NON-INTERVENTIONAL POST-AUTHORIZATION STUDY PROTOCOL

Study Title	A retrospective observational cohort study to evaluate the effectiveness of azacitidine monotherapy in treatment-naive patients with intermediate, high, and very high-risk myelodysplastic syndrome
Protocol ID	GS-US-545-5956
Protocol Version/Date:	Final: 14 January 2021
EU PAS Register No	EUPAS38242
Active substance	Azacitidine ATC code: L01BC07
Medicinal Product	Vidaza®, other trade names for generic versions of Vidaza®
Product reference	Vidaza®: NDA 050794
Procedure number	Not Applicable
Joint PASS	No
Research Question and Objectives	To evaluate the effectiveness of azacitidine in the real -world setting in patients with untreated intermediate, high, and very high-risk myelodysplastic syndrome
Country of study	United States
Contact Information:	The contact information will be provided on the Key Study Team Contact List.

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2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AZA	azacitidine
CI	confidence interval
CR	complete remission
eCRF	electronic case report form
DCR	duration of complete remission
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEAS	Effectiveness Evaluable Analysis Set
EHR	electronic health record
FAS	Full Analysis Set
Gilead	Gilead Sciences
GPP	Good Pharmacoepidemiology Practices
HI	hematologic improvement
iKM	iKnowMed
IRB	institutional review board
IPSS-R	Revised International Prognostic Scoring System
IWG	International Working Group
LADMF	Limited Access Death Master File
mCR	marrow complete remission
MDS	myelodysplastic syndrome
OR	objective response
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PR	partial remission
Q1	first quartile
Q3	third quartile
rw-CR	real-world complete remission
RWD	real-world data
rw-DCR	real-world duration of complete remission
rw-DOR	real-world duration of response
rw-OR	real-world objective response
rw-ORR	real-world objective response rate
rw-PR	real-world partial response
SSN	social security number

TTNT	time to next treatment
USON	The United States Oncology Network
US, USA	United States, United States of America

3. PROTOCOL SYNOPSIS

Gilead Sciences
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Study Title:	A retrospective observational cohort study to evaluate the effectiveness of azacitidine monotherapy in treatment-naive patients with intermediate, high, and very high-risk myelodysplastic syndrome (MDS)
Rationale and Background:	Magrolimab, an investigational CD47 targeting monoclonal antibody is being evaluated in combination with azacitidine (AZA) in patients with treatment-naive intermediate, high, and very high-risk MDS by the Revised International Prognostic Scoring System (IPSS-R), also known as higher-risk MDS (study 5F9005). In order to evaluate the contribution of magrolimab to the outcomes seen with the combination treatment, this retrospective study will be conducted to investigate the effectiveness of AZA monotherapy in the real-world setting. This retrospective cohort study will include patients who have initiated treatment with AZA in the past as identified from The United States Oncology Network (USON) database. This study will utilize USON's iKnowMed (iKM) electronic health record (EHR) and supplemental vitality status from the Limited Access Death Master File (LADMF). All necessary data will be abstracted by structured data query supplemented by chart review of unstructured data elements.
Research Question and Objectives:	The primary objective of this study is as follows: • To evaluate the effectiveness of AZA monotherapy, as assessed by complete remission (CR) rates defined by the International Working Group (IWG) 2006 MDS criteria in patients with intermediate-, high-, and very high-risk MDS The secondary objectives of this study are as follows: • To evaluate additional measures of effectiveness including the real-world CR (rw-CR) rate, objective response rate (ORR) defined by IWG 2006 MDS criteria, real-world objective response rate (rw-ORR), duration of complete remission (DCR) and its real-world equivalent, and the duration of response (DOR) and its real-world equivalent of AZA in this study population • To evaluate progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) of AZA in this study population

The exploratory objectives of this study are to evaluate the following in this study population:

[redacted]

Study Design:

This retrospective cohort study will include patients with intermediate-, high-, and very high-risk MDS who have been treated with AZA in routine clinical practice in the US who will be identified from the USON EHR database. This study will utilize USON's iKM EHR and supplemental vitality status from the LADMF. Data will be abstracted by structured data query and by chart review of unstructured data into an electronic case report form (eCRF).

All intermediate, high, and very high-risk patients with MDS who were initiated on AZA monotherapy will be eligible to be included in the study. The study will be conducted in 2 stages. In Stage 1, all patients meeting the inclusion/exclusion criteria based on structured data from the iKM EHR database and initiated AZA as first-line treatment between 01 January 2014 through 01 January 2020 will be identified. About twenty patients will be randomly selected among the patients for a pilot chart review. The purpose of the pilot is to assess data quality (fit-for-purpose assessment) including the quantification of missing data; no data analyses will be performed. In Stage 2, chart review will be conducted in all patients who initiated AZA from 01 January 2014 to 01 January 2020. To allow for a minimum of 1 year of follow-up after the initiation of AZA, the last patient initiation should be on or before 01 January 2020.

Patient demographics and baseline characteristics, including IPSS-R risk category, clinical characteristics, all supportive treatment before initiating AZA, concomitant medications, progression data, next line of therapy for the treatment of MDS, and survival status, will be collected from the date of initiation of AZA until 01 January 2021 or death, whichever is the earlier.

Data extracted from the EHR through an eCRF will be collected into an electronic data capture (EDC) system. Data from structured query will be compiled together with EDC data for analysis.

Population:

Adult (≥18 years) patients in the US with documented histological diagnosis of MDS as per medical record documentation in the EHR and who are classified as intermediate, high, or very high risk according to IPSS-R treated with AZA monotherapy as first-line treatment in standard clinical practice in line with AZA prescribing information.

Variables:	This is an observational retrospective cohort study. Only data available from routine medical practice will be collected within the study. Variables include patient demographics, clinical and disease characteristics, AZA treatment-related variables, laboratory assessments, and treatment response assessments.
Data Sources:	The primary data source will be the EHR. Eligible patients will be identified from the iKM EHR database. Supplemental vitality status will be obtained from the LADMF.
Study Size:	A sample size of approximately 400 patients will provide adequate precision to estimate CR rates. The width of a 2-sided 95% exact confidence interval (CI) of CR rate is ≤ 10% for an observed CR rate in the range of 5% to 25% if sample size is > 300.
Data Analysis:	Continuous variables will be summarized by mean, standard deviation, median, 25% quantile, 75% quantile, minimum and maximum. Categorical variables will be summarized by number and percentage of patients in each categorical definition including 95% CIs. Time-to-event endpoints will be described using the Kaplan-Meier method. The Full Analysis Set (FAS) includes all enrolled patients who took at least 1 dose of AZA. The Effectiveness Evaluable Analysis Set (EEAS) includes all FAS patients who had at least 1 response assessment or died after the index date. The effectiveness analyses (except DCR, real-world duration of complete remission [rw-DCR], DOR, and real-world duration of response [rw-DOR]) will be performed on the FAS. DCR and rw-DCR will be evaluated using FAS patients who achieve a CR and rw-CR, respectively. DOR and rw-DOR will be evaluated using FAS patients who achieve an objective response (OR) and real-world objective response (rw-OR), respectively. Sensitivity analyses will be performed for the primary and secondary endpoints (except DCR, rw-DCR, DOR, and rw-DOR) using EEAS. Details of analytical comparison with magrolimab and AZA combination therapy trial (5F9005) data will be included in the statistical analysis plan.
Milestones:	Start of data collection: first quartile (Q1) 2021 Interim and Progress report: Not Applicable End of Data collection: first quartile (Q1) 2021 Final Study report: third quartile (Q3) 2021

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPP) including archiving of essential documents.

4. AMENDMENTS AND UPDATES

Table 4-1. Protocol Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
None	NA	NA	NA	NA

NA not applicable

Protocol Modifications

Protocol modifications may only be made by Gilead.

5. MILESTONES

Table 5-1. Protocol Milestones

Milestone	Planned Date
Start of data collection	Q1 2021
End of data collection	Q1 2021
Final report of study results	Q3 2021

Q1 first quartile; Q3 third quartile

6. RATIONALE AND BACKGROUND

6.1. Rationale for the Current Study

Myelodysplastic syndrome (MDS) is a pre-malignant condition characterized by peripheral cytopenias due to production of dysfunctional, dysplastic bone marrow (BM) cells. Low- and very low-risk patients, as defined by the Revised International Prognostic Scoring System (IPSS-R) {Greenberg 2012}, are often treated with erythroid and myeloid growth factor support and carry a low risk of leukemic progression.

In contrast to lower risk MDS, intermediate-, high-, and very high-risk MDS, collectively known as 'higher risk' MDS, carries a high risk of leukemic progression. Azacitidine (AZA) is the standard of care for these patients in the frontline setting. However, complete remission (CR) rates are low with AZA therapy, and overall survival (OS) is only approximately 13 months {Silverman 2002}. Thus, novel therapies that replace or augment the effectiveness of AZA are needed to extend survival for patients with MDS.

Magrolimab has been investigated in a Phase 1b single-arm study (Study 5F9005) in multiple subtypes of acute myeloid leukemia, very low-/low-risk MDS, and intermediate-/high-/very high-risk MDS, both as monotherapy and in combination with AZA. Specifically, magrolimab is being evaluated in combination with AZA in frontline MDS in patients with intermediate-, high-, and very high-risk MDS by IPSS-R in a potentially registrational cohort. In order to evaluate the contribution of magrolimab to the outcomes seen with the combination treatment for this specific population, this retrospective study will be conducted to investigate the effectiveness of AZA monotherapy in the real-world setting. A separate analysis plan will be developed for comparison with trial data.

This protocol describes the objectives and methodology used to obtain and analyze real-world data (RWD), including patient level data, derived from electronic health records (EHR).

7. RESEARCH QUESTIONS AND OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the effectiveness of AZA monotherapy as assessed by CR rate defined by the International Working Group (IWG) 2006 MDS criteria in patients with intermediate-, high-, and very high-risk MDS

The secondary objectives of this study are as follows:

- To evaluate additional measures of effectiveness including the real-world CR (rw-CR) rate, objective response rate (ORR) defined by IWG 2006 MDS criteria, real-world objective response rate (rw-ORR), duration of complete remission (DCR) and its real-world - equivalent, and the duration of response (DOR) and its real-world equivalent of AZA in this study population

- To evaluate progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) of AZA in this study population

The exploratory objectives of this study are to evaluate the following in this study population:

[redacted]

8. RESEARCH METHODS

8.1. Study Design

This is an observational cohort study utilizing a retrospective chart review of patients with higher-risk MDS treated in a real-world setting with AZA according to routine clinical practice in the United States.

Study data will be analyzed from EHR at the US Oncology Network (USON) and supplemental vitality status from the Limited Access Death Master File (LADMF). Structured data will be collected via programmatic queries of iKnowMed (iKM). To supplement these structured data elements, a targeted chart review will be performed to capture unstructured data on all patients.

8.1.1. Primary Endpoint

Complete Remission Rate is defined as the proportion of patients who achieve a CR as documented within their EHRs, with confirmation of corresponding BM and peripheral blood parameters as defined per IWG 2006 MDS response criteria {Cheson 2006}, during the treatment period with AZA or prior to the initiation of next MDS treatment.

Definitions of responses categories are shown in Table 8-1 below.

Table 8-1. Definition of Responses Categories

Category	Definition
Complete Remission (CR)	• Documented "complete remission" or "complete response" or "No evidence of disease" in the EHR *and* • All peripheral blood[a] (within a 2-week period before or after the date of BM biopsy) and BM indices meeting the threshold for CR as defined in the IWG 2006 MDS response criteria *and* • All peripheral blood results[a] and the corresponding BM biopsy completed within a 4-week period before or after the CR documentation date • Cases that have the required peripheral blood and BM indices meeting the threshold for CR as defined in the IWG 2006 MDS response criteria but lack EHR documentation of CR will be adjudicated by an independent assessor
Real-world CR (rw-CR)	• EHR documentation of CR (as above) with or without all corresponding IWG 2006 indices; partial availability of indices will also fall into this category
Partial Remission (PR)	• Documented "partial remission" or "partial response" or "improved disease" or "responding disease" or similar terms[b] in the EHR *and* • All peripheral blood[a] (within a 2-week period before or after the date of BM biopsy) and BM indices meeting the threshold for PR as defined in the IWG 2006 MDS response criteria *and* • All peripheral blood results[a] and the corresponding BM biopsy completed within a 4-week period before or after the PR documentation date • Cases that have the required peripheral blood and BM indices meeting the threshold for PR as defined in the IWG 2006 MDS response criteria but lack EHR documentation of PR will be adjudicated by an independent assessor

Category	Definition
Real-world PR (rw-PR)	• EHR documentation of PR (as above) with or without all corresponding IWG 2006 indices; partial availability of indices will also fall into this category
Marrow CR (mCR)	• Based on BM blast count, without requirement of EHR documentation • BM: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment count
Hematologic Improvement (HI)	• HI indices as defined in the IWG 2006 criteria, without requirement of EHR documentation
Relapse After CR or PR	At least 1 of the following: • Return to pretreatment BM blast percentage • Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hb concentration by ≥ 1.5 g/dL • Transfusion dependence
Stable disease (SD) or Real-World Stable Disease (rw-SD) or Indeterminate Response	• EHR documentation of disease as "stable" *and* • IWG 2006 indices not meeting the threshold for PD (see below) for a minimum of 8 weeks
Progressive Disease (PD)	• EHR documentation of "progressed disease" or "worsening of disease" or similar terms or For patients with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5%-10% blasts: ≥ 50% increase in blasts to > 10% blasts • 10%-20% blasts: ≥ 50% increase in blasts to > 20% blasts • 20%-30% blasts: ≥ 50% increase in blasts to > 30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hb by ≥ 2 g/dL • Transfusion dependence

BM bone marrow; CR complete remission; EHR electronic health record; Hb hemoglobin; HI hematologic improvement; IWG International Working Group; mCR marrow complete remission; MDS myelodysplastic syndrome; PD progressive disease; PR partial remission; rw CR real world CR; rw PR real world partial remission; rw SD real world stable disease
Cytogenetic responses are not defined for simplicity.
All responses meeting the CR, rw CR, PR, and rw PR will be subject to adjudication by an independent assessor who will be a board certified hematologist.

a If the peripheral blasts are available, they would be used in the response adjudication. If not available, they will be considered as absent (0%). The results of Hb, platelets and absolute neutrophil count for meeting the threshold for IWG 2006 MDS response criteria should have been obtained from the same sample (within the 4 week window of response documentation date).

b In order to align with McKesson's standard reviewer training of response documentation and to reduce confusion, 'improved disease' or 'responding disease' will be documented as "Response Not Otherwise Specified (NOS)" in eCRF. During analysis this can be combined with/re categorized into "partial remission" group.

8.1.2. Secondary Endpoints

Real -World Complete Remission (rw-CR) Rate is defined as the proportion of patients who achieve a CR as documented within their EHRs with or without confirmation of corresponding BM and peripheral blood parameters as defined per IWG 2006 MDS response criteria, during the treatment period with AZA or prior to the initiation of next MDS treatment.

Objective Response Rate (ORR) is defined as the proportion of patients who achieve a CR, or PR as documented within their EHRs with confirmation of corresponding BM and peripheral blood parameters as defined per IWG 2006 MDS response criteria, or achieve an mCR or HI, during the treatment period with AZA or prior to the initiation of next MDS treatment.

Real -World Objective Response Rate (rw-ORR) is defined as the proportion of patients who achieve a CR, or PR, as documented within their EHRs with or without confirmation of corresponding BM and peripheral blood parameters as defined per IWG 2006 MDS response criteria, or achieve an mCR or HI, during the treatment period with AZA or prior to the initiation of next MDS treatment.

Duration of CR (DCR) is defined as the interval from the first EHR documentation of a CR with confirmation of corresponding BM and peripheral blood parameters as defined per IWG 2006 MDS response criteria to the earlier of the first documentation of relapse, disease progression, or death from any cause.

rw-DCR is defined as the interval from the first EHR documentation of a CR with or without confirmation of corresponding BM and peripheral blood parameters as defined per IWG 2006 MDS response criteria to the earlier of the first documentation of relapse, disease progression, or death from any cause.

Duration of Response (DOR) is defined as the interval from when the criteria are first met for OR to the earlier of the first documentation of relapse, disease progression, or death from any cause.

rw-DOR is defined as the interval from when the criteria for rw-OR are first met to the earlier of the first documentation of relapse, disease progression, or death from any cause.

Progression -Free Survival is defined as the interval from the date of initiation of AZA to the earlier date of the first documentation of relapse, disease progression or death from any cause.

Time to the next treatment is defined as the interval from the date of initiation of treatment with AZA to the earlier date of the initiation of next anti-leukemic treatment of MDS (excluding palliative care or palliative radiation) or death from any cause.

Overall Survival is defined as the interval from the date of initiation of AZA to death from any cause.

8.1.3. Exploratory Endpoints

CCI [redacted]

8.1.4. Study approach

Two types of variables will be collected and analyzed in the study as categorized below:

- *Structured*: these are controlled, mapped fields of the EHR that can be extracted through queries of the iKM database
- *Unstructured*: this is information contained in unstructured fields of the EHR (eg, progress notes, scan reports) that is collected through chart review

In addition, supplemental vitality status information from the LADMF will be used.

The data collection during the study will be conducted using a staged approach.

Stage 1: The purpose of this stage is to assess patient attrition and completeness of data elements. The following steps will be included:

- Identify study population from structured data (by applying inclusion/exclusion criteria using structured data).
- Develop a pilot chart review tool focusing on study endpoints (electronic Case Report Form [eCRF]).
- Perform pilot chart review for about 20 patients randomly selected from the study population (first 20 qualified patients among a total of 40 patients selected using SAS® with a random seed).

- Provide a data summary assessing completeness of data elements focusing on variables related to endpoints (ie, response/progression) and important covariates.
- Data analysis will not be performed during Stage 1.

Stage 2: The purpose of this stage is to expand chart review to the full population. Depending on the data completeness assessment of Stage 1, the sponsor may proceed to Stage 2 of the chart review for the full population.

- Finalize the eCRF based on Stage 1 assessment.
- Modify protocol, if required, based on data availability and completeness.
- Perform chart reviews among the full sample that meet additional inclusion/exclusion criteria in charts.
- Perform data analysis for the whole population including those in Stage 1.

8.2. Setting

Patients who fulfill the inclusion criteria will be identified from the iKM EHR database.

Patients who were initiated on AZA prior to 01 January 2020 will be eligible for enrolment into the study allowing a minimum of 1-year follow-up.

- In Stage 1, all patients who meet the inclusion/exclusion criteria based on structured data and who initiated AZA as first line treatment between 01 January 2014 through 01 January 2020 will be identified. About twenty patients will be randomly selected among the patients for a pilot chart review.
- In Stage 2, chart review will be performed in all patients who initiated AZA from 01 January 2014 to 01 January 2020.

The index date is defined as the initiation date of AZA monotherapy in the firstline setting for higher-risk MDS.

Patients' baseline information will be assessed based on data collected, defined as below:

- For peripheral blasts, Hb, platelets, neutrophils: the latest assessment within 30 days on or prior to the index date will be used as baseline value. If no assessment is available within 30 days on or prior to the index date, the earliest assessment within 7 days after the index date will be considered as baseline value.
- For age, weight, Eastern Cooperative Oncology Group (ECOG) score, BM blasts, all other labs (except Hb, platelets, and neutrophils): the latest assessment within 30 days on or prior to the index date will be used as baseline value. If no assessment is available within 30 days on or prior to the index date, the earliest assessment within 30 days after the index date will be considered as baseline value.

- For height, IPSS-R, cytogenetic risk, transfusion dependence: the latest assessment within 30 days prior to the MDS diagnosis date up to the index date will be used as baseline value.
- For MDS classification and secondary MDS: the latest assessment on or prior to the index date will be used as baseline value. If no assessment is available on or prior to the index date, the earliest assessment after the index date will be considered as baseline value.

Patients' prior supportive treatments before initiating AZA for higher-risk MDS will be assessed during patients' prior medical histories, defined as patients' available histories in the iKM EHR. This will vary based on the length of disease and the time within USON clinics. The prior medical history period will end the day prior to the index date.

Unstructured (chart review) patient level data, extracted from EHR through an eCRF, will be collected into an electronic data capture (EDC) system.

Structured patient level data will be directly extracted from the iKM EHR.

8.2.1. Data Collection Principles

Patient data, including effectiveness, next line of therapy for the treatment of MDS, and survival status, will be collected from the date of initiation of AZA until 01 January 2021 or death, whichever is the earlier, as shown in Table 8-2 below.

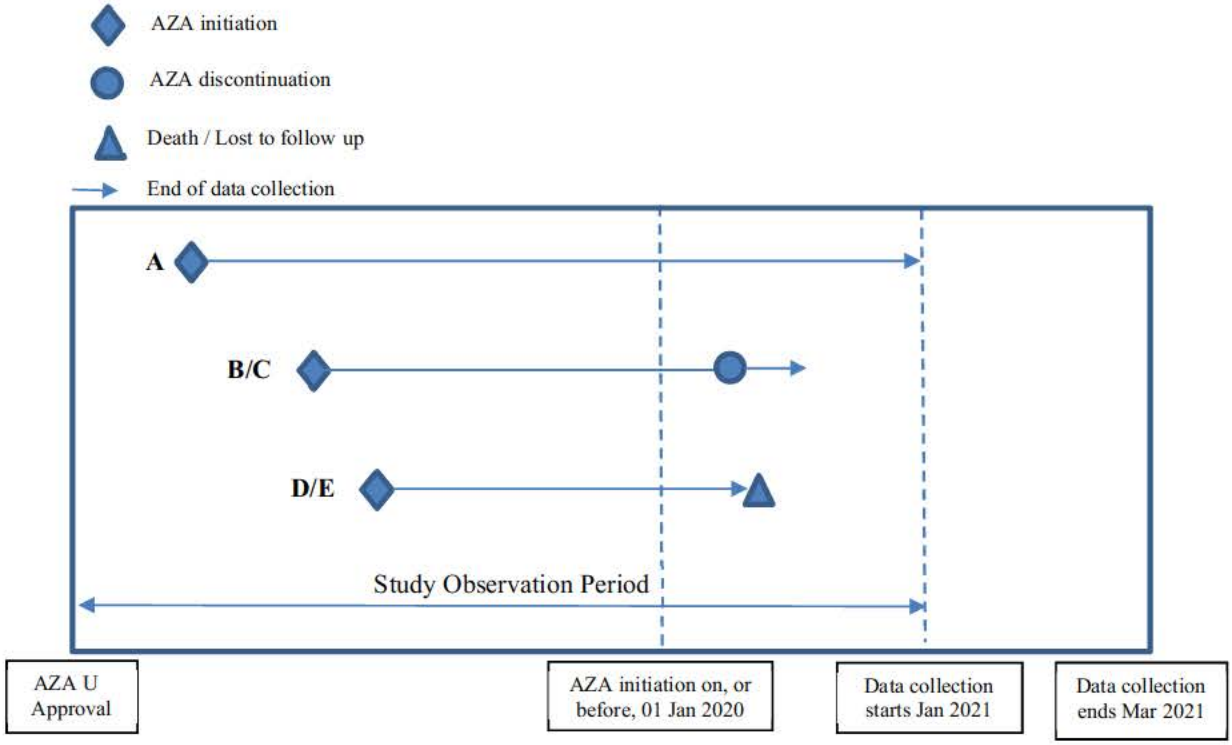
Table 8-2. Definition of Data Collection End Date

Scenarios		Data Collection End Date
A	Patient remains on AZA throughout (beyond 01 January 2021)	01 January 2021
B	Patient has progression on AZA and AZA is discontinued	30 days after discontinuation of AZA (Data relating to survival and next treatment will be collected beyond this date.)
C	Patient discontinues AZA due to toxicity or investigator/patient decision	30 days after discontinuation (Data relating to date of progression, survival, and next treatment will be collected beyond this date.)
D	Patient dies while receiving AZA	Date of death
E	Patient is lost to follow-up	Date of last available data

AZA azacitidine
In all scenarios, data collection starts on the date of AZA initiation.

The different scenarios for patient inclusion are shown in Figure 8-1 below.

Figure 8-1 Scenarios for Patient Inclusion



AZA azacitidine; Q1 first quartile; US United States

8.2.2. Eligibility Criteria

Study population will be identified by first applying inclusion/exclusion criteria in structured data in Stage 1. Then in Stage 2, additional inclusion/exclusion criteria of data only available through charts will be applied to further screen patients. Patients who meet all criteria from both stages will be the final study sample.

For the identification of about 20 patients for pilot chart review, some (but not all) of the additional inclusion/exclusion criteria of data only available through charts will be applied.

Table 8-3. Eligibility Criteria

	Stage 1 Criteria applied during structured data extraction	Stage 1 Criteria to confirm during pilot chart review (Approximately 20 patients)	Stage 2 Criteria to confirm during full chart review (full sample)
Inclusion Criteria Patients must meet all the following inclusion criteria to be eligible:			
1) Male or female ≥18 years of age	X		
2) Documented histological diagnosis of MDS defined as per medical record documentation in the EHR	X	X	X
3) Documented IPSS-R MDS risk category of intermediate, high, or very high risk	X	X	X
4) Initiation of AZA monotherapy during the Study Index Period	X	X	X
5) Received at least a single dose of treatment with AZA in line with US Prescribing information; the following dosing regimens are permitted: a) AZA 75 mg/m^2 Days 1-7 of a monthly cycle b) AZA 75 mg/m^2 Days 1-5, 8-9 of a monthly cycle (5 days on, 2 days off on the weekend, 2 days on) c) AZA 75 mg/m^2 Days 1-5 of a monthly cycle	X	X	X
6) Patients should not have received any anti-leukemic therapies for the treatment of MDS prior to the initiation of AZA. (Prior and concurrent therapy with hydroxyurea, oral etoposide, erythroid and/or myeloid growth factors, or any symptomatic treatment is allowed. Patients with MDS who received prior anti-cancer therapy from prior malignancies are permitted.)	X		X
7) Patients must have at least 1 posttreatment encounter in the EHR.	X		
8) WBC count ≤ 20 × 10^3/μL at the time of AZA initiation (use of hydroxyurea to reduce WBC prior to AZA initiation, as documented within the EHR is acceptable).	X		
9) Adequate hepatic and renal function at the time of AZA initiation (within 30 days of index) as evidenced by the following documentation in the EHR: a) AST and ALT ≤ 5 × upper limit of normal (ULN) b) Bilirubin ≤ 1.5 × ULN, or 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent c) Serum creatinine ≤ 1.5 × ULN or calculated glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m^2	X		

	Stage 1 Criteria applied during structured data extraction	Stage 1 Criteria to confirm during pilot chart review (Approximately 20 patients)	Stage 2 Criteria to confirm during full chart review (full sample)
Exclusion Criteria			
1) Any prior anti-leukemic therapy including chemotherapy (excluding hydroxyurea or oral etoposide), targeted therapies, immunotherapy or radiotherapy	X	X	X
2) Prior treatment with hypomethylating agents and/or low dose cytarabine. Prior treatment with lenalidomide or similar agents is permitted if treatment is utilized for symptomatic support (ie, anemia, RBC transfusion dependence).	X	X	X
3) Patients participated in an interventional clinical trial during study observation period.	X	X	X
4) Previous hematopoietic stem cell transplant within 6 months prior to initiation of AZA, active GVHD, or requiring transplant-related immunosuppression.	X	X	X
5) Patients who have had transformation of MDS into AML prior to initiation of AZA	X	X	X
6) Known inherited or acquired bleeding disorders			X
7) EHR documentation of clinical suspicion/ radiological evidence of active CNS involvement by leukemia			X
8) Acute promyelocytic leukemia	X		X
9) Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anti-cancer therapy as defined in Exclusion Criterion 1	X		X
10) Patients who initiated AZA treatment outside the approved label (except as described under the Inclusion Criterion 5) for example, in combination with other agents for the treatment of MDS			X

AML acute myeloid leukemia; ALT alanine aminotransferase; AST aspartate aminotransferase; AZA azacitidine; CNS central nervous system; ECOG Eastern Cooperative Oncology Group; EHR electronic health record; GVHD graft versus host disease; IPSS R Revised International Prognostic Scoring System; MDS myelodysplastic syndrome; RBC red blood cell; ULN upper limit of normal; US United States; WBC white blood cell

8.3. Variables

The variables to be collected are listed below in

Table 8-4. In this table, unstructured data refer to medical data including text-based descriptions in physician notes that were recorded during routine patient care. In addition, please see Section 8.2.1, Principles of Data Collection for guidance regarding timing (start and end time) of data collection for the study and for individual patients.

Table 8-4. Data Items and Timing for Surveillance

Data to be Provided if Available or Applicable	Stage	Source	Baseline (At AZA Initiation or Earlier as Applicable)	Study Period			Post-treatment Period
				Visit 1	Visit 2	Visit (n)	Post-treatment
Review of Eligibility Criteria	1&2		X				
Patient Demographics • Age at AZA initiation • Race • Sex • Height and weight • Geographical location of clinic	1&2	Structured	X				
Patient Demographics (Ethnicity)	2	Unstructured	X				
Clinical and Disease Characteristics							
MDS Diagnosis Date	1&2	Structured	X				
MDS Classification • RS and Single/Multilineage Dysplasia • Multilineage dysplasia • RS with multilineage dysplasia • Excess blasts • Isolated del 5q • Unclassifiable/unknown/ missing	1&2	Structured	X				
Therapy-Related or Secondary MDS (Yes/No/unknown)	1&2	Unstructured	X				
Date of AZA Initiation	1&2	Structured	X				
Documented IPSS-R Risk Category[a]	1&2	Structured	X				
Documented Cytogenetic Subgroup	1&2	Unstructured	X				
Documented Cytogenetics (Specify – Normal, del 11q, del 5q, del 12p, del 20q, etc)	2	Unstructured	X				
Documented TP53 Mutation	2	Unstructured	X	X	X	X	
BM Blasts % at MDS Diagnosis	1&2	Unstructured	X				
BM Blasts % at AZA Initiation	1&2	Unstructured	X				
BM Blasts During Treatment	1&2	Unstructured		X	X	X	X
Peripheral Blasts During Treatment	1&2	Unstructured		X	X	X	X

Data to be Provided if Available or Applicable	Stage	Source	Baseline (At AZA Initiation or Earlier as Applicable)	Study Period			Post-treatment Period
				Visit 1	Visit 2	Visit (n)	Post-treatment
Requirement for Blood Transfusion (record units and frequency)	2	Unstructured	X	X	X	X	
ECOG/Karnofsky Performance Status/	1&2	Structured	X	X	X	X	
Comorbidity[b]	1&2	Structured	X				
Prior Treatment for MDS Including Supportive Care[c]	1&2	Structured + Unstructured	X				
Information Collected at Baseline and During the Study							
Concomitant Medications	1&2	Structured + Unstructured	X	X	X	X	X
Complete Blood Count[d]	1&2	Structured	X	X	X	X	X
Serum Chemistry[e]	1&2	Structured[f]	X	X	X	X	X
Liver Function Tests[g]	2	Structured	X	X	X	X	X
AZA Treatment-Related Data							
Dose Changes[h]	2	Structured + Unstructured	X	X	X	X	
Dose Interruptions[i]	2	Structured + Unstructured	X	X	X	X	
Discontinuation[h]	1&2	Structured + Unstructured	X	X	X	X	
Reason for Treatment Discontinuation	1&2	Unstructured				X	X
Data Related to Effectiveness							
Date of Response Assessment (From Progress Notes and/or Attachment for the Bone Marrow Report)	1&2	Unstructured	X	X	X	X	
Response Category[j] (From Progress Notes and/or Attachment for the Bone Marrow Report)	1&2	Unstructured	X	X	X	X	
IWG 2006 Response Assessment, Where Available[k] (From Progress Notes and/or Attachment for the Bone Marrow Report)	1&2	Unstructured	X	X	X	X	X
If Progression, Date of Progression	1&2	Unstructured		X	X	X	X

Data to be Provided if Available or Applicable	Stage	Source	Baseline (At AZA Initiation or Earlier as Applicable)	Study Period			Post-treatment Period
				Visit 1	Visit 2	Visit (n)	Post-treatment
Last USON Visit Date	2	Structured + unstructured		X	X	X	X
Death Date	2	Structured + LADMF + unstructured		X	X	X	X
MDS Treatment After Discontinuation of AZA, if Applicable[l]	1&2	Structured + Unstructured		X	X	X	X
Hematopoietic Stem Cell Transplant	1&2	Unstructured		X	X	X	X

AZA azacitidine; BM bone marrow; ECOG Eastern Cooperative Oncology Group; IPSS R Revised International Prognostic Scoring System; IWG International Working Group; LADMF Limited Access Death Master File; MDS myelodysplastic syndrome; RS ring sideroblasts; USON US Oncology Network

a At MDS diagnosis or at AZA initiation
b As per National Cancer Institute comorbidity index. c Record drugs used and start end dates.
d Complete blood count includes hemoglobin, erythrocyte count; total leukocytes, absolute neutrophil count, lymphocytes, monocytes, and platelet count.
e Serum chemistry includes sodium, potassium, urea, uric acid, creatinine, and lactate dehydrogenase.
f Except for lactate dehydrogenase which is captured from Unstructured data.
g Liver function tests include alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, albumin, and total protein.
h Includes start and end dates and reason.
i Defined as stopping treatment permanently including date and reason for discontinuation.
j Response as documented within the electronic health record.
k Complete remission, partial remission, and stable disease including the assessment criteria used (eg, IWG 2006, IWG 2000, etc.).
l Drugs used and duration (start and end dates) this includes autologous/allogeneic hematopoietic stem cell transplant.

Due to privacy and compliance reasons, McKesson will be not be transferring the actual dates for any variables, including those for laboratory assessments and response assessments. A study day relative to the Index date for all variables including laboratory and response assessments will be transferred to Gilead Sciences in the final data set. Some additional data including month/year or "week of" dates could be shared after compliance review. Deidentified patient data will be provided; however, depending on the situation (small cell sizes or sensitive information like age > 90), some variables may be required to be aggregated or put into categories.

8.4. Data Sources

The primary data source for this retrospective cohort study will be the patient's EHR supplemented by a chart review. Patients will be identified from a large, comprehensive RWD database. A chart review will be conducted to extract ancillary data from the EHR. Supplemental vitality status will be obtained from the LADMF.

8.5. Study Size

A sample size of approximately 400 patients will provide adequate precision to estimate CR rates. The width of a 2-sided 95% exact CI of CR rate is ≤ 10% for an observed CR rate in the range of 5% to 25% if sample size is > 300.

95% CIs for observed CR rate for a given sample size are listed below:

Table 8-5. Observed CR Rates and 95% CI for Given Number of Responders and Sample Size

Observed CR rate	200 Patients 95% CI	250 Patients 95% CI	300 Patients 95% CI	350 Patients 95% CI	400 Patients 95% CI
5%	(2.4%, 9.0%)	(2.8%, 8.7%)	(2.8%, 8.1%)	(3.1%, 8.0%)	(3.1%, 7.6%)
10%	(6.2%, 15.0%)	(6.6%, 14.4%)	(6.8%, 14.0%)	(7.1%, 13.6%)	(7.2%, 13.4%)
15%	(10.4%, 20.7%)	(11.0%, 20.3%)	(11.2%, 19.6%)	(11.6%, 19.3%)	(11.6%, 18.9%)
20%	(14.7%, 26.2%)	(15.2%, 25.5%)	(15.6%, 25.0%)	(15.9%, 24.6%)	(16.2%, 24.3%)
25%	(19.2%, 31.6%)	(19.9%, 31.1%)	(20.2%, 30.3%)	(20.7%, 30.0%)	(20.8%, 29.5%)

8.6. Data Management

Data will be abstracted by structured data query and by chart review of unstructured data into an electronic case report form (eCRF). Data extracted from EHR through an eCRF, will be collected in an EDC system. Data from structured query will be compiled together with EDC data for analysis.The data collected are listed in the Variables section (Section 8.3) using the data collection principles. Review of the patient level data will be performed by trained personnel employed by McKesson.

For Stage 1, the main purpose is to assess data completeness. Therefore, data reconciliation, variable derivation, and data analysis will not be conducted. Instead, McKesson will only report the data completeness (ie, % of patients with data for each variable) for variables that are directly extracted from EHR. In addition, chart abstraction on select variables and outcome parameters will be conducted on approximately 20 patients. In Stage 2, full data abstraction of structured and chart data will be performed, as well as data QC. Study data will be stored on secure McKesson network drives with access restricted to authorized personnel only. Both structured and eCRF data will be transferred to Gilead via Gilead File Transfer Service (GFTS). Personal Health Information, which could identify the patients whose data are being utilized, will not be transferred to Gilead at any time; all data transferred to Gilead will be de-identified.

All data will be stored according to McKesson's retention policy. In accordance with Good Pharmacoepidemiology Practices guidelines, the study archive will be maintained for at least 5 years after final report or first publication of study results, whichever comes later. The data will be maintained on a secure data server with appropriate access restrictions.

8.7. Data Analysis

Data analysis will be performed by Gilead Sciences. Internal independent biostatistician and/or epidemiologist will perform the propensity score model with access to the baseline data only. No outcome data will be provided to them.

8.7.1. Analysis Sets

The Full Analysis Set (FAS) will include all enrolled patients who took at least 1 dose of AZA.

The Effectiveness Evaluable Analysis Set (EEAS) will include all FAS patients who had at least one response assessment or with a documented death after the index date.

8.7.2. Demographic and Baseline Characteristics

Continuous variables will be summarized by mean, standard deviation, median, 25% quartile, 75% quartile, minimum, and maximum. Categorical variables will be summarized by number and percentage of patients in each categorical definition including 95% CIs.

Demographic and baseline measurements will be summarized using standard descriptive methods and FAS. Demographic summaries will include age, sex, race/ethnicity, and geographic location. Baseline characteristics will include a summary of body weight, height, and body mass index. Baseline disease characteristics summaries will include but are not limited to IPSS-R score, MDS histological classification, ECOG score, and cytogenetics. Any Karnofsky performance score will be converted to ECOG {Center for International Blood & Marrow Transplant Research (CIBMTR) 2009}.

8.7.3. Safety Analyses

There are no safety analyses in this study.

8.7.4. Effectiveness Analyses

For the primary effectiveness analysis, CR rates will be evaluated using the FAS. The point estimate and the corresponding 95% CIs based on the Clopper-Pearson exact method will be provided. The same method will be applied to rw-CR, ORR, and rw-ORR using the FAS.

The time-to-event effectiveness endpoints including PFS, DCR, rw-DCR, DOR, rw-DOR, TTNT, and OS will be analyzed using the Kaplan-Meier method. Kaplan-Meier curves will be provided for the time-to-event endpoints. The endpoints of PFS, TTNT, and OS will use FAS. DCR and rw-DCR will include the FAS patients who achieve a CR or rw-CR, respectively. DOR and rw-DOR will include the FAS patients who achieve an OR or rw-OR, respectively.

CCI [redacted]

Sensitivity analyses will be performed for the primary and secondary endpoints (except DCR, rw-DCR, DOR, and rw-DOR) using EEAS.

The results of this study will be compared to the ongoing Phase 1b single -arm study of magrolimab + AZA (Study 5F9005) in patients with untreated higher-risk MDS. A detailed statistical analysis for comparison will be described in the statistical analysis plan.

8.8. Quality Assurance and Quality Control

In Stage 2, Gilead and/or McKesson will conduct quality checks in order to ensure quality and integrity of the data.

Major quality assurance steps are briefly described below:

- Training: Qualified and experienced chart abstractors will extract data from EHR systems and will be further trained on study -specific protocol and procedures including understanding of MDS and key clinical variables. Chart abstractors will be provided the Standard Operating Procedure or Study Handbook for guidance and reference.

- Reliability: Ten (10) charts will be distributed among all planned abstractors to be independently extracted twice and evaluated for inter-abstractor differences. A resolution session will be arranged for all abstractors as part of their training.

- eCRF and validation rules: To minimize errors in data transfer and data entry, all patient level information will be directly collected into an eCRF with built-in logic checks for variables with limits or out of bound value restrictions. Further, automated alerts will be built in to prevent potentially erroneous, incomplete, or inconsistent data.

- EDC: Data will be stored within McKesson's EDC system. The EDC system maintains records of changes to capture data overwriting or edits. Limited study personnel will be granted access to the EDC.

- Algorithm development: Algorithms will be developed to derive composite study variables or outcomes from multiple clinical and/or laboratory parameters to avoid manual interpretation. These algorithms will be reviewed by a board-certified hematologist and tested repeatedly for accuracies.

Major quality control steps are briefly described here:

- Random data check: At least 13% of randomly selected patient records will be checked for completeness, correctness, and consistencies. Sampling of charts for QC is based on the assumption of 90% chart accuracy, at 80% confidence, with a sampling error of 5%, based on binomial distribution of chart accuracy (yes/no). For 400 qualified charts, the number of charts for QC based on the calculation is 52.

- Source data verification: Pre-defined list of variables from patient records undergoing random data checks as described above will be verified for correctness from the original source chart.

- Algorithm validation check: Results from algorithms will be randomly checked for accuracy. Algorithms will be validated before applying to stage 2 chart data. Using stage 1 data, 10 patients will be randomly chosen, and results from the algorithms will be checked for the accuracy of derivation of the response endpoints.

- Outcome measure quality improvement: Clinical outcomes for MDS involves measurement of multiple clinical and laboratory parameters. To ensure complete and correct response assignment for patients, all responses meeting the CR, rw-CR, PR, and rw-PR will be subject to adjudication by an independent assessor who will be a board-certified hematologist.

- Aggregate data quality check: Periodic data quality check for missing values, inconsistencies, and completeness will be performed on aggregate data to date during and at the end of the data collection period.

8.9. Independent Adjudication of Responses

All response assessments meeting the protocol definitions of CR, rw-CR, PR, and rw-PR will be examined and adjudicated by an independent assessor who is a board-certified hematologist who specializes in the treatment of MDS. This assessor will be employed by McKesson with no direct Gilead involvement.

8.10. Limitations of the Research Methods

This study has the characteristic disadvantages of retrospective studies; for example, selection bias, information bias, misclassification bias, and history bias. To reduce selection bias, patients' eligibility criteria have been well defined in the protocol. A selection bias is introduced by the choice of healthcare providers that contribute their EHRs to USON's iKM EHR. This is mitigated by the fact that there is significant geographic dispersion within USON with all regions of the country receiving some coverage in the system. Overall, the iKM EHR system captures data on approximately 10% of patients with newly diagnosed cancer in the US. Approximately 1,200 physicians are affiliated with USON, operating in more than 470 cancer treatment center locations across the US. Each year, more than 1 million patients with cancer are treated within the USON database.

The total MDS patient pool that meets preliminary eligibility criteria for this study is in excess of 11,000 patients, which further reduces selection bias.

Information bias is prevented by using standard measurement instruments, including the use of eCRF and appropriate training of RWD partner personnel entering the data. The standards of training provided will be described under the Training Manuals of McKesson Life Sciences and will be available for inspection. Quality Assurance and Quality Control process for each database vendor will be described in the respective Service Agreement/Work Practice and will be available for inspection. There is minimal risk of history bias in this study as the standard of care for the first-line treatment of MDS has not changed over the Study Index Period. This study relies on a retrospective chart review of EHR. The EHR contains information pertaining to

managing patients in clinical practice rather than for research purposes. This may impede the standardization of the data collection methods and instruments and the reporting practices of the physician. Secondly, RWD databases are subject to coding errors. Problems with inadequate or inaccurate codes in the databases may introduce some level of misclassification bias in the study. Likewise, some variables of interest may not be as complete across the entire study population. Thirdly, each database has a close link to a dedicated network (McKesson Life Sciences USON) and, therefore, contains information on patients only when they are seen by physicians within that network. As such, services and procedures provided outside of the network (eg, emergency hospitalizations) are not captured by the database, including drugs received by patients from pharmacies not affiliated with the same network.

Misclassification of primary endpoints will be mitigated by use of complete ascertainment of all IWG response criteria and independent adjudication by a qualified hematologist employed by McKesson with no direct Gilead involvement.

Patient treatment history prior to the first encounter at a practice within the network may only be available in physician progress notes and may not be well captured or only partially captured in the EHR. Similarly, oral therapies are recorded in or prescribed through EHR-related systems, but fulfilment is not observable. In this study, attempts will be made to confirm receipt of oral therapies through chart review to help mitigate this potential limitation.

Death data are relatively complete. The primary source of death information will be structured and unstructured records of death in the iKM EHR database. McKesson has certification to access the LADMF of the Social Security Administration and, as such, this will be a supplementary source of vital (death) records in addition to the NDI of the Centers for Disease Control. Common patient identifiers (patient ID, name, and birth date) will be used to link patients from the iKM data warehouse and iKM chart review. The social security number (SSN) will be used to link patients from iKM and LADMF data sources. All patients within iKM are assigned a unique patient identifier by iKM version (eg, some large practices have separate installations by location). When linking to the LADMF, patient SSN is used. Some practices do not collect SSN and some patients may not report it.

Death information is updated weekly in the LADMF and is as current as it is reported to the Social Security Administration. However, death dates recorded in the LADMF are not complete due to limitations on access to records for research purposes {Navar 2019}. LADMF and hospital death records were compared after access restrictions imposed in 2011 {Levin 2019}. After 2011, LADMF sensitivity for in-hospital deaths was 14.8% (compared with 88.9% before 2011) and 28.9% for out-of-hospital deaths (compared with 71.4% before 2011). The LADMF specificity, however, was greater than 99% both prior to and after 2011. Peters and colleagues (2017) compared capture of death dates in the LADMF with a multi-phased approach that assessed online databases (including LADMF), EHR records, and provider follow-up {Peterss 2017}. The authors reported that 42.7% of death records were identified by the LADMF, and the remainder were identified from another online database (32.6%), EHR records (22.2%), and provider follow-up (3.5%). Overall, the sensitivity was 58.5%, with 100% specificity.

In a study of the iKM EHR database and LADMF, it was observed that 93.3% of all death records were captured in structured fields and 6.7% of death records were solely identified by the LADMF. Among deaths recorded by both structured data and the LADMF, concordance was 88.0%. When both structured and unstructured data are available, 99.4% of death records are captured from these sources, with 0.6% of death records solely identified by the LADMF. Between 2015 and 2019, the proportion of death records captured by structured data trended upward (slope 4.04).

Based on previous studies of other solid tumors, it is estimated that physician-assessed response will be available for greater than 60% of patients in the RWD. However, this may be impacted by BM reports and may vary considerably for patients with MDS. In standard clinical practice in the treatment of MDS, bone marrow biopsies are not routinely performed other than during diagnosis and at suspected disease progression. If BM biopsy results are unavailable for a significant proportion of patients, this will lead to an underestimate of the CR and PR rate (as defined in the Table 8-1) in the study. Therefore, the interpretation of data collected and analysed retrospectively will be dependent on the completeness and quality of the data.

8.10.1. Joint RWD Partner/Gilead Responsibilities

8.10.1.1. Quality Control of Data

McKesson Health Sciences is responsible for review of the data collected throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on the forms. However, secondary reconciliation and data quality check will be performed by Gilead personnel. The service agreement between Gilead and McKesson specifies the roles and responsibilities of each party. Details of quality assurance and quality control measures have been described in Section 8.8.

8.10.1.2. Study Discontinuation

Gilead reserves the right to terminate the study at any time. Should this be necessary, either Gilead and/or McKesson Health Sciences will arrange discontinuation procedures and notify the appropriate regulatory agencies and institutional review boards (IRBs), where applicable.

9. PROTECTION OF HUMAN SUBJECTS

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy.

As this is a retrospective observational study, there is no additional risk to participants as all data are collected from vendor EHR and patients will have no direct involvement in the study.

Confidentiality will be maintained by the assignment of a unique patient identifier to each participant. The unique patient identifier will be used on all study documentation and datasets in place of patient identifying information.

9.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (GPP).

9.2. Institutional Review Board

McKesson will submit this protocol and any accompanying material to an IRB, as applicable.

9.3. Informed Consent

No informed consent will be obtained for this study. All data used in this study will be anonymized and collected in RWD vendor databases and/or an eCRF with a unique patient identifier for each patient.

9.4. Confidentiality

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

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

All parties will ensure protection of patient personal data and will not include patient names on any Gilead forms, reports, publications or in any other disclosures, except where required by laws. This study involves analysis of secondary data, and all data are anonymized to protect the privacy of patients and providers.

The retrospective research study will be conducted in accordance with legal and regulatory requirements as well as with scientific purpose, value, and rigor, and will follow generally accepted research practices. It will be necessary to obtain IRB and Compliance/Privacy approval prior to initiation of the retrospective research study data extraction and analysis. The McKesson team will submit a request for exemption, waiver of informed consent, and authorization to the IRB. McKesson will submit the appropriate documents, including but not limited to this protocol, to the McKesson Compliance/Privacy department and the IRB for review. McKesson will handle all correspondence with McKesson Compliance/Privacy and the IRB; correspondence will be kept on file at McKesson.

10. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

This non-interventional study is observational in nature and data are derived from electronic health records or sources where individual patient data is de-identified. Therefore, individual case safety reports are not collected or reported in an expedited fashion. Adverse events will not be solicited in this study. Safety findings from this study will be presented in aggregate in the final study report.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Study Report and Publications

A non-interventional study report will be prepared.

12. REFERENCES

Center for International Blood & Marrow Transplant Research (CIBMTR). Forms and Instruction Manuel: Appendix L: Karnofsky/Lansky Performance Status 2009:

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108 (2):419-25.

Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. Blood 2012;120 (12):2454-65.

Levin MA, Lin HM, Prabhakar G, McCormick PJ, Egorova NN. Alive or dead: Validity of the Social Security Administration Death Master File after 2011. Health Serv Res 2019;54 (1):24-33.

Navar AM, Peterson ED, Steen DL, Wojdyla DM, Sanchez RJ, Khan I, et al. Evaluation of Mortality Data From the Social Security Administration Death Master File for Clinical Research. JAMA Cardiol 2019;4 (4):375-9.

Peterss S, Charilaou P, Ziganshin BA, Elefteriades JA. Assessment of survival in retrospective studies: The Social Security Death Index is not adequate for estimation. The Journal of thoracic and cardiovascular surgery 2017;153 (4):899-901.

Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 2002;20 (10):2429-40.

13. APPENDICES

Appendix 1. List of Stand-Alone Documents
Appendix 2. International Working Group 2006 criteria {Cheson 2006}
Appendix 3. Gilead Signature Page
Appendix 4. RWD Partner Signature Page

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	NDA 050794	Approved in 2004 by the FDA	Vidaza® US prescribing information

FDA Food and Drug Administration

Appendix 2. International Working Group 2006 criteria {Cheson 2006}

Table 13-1. 2006 International Working Group Response Criteria for Altering Natural History of MDS

Category	Response Criteria (Responses Must Last at Least 4 Weeks)
Complete Remission	BM: ≤ 5% myeloblasts with normal maturation of all cell lines Persistent dysplasia will be noted Peripheral blood • Hb ≥ 11 g/dL • Platelets ≥ 100×10^9/L • Neutrophils ≥ 1.0×10^9/L • Blasts 0%
Partial Remission	All CR criteria if abnormal before treatment except: BM blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR	BM: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Hematological Improvement	Please refer to Table 13-2 below
Stable Disease	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of BM blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse After CR or PR	At least 1 of the following: • Return to pretreatment BM blast percentage • Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic Response	Complete • Disappearance of the chromosomal abnormality without appearance of new ones Partial • At least 50% reduction of the chromosomal abnormality
Disease Progression	For patients with: • Less than 5% BM blasts: ≥ 50% increase in blasts to > 5% blasts • 5%-10% BM blasts: ≥ 50% increase to > 10% blasts • 10%-20% BM blasts: ≥ 50% increase to > 20% blasts • 20%-30% BM blasts: ≥ 50% increase to > 30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hb by ≥ 2 g/dL • Transfusion dependence

Category	Response Criteria (Responses Must Last at Least 4 Weeks)
Survival	Endpoints: • Overall: death from any cause • Event free: failure or death from any cause • PFS: disease progression or death from MDS • DFS: time to relapse • Cause-specific death: death related to MDS

BM bone marrow; CR complete remission; DFS disease free survival; FAB French American British; Hb hemoglobin; HI hematologic improvement; MDS myelodysplastic syndrome; PR partial remission

Table 13-2. 2006 International Working Group Response Criteria for Hematologic Improvement

Hematologic Improvement	Response Criteria (Responses Must Last at Least 8 Weeks)
Erythroid Response (HI-E) (Pretreatment Hb < 11 g/dL)	Hb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet Response (HI-P) (Pretreatment platelets, < 100×10^9/L)	Absolute increase of ≥ 30×10^9/L for patients starting with > 20×10^9/L platelets Increase from < 20×10^9/L to > 20×10^9/L and by at least 100%
Neutrophil Response (HI-N) (Pretreatment neutrophils < 1.0×10^9/L)	At least 100% increase and an absolute increase > 0.5×10^9/L
Progression or Relapse After HI	At least 1 of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hb by ≥ 1.5 g/dL • Transfusion dependence

Hb hemoglobin; HI hematologic improvement; RBC red blood cell

Appendix 3. Gilead Signature Page

GILEAD SCIENCES
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

A RETROSPECTIVE OBSERVATIONAL COHORT STUDY TO EVALUATE THE EFFECTIVENESS OF AZACITIDINE MONOTHERAPY IN TREATMENT-NAIVE PATIENTS WITH INTERMEDIATE, HIGH, AND VERY HIGH-RISK MYELODYSPLASTIC SYNDROME

FINAL PROTOCOL DATED 14 JANUARY 2021

This protocol has been approved by Gilead Sciences. The following signature documents this approval.

PPD

Gilead Study Director (Printed)
Author

Signature

Date

Appendix 4. RWD Partner Signature Page

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)	Signature
Date	

This protocol has also been approved by McKesson Specialty Health Outcomes Researcher:

PPD	
Outcomes Researcher Name (Printed)	Signature
Date	