grade 3 or 4 AEs, date of AE, emergency department visits and hospitalizations related to management of AEs).
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AML	acute myeloid leukemia
AZA	azacitidine
CHSS	Cardinal Health Specialty Solutions
CI	confidence interval
CR	complete response
CRF	case report form
CRh	complete response with partial hematologic recovery
CRi	complete response with incomplete hematologic recovery
CYP3A	cytochrome P450 3A
DEC	decitabine
DOR	duration of response
eCRF	electronic case report form
ED	emergency department
EFS	event-free survival
EMR	electronic medical record
FDA	Food and Drug Administration
GCSF	granulocyte colony-stimulating factor receptor

Abbreviation	Definition
GGT	gamma-glutamyltransferase
GLAS	glasdegib
HIPAA	Health Insurance Portability and Accountability Act
HMA	hypomethylating agent
HR	hazard ratio
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
KM	Kaplan-Meier
LDAC	low-dose cytarabine
MDS	myelodysplastic syndrome
MLFS	morphologic leukemia-free state
NIS	non-interventional study
OPEN	Oncology Provider Extended Network
OS	overall survival
PD	progressive disease
PHI	Protected Health Information
PR	partial response
RBC	red blood cell
RFS	relapse-free survival
SAE	serious adverse events
SAP	Statistical Analysis Plan
SD	stable disease

Abbreviation	Definition
SD	standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TD	transfusion dependence/dependent
TI	transfusion independence/independent
US	United States
VEN	venetoclax
WBC	white blood cell

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title

Real-World Observational Study of Outcomes for Acute Myeloid Leukemia (AML) Patients Treated With Glasdegib or Venetoclax in US Community Oncology Practices

Final, 01 May 2020

Main Author: Jonathan Kish, PhD, MPH, Cardinal Health Specialty Solutions

Rationale and background

Glasdegib (GLAS) and venetoclax (VEN) were approved in November 2018 for the treatment of AML in patients who are 75 years old or older or who have comorbidities that preclude intensive induction chemotherapy. Limited real-world observational studies of treatment patterns and outcomes for patients treated with either therapy have been conducted.

Research question and objectives

Primary

1) Document and understand the patient demographic, clinical, and disease-related characteristics of AML patients who initiated treatment with a GLAS-based regimen.
2) Assess treatment patterns of AML patients who initiated treatment with GLAS-based regimen (regimen, cycles, dose details, duration of therapy by line of therapy up to 2 lines).
3) Estimate the clinical outcomes of AML patients who initiated treatment with GLAS-based regimen.
    a. Transfusion independence (TI), disease response, event-free/relapse-free survival (EFS/RFS), and overall survival (OS) for AML patients treated with GLAS-based regimen.

Secondary

4) Document and understand the patient demographic, clinical, and disease-related characteristics of AML patients who initiated treatment with a VEN-based regimen.
5) Assess treatment patterns of AML patients who initiated treatment with a VEN-based regimen (regimen, cycles, dose details, duration of therapy by line of therapy up to 2 lines).
6) Estimate the clinical outcomes of AML patients who initiated treatment with a VEN-based regimen.
    a. TI, disease response, EFS/RFS, and OS for AML patients treated with a VEN-based regimen.
    b. Treatment related toxicities and adverse events (AEs) related to AML patients who initiated treatment with VEN-based regimens (type of Grade 3 or 4 AEs,

date of AE, emergency department [ED] visits, and hospitalizations related to management of AEs).

Study design

Retrospective medical chart review of US patients with AML treated with either a GLAS- or VEN-based regimen between 01 December 2018 and 31 December 2019. Up to 150 GLAS- or VEN-treated patients will be included. The study will be conducted in 5 sequential phases: Phase 1 (study concept feasibility) assesses the number of providers who have prescribed GLAS to an AML patient in Cardinal Health research network and the providers' willingness to participate in the research. Phase 2 tests the electronic data capture tool for clinical/operational functionality. Phase 3 (study conduct feasibility) will collect data on up to 15 patients treated with GLAS among providers who have completed all required AE reporting and data abstraction training and report having treated at least 1 eligible patient with GLAS specifically. Pfizer will evaluate based on the characteristics, treatment patterns, and outcomes of the 15 patients from Phase 3 to determine whether to proceed with further data collection. Phase 4 expands the GLAS cohort to include all patients treated with GLAS (Phase 4a), or a random selection, potentially including those who received GLAS as second-line or greater (pending the results of Phase 3), by those providers who participated in Phase 3. After data collection of all GLAS-treated patients is completed, and at the discretion of Pfizer, data collection for patients treated with VEN will occur (Phase 4b). Additional waves (a maximum of 3) of long-term follow-up (or if appropriate, the recruitment of new patients) successively in 4-month increments may occur after completion of all data collection for patients alive at each interval (Phase 5a-c, as applicable).

Population

1. Patients newly diagnosed with AML.
2. Initiated first-line or later therapy (ie, index therapy) for newly diagnosed AML with GLAS-based regimen (allowable combinations include GLAS plus low-dose cytarabine, GLAS plus azacytidine, or GLAS plus decitabine) or initiated first-line therapy with VEN-based regimen (allowable combinations including VEN plus low-dose cytarabine, VEN plus azacytidine, or VEN plus decitabine) in the following time periods*:
    a. Initiated first-line or later therapy for AML with any GLAS-based regimen between 01 December 2018 and 31 December 2019.†
    b. Initiated first-line therapy for AML with any VEN-based regimen between 01 December 2018 and 31 December 2019.

    ** These patients could have received systemic therapy for myelodysplastic syndrome (MDS, a precursor disease to AML, prior to diagnosis of AML).*

    † Patients who received GLAS as second-line or greater may be selected in Phase 4a pending the results of Phase 3.
3. ≥18 years of age at index therapy initiation.

4. ≥6 months of follow-up from initiation of index therapy unless the patient died, with known date of death.
5. Known cytogenetic risk profile at the time of index therapy initiation as defined below in Section 8.4.
6. ≥1 bone marrow biopsy completed following index therapy initiation.

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

1. Patients who received treatment for AML as part of a clinical trial.
2. Patients with diagnosis of any other malignancy (except for non-melanoma skin cancer) at the time of treatment of AML.
    a. Patients with diagnosis of AML and non-melanoma skin cancer at the time of treatment of AML will not be excluded.
3. A patient with a record of 1 or more of the following confounding diagnoses at any time during data availability: acute lymphoblastic leukemia; acute promyelocytic leukemia, aggressive systemic mastocytosis; hypereosinophilic syndrome and/or chronic eosinophilic leukemia; dermatofibrosarcoma protuberans; or gastrointestinal stromal tumors.

Variables

Patient demographics, clinical characteristics, and treatment patterns will be collected. In addition, patients response to GLAS or VEN therapy, dates of disease progression, toxicities occurring during treatment (VEN cohort only), and date of death/last follow-up will be abstracted.

Data sources

The patient's treating physician will abstract data from the patient's electronic health record into the data capture forms. All study data are secondary. Providers will be trained on data collection to ensure accuracy and reliability. No protected health information, except for dates of diagnosis, treatment, and outcomes, will be collected. The patients electronic medical record will not be shared directly with Cardinal Health or Pfizer.

Study size

The total proposed sample size across the 2 treatment arms is 150 patients.

Data analysis

Each cohort will be described independently; no comparisons of patient characteristics or outcomes between GLAS- and VEN-treated patients will be conducted. The primary clinical outcomes of interest include TI, duration of therapy, disease response, duration of response, EFS, RFS, and OS. Time to event outcomes will be analyzed using the Kaplan-Meier

method. Comparisons of time to event outcomes will be made using a Cox proportional hazards model or other parametric techniques as appropriate. Experience of toxicities will only be described for the VEN-treated cohort. Details of the data analysis will be provided in the statistical analysis plan.

Milestones

- Completion of feasibility assessment: Q2 2020
- Registration in the EU PAS register: Q2 2020
- Start of data collection: Q2 2020
- End of data collection: Q3 2020
- Final study report: Q4 2020

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Project kickoff	27 August 2019
Study protocol development	Q2 2020
Study protocol finalization/approval	Q2 2020
Case report form (CRF) development	Q2 2020
CRF finalization/approval	Q2 2020
Registration in the EU PAS register	Q2 2020
Institutional review board (IRB) preparation/submission/approval	Q2 2020
Statistical Analysis Plan (SAP) & table shells	Q2 2020
SAP & table shells finalization/approval	Q2 2020
Electronic CRF (eCRF) programming & testing	Q2 2020
Phase 2: eCRF pre-test (n=4)	Q2 2020
Phase 3: study conduct feasibility (n=15)	Q2 2020
Phase 3: data analysis	Q3 2020
Phase 4a/b: GLAS/VEN data collection expansion (n=150)	Q3 2020
Phase 4: data analysis	Q4 2020
Final study report (assume after Phase 4)	Q4 2020
Phase 5: long-term follow-up data collection (optional)	Q1 2021
Updated analyses	Q2 2021
Updated study report	Q2 2021

7. RATIONALE AND BACKGROUND

Acute Myeloid Leukemia (AML) is the most common form of fast-growing blood and bone marrow cell cancer. In the United States (US) in 2019, it is estimated there will be 21,450 new cases and 10,920 deaths from AML.[1] The average age at diagnosis is 68 years old, and the 5-year survival rate is 26.9%.[2] About 60%-70% of adults with AML can attain a complete remission following induction therapy with cytotoxic chemotherapies to reduce leukemic cells in the blood and bone marrow. Slightly more than 25% (45% of those who attain complete remission) are expected to survive 3 or more years and may be cured.[2] Remission rates are related to age, with the expected remission rate of more than 65% in those younger than 60 years old. Duration of remission is shorter in older patients, and increased morbidity and mortality during induction treatment are related to older age.[2]

Treatment of AML in elderly patients is particularly challenging due to higher comorbidity loads and the general toxicity of intensive treatments. Historically, the number of treatments available for newly diagnosed patients with AML for whom intensive chemotherapy is not an option has been limited (eg, low-dose cytarabine [LDAC], azacitidine [AZA], decitabine [DEC]). New treatment regimens have become available within the last 2 years including: glasdegib (GLAS) plus LDAC; venetoclax (VEN) plus hypomethylating agents (HMAs), AZA, DEC, or LDAC; and gemtuzumab ozogamicin. More novel regimens are currently in advanced clinical development. Given the potential for a dramatic change in how patients are treated, it is critical to understand the evolution of non-intensive chemotherapy AML treatment over the next several years.

GLAS was approved by the Food and Drug Administration (FDA) in November 2018 for newly diagnosed patients with AML who are 75 years old or older or who have comorbidities that preclude intensive induction chemotherapy.[6] US FDA approval was based on an open label randomized study (BRIGHT AML 1003, NCT01546038) of 115 patients with newly diagnosed AML who met at least 1 of the following criteria: a) age 75 years or older, b) severe cardiac disease, c) baseline Eastern Cooperative Oncology Group performance status of 2, or d) baseline serum creatinine >1.3 mg/dL. Patients were randomized 2:1 to receive GLAS, 100 mg daily, with LDAC 20 mg subcutaneously twice daily on Days 1 to 10 of a 28-day cycle (N=77) or LDAC alone (N=38) in 28-day cycles until disease progression or unacceptable toxicity. Efficacy was assessed based on an improvement in overall survival (OS) (date of randomization to death from any cause). Using a median follow-up of 20 months, median OS was 8.3 months (95% confidence interval [CI]: 4.4, 12.2) for the glasdegib + LDAC arm and 4.3 months (95% CI: 1.9, 5.7) for the LDAC alone arm (hazard ratio [HR] = 0.46; 95% CI: 0.30, 0.71, p=0.0002).[6] (Note, the final study report for NCT01546038 included 16 patients with myelodysplastic syndrome.[7])

VEN, in combination with HMA or LDAC, was also recently approved (FDA November 2018) for patients who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.[8] Approval was based on 2 open-label non-randomized trials (Study M14-387 [NCT02287233] and Study M14-358 [NCT02203773]). Outcomes

were assessed in terms of the percentage of patients who achieved complete response (CR) and/or CR with incomplete hematologic recovery (CRi). In a Phase 1b study, older patients (~ 65 years old) with previously untreated AML (n=57) were enrolled into 3 groups: A (n=23) received VEN and DEC (20 mg/m^2 daily for 5 days of each 28-day cycle); B (n=22) received VEN and AZA (75 mg/m^2 daily for 7 days of each 28-day cycle); C (n=12), a sub-study of VEN and DEC, received an oral cytochrome P4503A (CYP3A) inhibitor to determine its effect on pharmacokinetics. Daily target doses for VEN in different cohorts within groups A and B were 400 mg, 800 mg, and 1200 mg. In groups A and B, the CR/CRi rate was 60% (95% CI: 44.3, 74.3).[9] In a follow-up of this study, patients with de novo and secondary AML had the same CR/CRi rate of 67%.[10] A third study showed combination cytarabine and VEN in patients older than 60 years had CR/CRi rate of 54%.[11]

Limited real-world observational studies of treatment patterns, outcomes, and safety for patients treated with either therapy have been conducted. Given the potential for a dramatic change in how patients are treated, it is critical that the scientific and medical communities continue to work to document the evolution of AML treatment over the coming years. The present study is focused on real-world outcomes in adult patients with AML who in the frontline received non-intensive therapy defined as GLAS-based (including GLAS+LDAC, GLAS+AZA, or GLAS+DEC) or VEN-based therapy (including VEN+LDAC, VEN+AZA, or VEN+DEC) in combination with other agents. Although the present study is focused on the receipt of this therapy during first-line therapy, it is expected that most of the identified patients will also go on to receive subsequent treatment. The aim of this study is to describe treatment patterns and effectiveness outcomes in a sample of oncology patients treated for AML with non-intensive first-line treatments.

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

8. RESEARCH QUESTION AND OBJECTIVES

As GLAS- and VEN-based therapies for AML have only recently been approved in the US, patient profile and clinical outcomes of AML patients receiving GLAS- or VEN-based therapies have limited documentation. This study seeks to analyze real-word patient characteristics and clinical outcomes in patients with AML who receive frontline therapy with GLAS-based regimen or VEN-based regimen. The following objectives are pre-specified for this retrospective cohort study of patients with AML using a chart review methodology.

<u>Primary</u>

1) Document and understand the patient demographic, clinical, and disease-related characteristics of AML patients who initiated treatment with a GLAS-based regimen.

2) Assess treatment patterns of AML patients who initiated treatment with GLAS-based regimen (regimen, cycles, dose details, duration of therapy by line of therapy up to 2 lines).
3) Estimate the clinical outcomes of AML patients who initiated treatment with GLAS-based regimen.
    a. Transfusion independence (TI), disease response, event-free/relapse-free survival (EFS/RFS), and OS for AML patients treated with GLAS-based regimen.

Secondary

4) Document and understand the patient demographic, clinical, and disease-related characteristics of AML patients who initiated treatment with a VEN-based regimen.
5) Assess treatment patterns of AML patients who initiated treatment with a VEN-based regimen (regimen, cycles, dose details, duration of therapy by line of therapy up to 2 lines).
6) Estimate the clinical outcomes of AML patients who initiated treatment with a VEN-based regimen.
    a. TI, disease response, EFS/RFS, and OS for AML patients treated with a VEN-based regimen.
    b. Treatment related toxicities and adverse events (AEs) related to AML patients who initiated treatment with VEN-based regimens (type of Grade 3 or 4 AEs, date of AE, emergency department [ED] visits, and hospitalizations related to management of AEs).

9. RESEARCH METHODS

9.1. Study design

This study will be conducted through a multi-site medical chart review of AML patients treated at oncology clinics in the US. Providers in the Cardinal Health Oncology Provider Extended Network (OPEN) will be recruited to participate in the patient identification and data abstraction. All study data are secondary data and will have been collected retrospectively from existing clinical data originally collected as part of routine care.

Patient eligibility will be confirmed by the treating physician. Providers will abstract the patient level data necessary to achieve the research objectives into an electronic case report form (eCRF). No protected health information, except for dates of diagnosis, treatment, and outcomes, will be collected. The patients electronic medical record (EMR) will not be shared directly with Cardinal Health or Pfizer.

Two different types of AML patient cohorts will be identified as follows:

- GLAS-based: initiated first-line or later therapy (eg, index therapy) with GLAS+AZA, GLAS+DEC, GLAS+LDAC between 01 December 2018 and 31

December 2019 (allowable combinations include GLAS plus low-dose cytarabine, GLAS plus azacytidine, or GLAS plus decitabine)

- VEN-based: initiated first-line (index) therapy with VEN+AZA, VEN+DEC, VEN+LDAC between 01 December 2018 and 31 December 2019 (allowable combinations including VEN plus low-dose cytarabine, VEN plus azacytidine, or VEN plus decitabine)

The study will be conducted in 5 sequential phases. The total proposed sample size across the 2 treatment arms is 150 patients. Figure 1 illustrates the study period.

Phase 1: Study Concept Feasibility

Cardinal Health Specialty Solutions (CHSS) research operations team, the investigator, will conduct outreach to OPEN inquiring as to the number of physicians who have prescribed GLAS per the study selection criteria. Providers will also be queried regarding their acceptance of the rules and conditions associated with participation in the research study.

Phase 2: eCRF Testing

A total of 4 community oncologists will review the eCRF and abstract data for the purposes ensuring the requested clinical datapoints are available, the intent of the data point is clear, and the eCRF functions appropriately. Providers who participate in this testing phase are able to participate in further data collection. To test the eCRF providers will select 1 AZA-treated patient and complete data abstraction while Cardinal Health Specialty Solutions (CHSS) research operations team members watch data entry (via screen sharing), respond to questions from the providers, and ask questions of the providers as necessary. No data from this phase will be used in the final analytical dataset. After completion of eCRF testing, revisions to the eCRF will be made as necessary prior to the launch of study data collection.

Phase 3: Study Conduct Feasibility

CHSS will invite 15 providers who have indicated previously treating a patient with GLAS to participate in Phase 3. In Phase 3, each provider will abstract data for 1 GLAS-treated patient, randomly-selected, per the study selection criteria for a total of 15 patients. Providers will abstract data into the eCRF during a web-based, screen-sharing session with a member of the CHSS research operations team. Demographic, clinical, and disease-related characteristics of these patients, treatment patterns, and clinical outcomes will be described. After evaluating these data, Pfizer may elect to discontinue the study and not collect further data for either GLAS- or VEN-treated patients.

Phase 4a: GLAS Data Collection Expansion

Based on the results of Phase 3, Pfizer may elect to continue data collection. In addition, Pfizer may elect to expand data collection to include patients who received a GLAS-based regimen as second-line or greater should sufficient sample sizes of those patients be discovered during Phase 3 when provider enumerate all patient for whom they have prescribed a GLAS-based regimen. CHSS will allow data abstraction for the maximum number of GLAS-treated patients up to the total *a priori* sample size of 150 patients.

Depending upon the number of GLAS-treated patients and the length of follow-up for these patients, Pfizer may elect to discontinue the study and not collect data for the VEN-treated cohort.

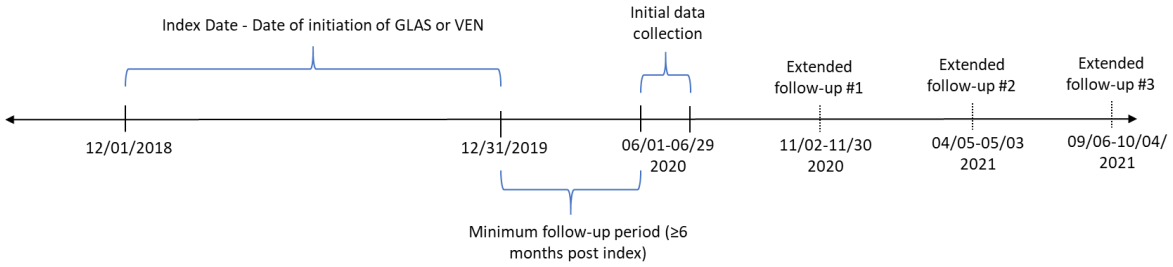
Phase 4b: VEN Data Collection

Should Pfizer elect to proceed with further data collection, CHSS will initiate Phase 4b, which will collect data for VEN-treated patients from those initial providers who participated in Phase 3 data collection. At the end of data collection, summary results for the VEN-treated patients will be provided.

Phase 5: Long-Term Follow-Up

As a retrospective observational study with an index period of 1 year between December 2018 and December 2019, longer follow-up of patients may be required to observed clinical outcomes of interest. As such, at the conclusion of the initial phases of data collection, additional wave(s) of follow-up may occur approximately 4 months later (a maximum of 3 additional updates, Phases 5a-c as applicable). The records of patients who were alive at the time of the initial data collection will be updated. In addition, new patients may be included during the follow-up periods; however, the total sample size is currently set at 150 regardless of when the patient was entered into the study.

Figure 1. Study Period*



* Initial data collection (Phase 3) lasts for 4 weeks. Exact start date of data collection may vary. Subsequent extended follow-ups at Pfizer discretion. Study may be stopped at any time post a data collection point.

9.1.1. Other Aspects of Study Design

All clinicians who participate in this research will be required to complete Pfizer training related to the identification and reporting of AEs/serious adverse events (SAEs) and data abstraction training. AE/SAE training materials will be provided to the participating clinicians prior to any data collection. Once the provider has completed (electronically signed) the AE/SAE training, the providers will participate in a web-based data abstraction training. During this virtual training, CHSS research operations team members will review the AE/SAE training and answer any questions from providers. During this session, the providers will be asked to review their EMR systems to identify all patients treated with a GLAS-based regimen per the study selection criteria and generate a unique numeric identifier

for each patient. The total number of patients will be noted, including patients who received a GLAS-based regimen as second-line or greater, and the identifier maintained by CHSS research operations and the provider. CHSS will then ask the provider to randomly select one of the GLAS-treated patients. To randomly select patients, providers will sequentially number patients and provide those sequential numbers to CHSS Research Operations who will then use a random number generator to select one of the numeric patient identifiers. Providers will launch the data collection platform (web-based) and begin data abstraction for the patient. CHSS research operations will clarify any data points during this data collection process and observe the provider entering data into eCRF. After completing data abstraction, the providers will be sent electronic links to complete data abstraction for all remaining GLAS-treated patients over the course of the next 4 weeks. Providers will be given randomly selected patient numbers from the list of all GLAS-treated patients (excluding the 1 patient already submitted) and asked to complete data abstraction in the order of the randomly selected patients for the remaining patients.

9.2. Setting

Providers from OPEN will identify patients meeting the study selection criteria. OPEN is a community of over 7,000 oncologists, hematologists and urologists providing care to cancer patients geographically distributed across the US and practicing in both community and academic research settings. OPEN community members include medical doctors, nurse practitioners, pharmacists and other individuals providing care to cancer patients. Community members are not limited to any specific group purchasing organization or any other membership requirements. Community members are included in OPEN if they and their practice utilize Cardinal Health's proprietary Point-of-Care claims remittance software for practice management purposes or if they have participated in Cardinal Health sponsored research activities. Providers within the OPEN database are evenly distributed between regions (Northeast, Midwest, South, and West regions) across different size practices (small, medium, or large practice) and years of experience in providing cancer care.

To be eligible for participation in this research study, a board certified hematologist/oncologist must have treated or be treating at least 1 AML patient who meets the eligibility criteria for the study, agree to participate in a study sponsored by Pfizer, agree to complete and adhere to the Pfizer AE/SAE reporting protocols, and agree to conduct the initial data abstraction with CHSS research operations team members monitoring data entry into the eCRF. Providers must also be able to participate in the research monitored by a central Institutional Review Board (IRB). No site-specific IRB approval will be sought and providers requiring this approval will not be eligible.

After IRB approval of the research protocol, the eCRF will be pre-tested with 4 providers. Data collected as part of the pre-test will not be used in the final analytical dataset. After testing and revisions (if necessary), providers who completed a feasibility assessment for the research will be contacted and asked to participate in the research. Data collection will be conducted over the course of 4 weeks for each phase. Providers are compensated at fair

market value for each completed and verified eCRF assuming a rate of payment based on one hour of data collection and for the time required to complete the AE/SAE reporting and data abstraction training.

9.2.1. Inclusion criteria

Patients must meet all the following inclusion criteria to be eligible for inclusion in the study. Providers will be asked to confirm the criteria are met by answering a set of questions in the patient eligibility portion of the eCRF which correspond to these criteria. Automatic date and logic checks are employed to ensure that a patient identified is eligible for the study.
For this study, the following inclusion criteria will be used:

1. Patients newly diagnosed with AML.
2. Initiated first-line or later therapy (i.e., index therapy) for newly diagnosed AML with GLAS-based regimen or initiated first-line therapy with VEN-based regimen in the following time periods*:
    a. Initiated first-line or later therapy for AML with GLAS-based regimen between 01 December 2018 and 31 December 2019.†
    b. Initiated first-line therapy for AML with VEN-based regimen between 01 December 2018 and 31 December 2019.

    * *These patients could have received systemic therapy for myelodysplastic syndrome (MDS, a precursor disease to AML, prior to diagnosis of AML).*

    † *Patients who received GLAS as second-line or greater may be selected in Phase 4a pending the results of Phase 3.*
3. ≥18 years of age at index therapy initiation.
4. ≥6 months of follow-up from initiation of index therapy unless died, with known date of death.
5. Known cytogenetic risk profile at the time of index therapy initiation as defined below in Section 8.4.
6. ≥1 bone marrow biopsy completed following index therapy initiation.

9.2.2. Exclusion criteria

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

1. Patients who received treatment for AML as part of a clinical trial.
2. Patients with diagnosis of any other malignancy (except for non-melanoma skin cancer) at the time of treatment of AML.
    a. Patients with diagnosis of AML and non-melanoma skin cancer at the time of treatment of AML will not be excluded.

3. A patient with a record of 1 or more of the following confounding diagnoses at any time during data availability: acute lymphoblastic leukemia; acute promyelocytic leukemia, aggressive systemic mastocytosis; hypereosinophilic syndrome and/or chronic eosinophilic leukemia; dermatofibrosarcoma protuberans; or gastrointestinal stromal tumors.

9.3. Variables

Providers: Provider characteristics include practice location, practice size, practice setting (e.g., community versus academic), urban versus rural location, years in practice, medical specialty, number of AML patients they personally see in an average month, and number of AML patients seen at their practice in an average month will be collected for each participating provider.

The following table summarizes the key variables to be collected from patient medical records via eCRF by treating physicians. Detailed definitions will be included in the statistical analysis plan (SAP) and case report form (CRF) documents which may include variables not listed below.

Table 9.3.1 Study Variables

Variable	Role	Operational definition
Index therapy	Exposure	First-line therapy with GLAS or VEN for AML
Age at AML diagnosis	Baseline characteristic	Calculated from date of AML diagnosis and year of birth
Age at initiation of index therapy	Baseline characteristic	Calculated from date of initiation of index therapy and year of birth
Sex	Baseline characteristic	M, F
Race	Baseline characteristic	White, Asian, Black or African-American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other, Unknown
Ethnicity	Baseline characteristic	As collected (Hispanic, non-Hispanic)
3-digit zip and state	Baseline characteristic	As collected (for zip codes representing <20,000 people, zip code=000); Mapped to the US region as appropriate (Northeast, South, Midwest, West)
Easter Cooperative Oncology Group performance score	Baseline characteristic	0, 1, 2, 3, 4, unknown
Molecular profile	Baseline characteristic	NPM1, FLT3-ITD, IDH 1/2, K, TP53
Provider assessment of cytogenetic risk status	Baseline characteristic	Favorable, Intermediate, Poor
Cytogenetic abnormalities detected	Baseline characteristic	t(8;21)(q22;q22.1); RUNX1-RUNX1T1; inv(16)(p13.1q22) or t(16;16)(p13.1;q22) t(9;11)(p21.3;q23.3 t(6;9)(p23;q34.1); t(v;11q23.3); t(9;22)(q34.1;q11.2); inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); −5 or del(5q); −7; −17/abn(17p); Complex karyotype, Monosomal karyotype
Antecedent history of MDS	Baseline characteristic	Y/N (Yes: secondary; No: De novo) Date of MDS diagnosis
Prior HMA therapy for MDS	Baseline characteristic/potential confounder	For patients who have antecedent history of MDS: HMA therapy regimen used (AZA, DEC, other please specify [open text])
Serum creatinine	Baseline characteristic	mg/dL
Neutrophils	Baseline characteristic	White blood cells (WBC)/microL
Platelets	Baseline characteristic	micro/L
Bone marrow blasts	Baseline characteristic	<20-30, >30, missing/unknown
Comorbidities including Charlson components	Baseline characteristic	A list with components of Charlson comorbidity index will be presented
Cardiac disease	Baseline characteristic/potential confounder	Cardiac disease associated with conduction abnormalities or structural/functional deficits
Pulmonary disease	Baseline characteristic/potential confounder	Restrictive or obstructive disorders

Variable	Role	Operational definition
Liver disease	Baseline characteristic/potential confounder	Elevated alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or gamma-glutamyltransferase (GGT)
Renal disease	Baseline characteristic/potential confounder	Renal dialysis, renal transplant
Red blood cell (RBC)/platelet transfusion dependency (TD)	Outcome	Date of first transfusion during index therapy (both RBC and/or platelets), date of last transfusion during index therapy (both RBC and/or platelets) No dependency, RBC TD, Platelet TD, RBC and platelet TD
Growth factors use	Outcome	Granulocyte colony-stimulating factor receptor (GCSF) lenograstim, filgrastim, long acting pegylated filgrastim, lipegfilgrastim
TI	Outcome	Defined as no RBC or no platelet transfusion for at least 56 consecutive days after initiation of index therapy) – provider reported
Reason for index treatment selection	Outcome	Efficacy of regimen, safety of regimen, quality of evidence, consistency of evidence, affordability of regimen, insurance approval time, patient choice, other
Number of cycles of index therapy	Outcome	Number/frequency of cycles of GLAS-based, VEN-based
Duration of index therapy	Outcome	Calculated by start and end dates of GLAS-based, VEN-based
Rationale for treatment discontinuation	Outcome	Scheduled duration of therapy completed, progression, toxicity, patient choice
AEs experienced during index therapy with VEN	Clinical outcome	A list of AEs will be created and shown to providers; an option for “other, please specify” will be provided along with free text data entry. This list will include but not limited to tumor lysis syndrome, low WBC condition (e.g., infections, hemorrhage, pneumonia, sepsis, neutropenia, anemia, thrombocytopenia)
Hospitalizations and ED visits related to management of AEs in the VEN-based cohort during index therapy	Clinical outcome	AE related ED visits, AE related hospitalizations date of event
Date of response assessment	Clinical outcome	Date of assessment of initial and/or best response to therapy

Variable	Role	Operational definition
First/best response to index therapy	Outcome	Complete response, morphological leukemia free state (MLFS), partial response, stable disease, progressive disease, unknown/too early to tell. *If provider reports CR, then the following:* Complete remission - platelet counts of >100,000 per microliter and absolute neutrophil count of >1000 per microliter, Cri (incomplete blood count recovery), platelet count of <100,000 per microliter and absolute neutrophil count of < 1,000 per microliter. CRh (partial hematologic recovery), platelet count of >50,000 per microliter and absolute neutrophil count of >500 per microliter.
Time to best response	Outcome, calculated variable	Time to best response will be calculated from the date of initiation of index therapy until the response assessment at which best response was achieved.
Duration of response (DOR)	Outcome, calculated variable	Time from best response determination until relapse or death among patients with CR/CRi/CRh, PR, or MLFS
Lines of therapy post index therapy	Treatment patterns	Numeric value
Agents received in subsequent line of therapy	Treatment patterns	A list of treatment regimens will be created and shown to providers; an option for "other, please specify" will be provided along with free text data entry by each line of therapy up to 3 lines
Relapse occurred post-index therapy (subsequent line of therapy if received)	Treatment patterns	Y/N Date of relapse
Patient status at last follow-up	Outcome	Patient deceased, patient is still receiving last indicated line of therapy, other, don't know data not available
Date of death	Outcome	MM/DD/YYYY
EFS/RFS	Outcome, calculated variable	EFS from initiation of index therapy (where event defined as treatment discontinuation for any reason. RFS from initiation of index therapy where event defined as relapse or death If receiving index therapy censor date is last visit date with provider/at office.
OS	Outcome, calculated variable	OS from initiation of index therapy will be calculated for each of the study cohorts. If alive at data cut-off patient censored on last visit date with provider/at office

*Appropriate definitions will be provided to the physicians in the CRF, and they will be requested to substantiate by the progress notes and laboratory results.

9.4. Data sources

Providers will complete data abstraction into the eCRF using all structured and unstructured data, including laboratory, pathology, and radiology files from the selected patients' EMR.

9.5. Study size

As no *a priori* hypotheses are specified for this study, a sample size calculation is not applicable. Prior to study start in November 2019, a feasibility assessment of the OPEN database was conducted to understand the number of patients with AML managed or treated by providers within OPEN and specifically the number treated with GLAS post-approval. A total of 30 providers indicated they had treated at least 1 AML patient in the past 2 years. Providers reported treating a total of 320 AML patients deemed ineligible for high intensity induction chemotherapy. Providers were asked to indicate the treatment regimens received by those 386 patients. Feasibility assessment indicated 11 providers prescribed GLAS to 39 patients and 21 providers prescribing VEN to 86 patients. The results of this feasibility were used to generate the proposed samples sizes for this study (**Table 9.5.1**).

Table 9.5.1 Standard Error around a Point Estimate.

Point estimate:	Sample size					
	n=30	n=50	n=100	n=200	n=250	n=300
5%/ 95% responding to categorical variable	± 7.8%	± 6.0%	± 4.3%	± 3.0%	± 2.7%	± 2.5%
20%/ 80% responding to categorical variable	± 14.3%	± 11.1%	± 7.8%	± 5.5%	± 5.0%	± 4.5%
30%/ 70% responding to categorical variable	± 16.4%	± 12.7%	± 9.0%	± 6.4%	± 5.7%	± 5.2%
40%/ 60% responding to categorical variable	± 17.5%	± 13.6%	± 9.6%	± 6.8%	± 6.1%	± 5.5%
50%/ 50% responding to categorical variable	± 17.9%	± 13.9%	± 9.8%	± 6.9%	± 6.2%	± 5.7%

9.6. Data management

All study data will be entered into the eCRF. The eCRF is designed to allow providers to efficiently move through the patient chart or EMR based on the journey of the patient through the course of their disease. The eCRF conforms to the rules and regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 governing the abstraction and storage of protected health information (PHI). Limited and necessary to achieve study objectives PHI (e.g., treatment date, date of death) will be collected in the course of the chart review or stored in the eCRF.

Physicians will be compensated through an honoraria payment for each completed and validated eCRF. Participating physicians will be asked to complete the chart review individually, meaning that site research staff or supportive staff will not complete any data abstraction.

Cardinal Health will be responsible for the programming, testing, and hosting of data from submitted eCRFs. Providers will access the eCRF through a secure web-based portal, including during the field-testing procedures, with all data stored on encrypted, password protected, and HIPAA compliant servers housed within the Cardinal Health electronic data storage infrastructure. Cardinal Health will perform extensive testing of the eCRF to ensure functionality across web-based user environments, looping logic to ensure proper alignment of data-related fields (required responses to certain fields prior to entering data into subsequent field), and other programmatic checks to ensure the reduction of the input of erroneous data (such as specifying maximums for year of birth or initiation of index treatment within the dates of the enrollment period). In addition, the eCRF will be field-tested among 4 providers to ensure its functionality, the correct interpretation of the questions in relation to the data points of interest, and the length of time required for completion for a single patient. The pre-test results will be reviewed by Pfizer with Cardinal Health staff; however, Pfizer will not have access to the individual data collected. Any changes made to the eCRF document as a result of the pre-test will require the resubmission of the eCRF and study protocol to the IRB.

9.6.1. CRFs/ Electronic data record

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 authorized 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 form 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 an authorized staff member of the investigator 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.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts. In some cases, the CRF may also serve as the source document. In these cases, a document should be available at Cardinal Health and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

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, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in 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, (e.g., 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 or for longer if 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

9.7.1. Analysis overview

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.

Statistical analyses will be performed using statistical software packages including SAS and Stata. All tests will be two-tailed, and the level of significance will be set at α=0.05. Statistical tests will only be conducted if the sample size is adequate for comparisons. The analytical plan for each study objective is described in this section. Study objectives are listed in italic font for reference.

9.7.2. Analysis of baseline characteristics

Patient demographics and clinical characteristics will be summarized using descriptive statistics for the 2 treatment groups: mean, standard deviation (SD), median, range will be calculated for continuous variables and for categorical data, counts and proportions will be calculated.

Univariate analyses of baseline characteristics will be conducted to compare mean (medians where appropriate) and proportions across treatment groups using t-tests (Wilcoxon where appropriate) and chi-square (Fisher's exact where cell size is fewer than 5).

9.7.3. Analysis of treatment duration, and response

The mean (median, SD) duration of index therapy will be reported for the 2 treatment cohorts. Treatment response to index therapy, measured by CR/CRi/CRh/MLFS, PR, SD, duration of response (DOR), and TI, will be reported for each of the 2 treatment groups. Time to CR/CRi/CRh, PR, SD (as best response), DOR for index therapy, time on SD, time to progression, and TI will be assessed by construction of Kaplan-Meier (KM) curves for each treatment group; median (95% CI) time to CR/CRi/CRh, PR, SD, DOR, and TI will be reported for each treatment group.

Survival analyses including EFS/RFS, and OS will be assessed in 2 ways. The first will estimate median and 95% CIs of EFS/RFS, and OS, and the second will estimate the proportion and 95% CIs who have yet to progress and still alive at key landmarks (e.g., 3 months, 6 months, and 12 months following initiation of index therapy as appropriate given variable follow ups across treatment groups). Both analyses will use KM estimates and KM lifetables. Non-Binary (NB): progression/relapse is not assessed at prespecified timepoints as prescribed by a protocol as it is in the controlled trial setting. As such, interpretation of progression-based endpoints should be considered within this context.

Adjustments for potential confounders will be made in multivariable analyses involving Cox proportional hazard models. Additionally, adjusted EFS/RFS, and OS will be assessed by estimating HRs associated with index therapy, sample size permitting.

9.8. Quality control

During data collection, Cardinal Health clinical research staff review all submitted eCRFs for quality control. The Cardinal Health clinical research team will inspect each submitted eCRF for implausible dates (i.e., date of death prior to last date of treatment), non-standard treatments (e.g., treatment regimens unknown to be used for the cancer under study), lab and radiology results which are inconsistent with known clinical parameters, or other clinical data which is inconsistent with known standards and outcomes. In addition to review of the submitted data by the clinical research team, the study statistician will conduct an analysis of submitted data to identify any data points inconsistent (outliers) with the study population average. This analysis will include a descriptive analysis of the provider characteristics, demographics, baseline clinical and disease characteristics, and characteristics of treatment patterns. Data points flagged as outliers will be delivered to the clinical research team.

Should outliers be discovered, Cardinal Health clinical research will contact the provider submitting the eCRF for data validation. All providers are informed in their contractual agreement that follow-up with clinical staff at Cardinal Health may be required. Participating providers are asked to create a 4-digit unique identifier code per patient which is provided to

Cardinal Health through the eCRF and used for identifying the patient record for validation between Cardinal Health and the provider. Individual eCRFs, which cannot be validated, will be removed from the study dataset. A provider who is unable to validate a data point will only not be compensated for the patient record which was removed. All other data will be considered valid provided additional patients from that provider are not selected for random validation.

As providers will be trained on data collection, no random data validation will be conducted. However, CHSS research analytics will evaluate all reported data points to identify data outliers and providers may be selected to validate their responses for specific patients. Patients for whom the data are deemed questionable by Cardinal Health staff will be excluded; providers will not be compensated for excluded data. No resampling to replace the excluded eCRF will occur. Providers who are non-responsive to any validation request will be removed from the database and all remaining eCRFs from the provider are subject to additional clinical review.

9.9. Strengths and weaknesses of the research methods

Not all patient characteristics will be included in the data collection (e.g., income and other variables that may influence physician-prescribing behavior or treatment decisions) and cannot be accounted for in the descriptive or multivariate analyses. Loss to follow-up during the study period may occur if patients transfer care to other providers and centers. As such, treatments, visits, and outcomes occurring after the date of last visit may be missing. Treatment patterns reflected in the study represent only the practices of physicians who have agreed to participate, and may vary from non-responding physicians, i.e., those who refused study participation or who did not respond to the screening invitation. This study employs purposive sampling that selects physicians and patients based on pre-specified selection criteria and hence this may not be representative of all patients with AML treated with GLAS or VEN or representative of all physicians treating patients with these regimens. Toxicity and AEs may be underreported/under-documented in a routine clinical setting as they may occur outside of the office setting and often go unreported compared to what would be expected from a controlled trial or prospective observational study setting. Grade of toxicity will not be reported due to lack of prospective data collection. Although physicians will be required to record all patient experiences in the medical charts, there may be some undercounting of events that are unknown to physicians which occurred outside the office. Thus, the accuracy and completeness of data collected in this study is limited by the quality of data in the patient's medical chart.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

All study materials, including the research protocol and paper-version of the eCRF, will be reviewed by a central IRB prior to any data abstraction including field-testing of the eCRF. Providers are required to be able to participate in research monitored by a central IRB. At all times, patients' PHI will be kept confidential in accordance with HIPAA. The eCRF will not capture any data related to the patients' name, full date of birth, social security number, health insurance plan number, medical record number, or other such PHI although PHI related to dates of treatment or clinical events will be collected. A waiver for obtaining informed consent from the provider or patient is sought for this research given the minimal risk imposed by the data elements to be collected.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology (ISPE), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki.[13, 14]

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational 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.

The personal data will be stored at the study site in encrypted form and will be password protected to ensure that only authorized 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 when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by 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. 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.

10.2. Patient consent

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

10.3. Patient Withdrawal

Not applicable

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

The study will be submitted to a centralized independent IRB in the US for approval of the methodological approach and for obtaining a waiver of informed consent. An exemption will be sought on the basis that the study will collect only secondary data, limited and only necessary PHI (e.g., treatment dates, date of death) will be collected and all data will be de-identified and aggregated. The dataset including PHI (e.g., treatment dates, date of death) will be provided to the study sponsor for additional post-hoc analyses.

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 issued by the ISPE, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, the STROBE guidelines, and with the ethical principles laid down in the Declaration of Helsinki (Vandenbrouke 2007).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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) AE 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 CRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- 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 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 (e.g., 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:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., 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 STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Not applicable