Title	A post-authorisation, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)
Protocol version identifier	CC-5013-MDS-012, Amendment 3 (Version 2.0)
Date of protocol amendment	28-Mar-2023
Date of original protocol	03-Mar-2014 (approval date of Version 2.0)
EU PAS register number	ENCEPP/EUPAS22604
Active substance	Lenalidomide (ATC code: L04AX04)
Medicinal product	Revlimid®
Product reference	EU/1/07/391/001-014
Procedure number	EMEA/H/C/000717/II/0056
Marketing authorisation holder (MAH)	Bristol-Myers Squibb Pharma EEIG
Joint PASS	No
Research question and objectives	The primary research question of this retrospective study is to describe the pattern of use of lenalidomide in the clinical routine practice of MDS in countries of the European Union (EU) in which Revlimid® (lenalidomide) is marketed for *the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate* and where these patients have access to the drug post EU-approval for the MDS indication. The study will also allow the collection of further information regarding the safety of Revlimid (lenalidomide) outside of the EU-approved indication (ie, in patients with any type of MDS other than transfusion-dependent International Prognostic Scoring System [IPSS] low- or intermediate-1 [int-1]-risk MDS with isolated del(5q)). **Primary Objective** To describe the pattern of use of lenalidomide in the clinical routine practice of MDS patients in the countries concerned **Secondary Objectives** To further describe the safety of lenalidomide both within the EU approved indication [on-label cohort] and outside of the EU approved indication (ie, in patients with any type of MDS other than transfusion-dependent International Prognostic Scoring System [IPSS] low- or intermediate-1 [int-1]-risk MDS with isolated del(5q)) [off-label cohort] in terms of: • progression to acute myeloid leukemia (AML) • hematological and non-hematological adverse events, including infections, bleeding, thromboembolic events • major cardiac events and second primary malignancies (SPM) other than AML (which is considered as disease progression in patients with MDS) • evaluation of risk factors collected in the routine care setting associated with progression to AML among MDS patients treated with lenalidomide within and outside of the EU approved indication, dependent on both sufficient patient numbers and availability of data within the selected data sources

Approved v2.0 [redacted]

Country(-ies) of study	Implementation of this retrospective drug-utilisation study is a condition of the EU marketing authorisation for lenalidomide in the MDS indication (Revlimid, European Commission Decision, Annex IID). Hence, this retrospective drug-utilisation study will be implemented in countries of the EU in which Revlimid (lenalidomide) is approved and marketed for the MDS indication and where these patients were subsequently granted access to the drug through reimbursement schemes. For representativeness and in order to meet the primary drug-utilisation objective and the secondary safety objectives, the study will include results from the selected data sources that represent at least 10 countries of the EU. More EU countries will potentially be included, once they gain reimbursement. Additionally, the company-sponsored Connect® Myeloid Disease Registry (United States [US] Cohort Registry) will be used to address the secondary safety objectives (but not the primary drug-utilisation objective due to a different MDS indication approved in the US).
Author(s)	[redacted]
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MAH contact person	[redacted]

SIGNATURE PAGE

[redacted]

Signature of Bristol Myers Squibb (BMS) Therapeutic Area Head

[redacted]

Printed Name of BMS Therapeutic Area Head

Date Signed _____

[redacted]

Signature of BMS Qualified Person for Pharmacovigilance

[redacted]

or

[redacted]

Printed Name of Qualified Person for Pharmacovigilance

Date Signed _____

SUMMARY OF KEY CHANGES PROTOCOL AMENDMENT 3 (VERSION 2.0)

The key changes included in this amendment are summarised below:

- **Study size**

The study sample size was refined down from earlier projections due to the low rate of new eligible patients entering the registries compared to when the registries first started collecting data on patients treated with lenalidomide. Possible reasons for these changes may reflect the broader acceptance of lenalidomide in standard care for low-risk MDS patients, whereas the specialised registries participating in this study seem to include a greater proportion of higher risk patients who are often treated with medications other than lenalidomide, such as azacitidine. These registries also exhibited a degree of missing data greater than was originally expected, limiting the number of patients to be included in the study for the final analyses. Another unforeseen event that affected the number of new patients available was the coronavirus disease (COVID-19) pandemic, which affected the staffing resources of the registries, leading to lower-than-expected new patient numbers captured in the registries in recent years. In addition, reimbursement of lenalidomide for the MDS indication has not been approved in some EU countries, which has reduced some contributions to the academic EUMDS registry. Therefore, the proposed sample size has been changed from 500 to at least 460 patients. Based on the proportion of off-label patients and the proportion of AML progression cases that was previously used to justify the sample size, the calculated confidence interval around the estimated 50% of off-label patients has widened by approximately 0.4% from 95% CI = 45.6%, 54.4% to CI = 45.4%, 54.6%. the calculated confidence interval around the estimated 17% of AML cases has widened by approximately 0.4% from 95% CI = 12.7%, 22.4% to CI = 12.3%, 22.4%. By the sponsor's estimation this still provides sufficient statistical precision for this study.

Revised: Abstract; Section 7.1.1; Section 7.5

- **Date of eligibility**

The beginning date for eligibility of patient data on this study was defined as the date when patients have access to the drug. In the previous amendment, this was specified as the date from which the drug received approval for reimbursement. However, experience has shown that several patients had access to the drug immediately after approval in the EU for the MDS indication rather than waiting for reimbursement. Thus, to maximise the number of patients eligible for inclusion, the protocol has been revised to define the date of eligibility as the date of EU-approval for the MDS indication. This change will not affect the real-world European drug-utilisation patterns. It should also be noted that the sponsor still only considers countries that have granted reimbursement at the time of this protocol amendment.

Revised: Abstract; Sections 6.1, 7.1.1, 7.2.1, 7.5

- **Exclusion criteria**

A clarification was added to the exclusion criteria to explicitly specify a pre-existing criterion, that patients treated with the study drug in an interventional therapeutic clinical trial for MDS are

ineligible to be entered into the study, since this study investigates the actual real-world European drug-utilisation patterns of lenalidomide.

Revised: Section 7.1.2.2

- **Summary of Protocol Amendments**

The Amendments and Updates section has been updated to summarise the main changes implemented through this Amendment No. 3 (Version 2.0).

Revised: Section 3 Amendments and Updates.

- **Milestones**

The milestones have been updated to reflect the change of the estimated end of study data collection and the final report of study results by 9 months. This change is considered required in order to achieve at least 460 patients in this study and also accounts for the time required for the PRAC's assessment of this amendment.

Revised: Abstract; Section 4

- **Key Personnel**

Key personnel have been updated to reflect changes in the responsible staff at the time of finalisation of this amendment.

Revised: Title Page; Signature Page; Section 1; Annex 2

- **Change of company data ownership**

As the ownership of the Connect® Myeloid Disease Registry has changed from Celgene to BMS, text referring to "Celgene-sponsored" has been updated to "company-sponsored" for clarification.

Revised: Title Page; Abstract; Sections 1, 7.1, 7.2, 7.4 and 7.5

- **Other**

Minor editorial changes have been made throughout the document. Places in the text that referred to the EU authorisation of lenalidomide have been changed to EU-approval for consistency.

Revised: Title Page; Abstract; Sections 1, 6.1, 7.1, 7.2 and 7.5

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AML	Acute myeloid leukemia
ATC	Anatomical Therapeutic Chemical
ATU	Authorisation Temporaire d'Utilisation
BMS	Bristol Myers Squibb
CBC	Complete blood count
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRO	Contract Research Organisation
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
del(5q)	Deletion involving the long arm of chromosome 5
EC	European Commission
EMEA	European Medicines Agency (currently referred to as the EMA)
EMR	Electronic medical record
ESA	Erythropoiesis-stimulating agent
EU	European Union
EUMDS Registry	European Myelodysplastic Syndromes Registry
GESMD	Spanish Group of MDS
GFM	French MDS Group
HCP	Healthcare provider
HR	Hazard ratio
HRQoL	Health-related Quality of Life
ICD-10	International Classification of Diseases, 10th revision
int-1	Intermediate-1
int-2	Intermediate-2
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
IWG	International Working Group
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic syndromes
MM	Multiple myeloma
NCA	National Competent Authority

Abbreviation	Definition
NCI	National Cancer Institute
OS	Overall survival
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PD	Progression of disease
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RE SMD	Registro español de síndromes mielodisplásicos
Q1	First quarter
Q4	Fourth quarter
RBC	Red blood cell
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SPM	Second primary malignancy
US	United States
WBC	White blood cell
WHO	World Health Organization

1 RESPONSIBLE PARTIES

This post-approval retrospective study is sponsored by Celgene International Sàrl and represents a condition of the European Union (EU) marketing authorisation for lenalidomide in the myelodysplastic syndromes (MDS) indication. The data on patients treated with lenalidomide for MDS will only be available within a country following the approval of the product for the MDS indication in a country which subsequently granted reimbursed access, and once available in the selected data source. Hence, this retrospective drug-utilisation study will be implemented in countries of the EU in which Revlimid® (lenalidomide) is marketed for MDS and where these patients have access to the drug post EU-approval for the MDS indication. Therefore, to meet the primary drug-utilisation objective and the secondary safety objectives, this study will be limited to countries that gave a subsequent decision to fully reimburse lenalidomide for the MDS indication and the extent of data per country will be related to time since the EU-approval for the MDS indication and availability of data with the exception of eligible patients from the company-sponsored Connect® Myeloid Disease Registry (United States [US] Cohort Registry) who will be included regardless of start date of treatment.

Due to the purely retrospective nature of this lenalidomide retrospective study, no principal investigator or coordinating investigator has been identified, and a Celgene emergency Contact is not provided.

For operational inquiries regarding the lenalidomide retrospective drug-utilisation study protocol, contact information is provided in Table 1.

Table 1: Contact Information for Operational Inquiries

Sponsor:	Bristol Myers Squibb [redacted]
CRO:	Not Applicable
CRO Study Manager:	Not Applicable
BMS Study Manager:	Global Development Operations
BMS Physician:	[redacted]

CRO = contract research organisation.

2 ABSTRACT

Title: A post-authorisation, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)

Rationale and Background: Revlimid® (lenalidomide) is a drug belonging to the proprietary series of drugs with immunomodulatory and other properties, and is currently registered in several countries worldwide, including the European Union (EU), for the treatment of multiple myeloma in combination with dexamethasone in adult patients who had received at least one previous therapy, for the treatment of adult patients with previously untreated multiple myeloma (MM) who are not eligible for transplant, and for the treatment of adult patients with

relapsed or refractory mantle cell lymphoma. Lenalidomide also is licensed in more than 20 countries including the United States (US), Australia, Japan, New Zealand, Israel, and Switzerland for the treatment of transfusion-dependent anaemia due to International Prognostic Scoring System (IPSS) low- or intermediate-1 (int-1)-risk MDS with deletion 5q (del(5q)), with or without additional cytogenetic abnormalities. In the EU, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive Opinion on 25-Apr- 2013 for the use of Revlimid in the "treatment of transfusion-dependent anaemia due to low- or int-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate," variation EMEA/H/C/717/II/056. The European Commission (EC) Decision was adopted on 13-Jun-2013 based on a condition to the EU marketing authorisation for the Marketing Authorisation Holder (MAH) to implement a non-interventional post-authorisation safety study (PASS) (Revlimid, Annex IID to the EC Decision). As per the condition to the marketing authorisation, the MAH implemented this retrospective drug-utilisation study to describe the post-marketing pattern of use of lenalidomide in MDS both within and outside of the EU approved indication.

This lenalidomide retrospective study will also aim to gather additional safety information among MDS patients treated with lenalidomide outside the EU approved indication including the risk of progression to acute myeloid leukemia (AML) in a routine-care setting.

This study, and the analyses to be performed depends on both sufficient patient numbers and availability of data within the selected data sources.

Research Question and Objectives:

The primary research question of this retrospective drug-utilisation study is to describe the pattern of use of lenalidomide in the clinical routine practice of MDS in countries of the EU in which Revlimid (lenalidomide) is marketed for *the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate* and where these patients have access to the drug post-approval by the European Commission for the MDS indication.

The study will also allow the collection of further information regarding the safety of Revlimid (lenalidomide) outside of the EU approved indication (ie, in patients with any type of MDS other than transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q)).

Primary Objective:

To describe the pattern of use of lenalidomide in the clinical routine practice of MDS patients in the countries concerned

Secondary Objectives:

- To further describe the safety of lenalidomide – both within the EU approved indication [on-label cohort] and outside of the EU approved indication (ie, in patients with any type of MDS other than transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q)) [off-label cohort], in terms of:
  - progression to AML
  - hematological and non-hematological adverse events, including infections, bleeding, thromboembolic events
  - major cardiac events and second primary malignancies (SPM) other than AML (which is considered as disease progression in patients with MDS)
  - evaluation of risk factors collected in the routine-care setting associated with progression to AML among MDS patients treated with lenalidomide within and outside of the EU approved indication, dependent on both sufficient patient numbers and availability of data within the selected data sources

Study Design: This is a post-authorisation, non-interventional, retrospective, drug-utilisation study. This study will be run in countries in the EU in which Revlimid (lenalidomide) will have been marketed in the new MDS indication, and where MDS patients will have access to the drug post EU-approval for the MDS indication. The only exception is that eligible patients from the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) will be included regardless of start date of treatment to assess the secondary safety objectives (but not the primary drug-utilisation objective due to a different MDS indication approved in the US). This retrospective drug-utilisation study will include patients with MDS treated with lenalidomide, irrespective if within or outside the approved indication in the EU (eg, patients commencing lenalidomide treatment for

transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q) or with additional cytogenetic abnormalities, or IPSS risk categories intermediate-2 (int-2) -or high, or patients with MDS without del(5q) will also be recorded).

The sources of data for the primary drug-utilisation objective and the secondary safety objectives in this study will include, but will not be limited to: the existing academic European Myelodysplastic Syndromes (EUMDS) Registry, the Spanish Registry of MDS (RE SMD [registro español de síndromes mielodisplásicos]), the Düsseldorf MDS Registry, the online French Registry of MDS, and the Danish National Acute Leukemia Registry. Additionally, the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) will be used to address the secondary safety objectives. See section on Data Sources for further details.

At least 10 EU countries included in the selected data sources have lenalidomide reimbursement and will be included. More EU countries will potentially be included, once they gain reimbursement. The study is planned to collect retrospective data from subjects with MDS treated with lenalidomide according to the inclusion criteria, until at least 460 patients are included. An interim descriptive report was prepared 1 year after study start. Within the interim descriptive report, available data on eligible patients regarding the pattern of use of lenalidomide within and outside the EU approved indication, namely the distribution of MDS patients according to predefined categories (eg, transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q), or with additional cytogenetic abnormalities, or IPSS risk categories int-2 or high, or patients with MDS without del(5q)) was presented. On 29-Mar-2019, the first interim descriptive report was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) in order to discuss if the data collected on lenalidomide use, across different groups of MDS patients, are sufficient to allow successful completion of this study. The Assessment Report adopted by the CHMP on 27-Jun-2019 included a request to submit another interim descriptive report in Quarter (Q)1 2020. On 27-Mar-2020, the second interim descriptive report was submitted to PRAC (EMEA/H/C/000717/ANX/041.8). The final Assessment Report, adopted by the CHMP on 10-Dec-2020, concluded that the post-authorisation measure for the second interim report was fulfilled with no further action required.

The final data analysis will occur after at least 460 patients have been included. Data will be collected for both on- and off-label patients, to cover the period from date of first lenalidomide dose (baseline) until the date of death or last follow-up available at the time of the retrospective data collection (whichever occurs first) including for patients lost to follow-up or who discontinue the drug for any reason. Data collected at baseline will include those data that could have been generated earlier but are relevant at the baseline date (for example, information related to diagnosis). Time to progression to AML or time to any other kind of event will be counted from the date of first lenalidomide dose (baseline). (See section that follows [Populations and Cohorts] for definitions of off-label cohort and on-label cohort.)

Population and Cohorts:

Overall population: Those MDS patients who have received at least one dose of lenalidomide and who started their treatment after lenalidomide has obtained EU Regulatory approval for the MDS indication and in countries that subsequently had a positive reimbursement decision with the exception of eligible patients from the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) who will be included regardless of start date of treatment.

This population will include both prevalent (patients whose initial MDS diagnosis is **prior** to the date of EU-approval for the MDS indication, but whose initiation of lenalidomide treatment occurs on or after the date of EU-approval for the MDS indication) and incident patients (patients whose initial MDS diagnosis and initiation of treatment with lenalidomide is **after** the date of EU-approval for the MDS indication).

MDS licensed indication cohort (ie, on-label cohort): All patients with transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q) in the EU who started their treatment after lenalidomide has obtained EU Regulatory approval for the MDS indication and in countries that gave a subsequent positive reimbursement decision.

Other MDS indication cohort (ie, off-label cohort): All patients with any type of MDS other than transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q) in the EU who started their treatment after lenalidomide has obtained EU Regulatory approval for the MDS indication and in countries that gave a subsequent positive reimbursement decision with the exception of eligible patients from the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) who will be included regardless of start date of treatment.

Variables:

The following data variables will be collected from the registries according to local medical practice and availability of data.

Demographics and Clinical Variables for On- and Off-label Cohorts

- Patient demographics
- Date of MDS diagnosis and indication for which lenalidomide is used
- Date of first dose of lenalidomide
- Cytogenetic abnormalities
- Prior MDS-associated therapy
- Bone marrow and peripheral blood morphology (including bone marrow blasts)
- Transfusion burden
- Hemoglobin level, platelet and neutrophil counts
- Ferritin level
- Endogenous erythropoietin level
- Data on risk classifications (IPSS)
- Relevant medical history
- Comorbidities

Therapy and Other Treatment Variables for Both On- and Off-label Cohorts

- Lenalidomide: Starting dose, dose adjustments, dose interruptions
- Other MDS concomitant medications (eg, iron chelating agents, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor, hypomethylating agents, etc): Yes/no, dose, response, duration of use
- Prior erythropoiesis-stimulating agent (ESA) treatment (yes/no, prior response, most recent treatment, duration of treatment)
- Concurrent ESA use: Yes/no, dose, response, duration of use
- Other previous therapies for MDS
- Relevant concomitant medications such as thromboprophylaxis
- Red blood cell (RBC) transfusion: Yes/no, number of units over last 8 weeks

Outcome Variables for Safety for Both On- and Off-label Cohorts

- Progression to AML: Yes/no, date of event, method of documentation
- Death: Date, cause, method of documentation
- Adverse events (AEs): Incidence of hematologic and non-hematologic AEs (using AE definitions from the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] where feasible)
- SPMs other than AML (which is considered as disease progression in patients with MDS).

Data Sources: Celgene assessed the feasibility of this protocol using various potential data sources across the EU for the identification of off-label prescriptions and existence of longitudinal data to measure long-term outcomes of patients with MDS, including progression to AML. The sources of data for this study will include, but will not be limited to:

- the existing academic European Myelodysplastic Syndromes (EUMDS) Registry
- the Spanish Registry of MDS or RE SMD (registro español de síndromes mielodisplásicos), coordinated by the Spanish Group of MDS [GESMD]
- the Düsseldorf MDS Registry
- the online French Registry of MDS, coordinated by the French MDS group [GFM])
- the Danish National Acute Leukemia Registry.

Additionally, the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) will be used to address the secondary safety objectives (but not the primary drug-utilisation objective due to a different MDS indication approved in the US, which is for the treatment of patients with *transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes [MDS] associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities*). The company-sponsored Connect® Myeloid Disease Registry is a non-interventional, prospective, longitudinal, observational, multicenter, US Cohort Registry study of patients with confirmed cases of newly diagnosed MDS, idiopathic cytopenia of undetermined significance, and AML.

A limitation of the selected EU data sources is that they collect data only from specific countries or patient catchment areas, hence they cannot provide complete representation of the actual real-world European drug-utilisation patterns. However, the EUMDS Registry captures high quality data from 17 EU countries, and it will be used to mitigate this limitation. Of these 17 countries in the selected data sources, results will be included from at least 10 EU countries that have lenalidomide reimbursement for the MDS indication. More EU countries will potentially be included, once they gain reimbursement for the MDS indication. In addition, the Spanish Registry of MDS, the Düsseldorf MDS Registry, the online French Registry of MDS, and the Danish National Acute Leukemia Registry will provide a comprehensive coverage of MDS patients in these four countries to complement the data in the EUMDS Registry. Adjustments will be made for any patients in the four national registries that overlap with patients in the EUMDS Registry.

To protect privacy and according to the local regulations, analysis of study endpoints will be conducted using aggregated data (majority of analyses) or performed by the registries (Kaplan-Meier and multivariate analyses). To do the analyses which are based on aggregated data, datasets limited to the necessary variables will be compiled from pseudononymized datasets provided to the sponsor by each registry, and processed in accordance with the applicable regulations regarding privacy protection.

Study Size: The study population will be composed of at least 460 patients with MDS treated with lenalidomide after the granting of Regulatory approval of Revlimid (lenalidomide) for use in the treatment of MDS in the EU (EC Decision, 13-Jun-2013) and in countries that gave a subsequent positive reimbursement decision for the MDS indication. The final data analysis will occur when at least 460 patients have been included and will be based on data from all eligible patients available at that time.

An interim descriptive report was prepared 1 year after study start. Within the interim descriptive report, available data on eligible patients regarding the pattern of use of lenalidomide within and outside the EU approved indication, namely the distribution of MDS patients according to predefined categories (eg, transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q), or with additional cytogenetic abnormalities, or IPSS risk categories int-2 or high, or patients with MDS without del(5q)) was presented. On 29-Mar-2019, the first interim descriptive report was submitted to the PRAC in order to discuss if the data collected on lenalidomide use, across different groups of MDS patients, are sufficient to allow successful completion of this study. The Assessment Report adopted by the CHMP on 27-Jun-2019 included a request to submit another interim descriptive report in Quarter (Q)1 2020. On 27-Mar-2020, the second interim descriptive report was submitted to PRAC (EMEA/H/C/000717/ANX/041.8). The final Assessment Report, adopted by the CHMP on 10-Dec-2020, concluded that the post-authorisation measure for the second interim report was fulfilled with no further action required.

The primary objective of the study is to evaluate the proportion of patients outside of the EU approved indication (off-label). Assuming that the percentage of off-label patients will be around 50%, a sample size of at least 460 patients would yield a 95% confidence interval (CI) = (45.4%, 54.6%). The assumption of 50% is based on the second Interim Report submitted to PRAC on 27-Mar-2020 (EMEA/H/C/000717/ANX/041.8). The sample size calculated would not only allow to investigate this assumption, but also to detect smaller percentages if the true proportion would be smaller.

The main secondary objective of the study is to assess incidence and time to progression to AML in off-label patients. Assuming a proportion of around 50%, at least 230 patients in the study will be off-label. Assuming the proportion of patients progressing to AML will be similar to those on-label, ie, 17%, 230 off-label patients will yield a 95% CI = (12.3%, 22.4%).

Incidence and time to progression to AML in on-label patients will be assessed as well for reference. Kaplan-Meier curves and hazard-ratios between on- and off-label patients will be derived and adjusted in multivariate analyses for confounding and risk factors. This will be requested to each registry, and the sponsor will provide all registries with the same statistical guidance to perform those specific analyses.

Data Analysis:

The following analyses will be performed according to the availability of data from the data sources.

For all variables

- Descriptive statistics (mean, standard deviation, median, interquartile range, minimum, and maximum) will be provided for continuous variables; categorical variables will be summarised using frequency and percentages.

Demographic data and baseline characteristics

- Demographic data and baseline characteristics will be described including age, time from diagnosis to treatment, RBC transfusion burden, complete blood counts (CBCs) (white blood cells [WBC], platelets, hemoglobin levels), ferritin level, relevant medical history, co-morbidities, previous treatment of MDS and response to previous treatments, current co-medications, morphology and cytogenetic results (MDS subtype, blast count, karyotype), and data on risk classifications (IPSS).

Study drug exposure

The primary objective of the study is to describe the pattern of use of lenalidomide in the clinical routine practice of MDS patients. The proportion of patients receiving lenalidomide outside of the EU approved indication will be provided and will be associated with its 2-sided 95% CI. For lenalidomide, indication for which lenalidomide is used and dosing including any adjustments will be summarised using descriptive statistics. Duration of dosing will be similarly summarised together with a summary of dosing interruptions. Duration of exposure and cumulative dose of lenalidomide will also be described. Data on the use of relevant concomitant medication will also be reported.

Safety analysis

Safety analyses will be based on both the on- and off-label cohorts.

The cumulative incidence of progression to AML will be descriptive and stratified according to risk factors; 95% CIs will be calculated for each of the two cohorts.

Each registry will be requested to produce Kaplan-Meier curves for on- and off-label patients separately and to calculate the hazard ratio of on- versus off-label patients. They will also be requested to perform multivariate analyses using a Cox model including and on-/off-label indication and prognostic factors as described in the Statistical Analysis Plan on their own individual data. The respective outcomes will be provided by each registry to the study sponsor. Safety for both on- and off-label cohorts will be determined based on the incidence and severity (using AE definitions from NCI CTCAE where feasible) of reported hematological and non-hematological adverse events, including SPM other than AML (which considered as disease progression in patients with MDS). In particular episodes of neutropenia, thrombocytopenia, venous thromboembolic events, infections, bleeding, major cardiac events and SPM will be collected throughout the retrospective observational period as part of the clinical routine.

As there is no international standard to define transfusion dependence and there is a risk of error in transfusion coding, an additional sensitivity analysis will be completed to assess the impact of transfusion on the size of the on- and off-label cohorts. This sensitivity analysis will describe the proportion of off-label patients based only on IPSS categories other than low and int-1, and any karyotype other than isolated del(5q).

All safety analyses will be mainly descriptive or explorative in nature.

Interim Descriptive Report:

An interim descriptive report was prepared 1 year after study start. Within the interim descriptive report, available data on eligible patients regarding the pattern of use of lenalidomide within and outside the EU approved indication, namely the distribution of MDS patients according to predefined categories (eg, transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q), or with additional cytogenetic abnormalities, or IPSS risk categories int-2 or high, or patients with MDS without del(5q)) was presented. On 29-Mar-2019, the first interim descriptive report was submitted to the PRAC in order to discuss if the data collected on lenalidomide use, across different groups of MDS patients, are sufficient to allow successful completion of this study. The Assessment Report adopted by the CHMP on 27-Jun-2019 included a request to submit another interim descriptive report in Quarter (Q)1 2020. On 27-Mar-2020, the second interim descriptive report was submitted to PRAC (EMEA/H/C/000717/ANX/041.8). The final Assessment Report, adopted by the CHMP on 10-Dec-2020, concluded that the post-authorisation measure for the second interim report was fulfilled with no further action required.

Sample Size Estimation:

The statistical analyses will be descriptive in nature, ie, no formal comparison will be made between patient populations exposed to lenalidomide within or outside the EU approved indication with regards to the safety of lenalidomide. The data on patients treated with lenalidomide for MDS will only be available within an EU country following EU approval for the MDS indication and once available in the selected data source. Therefore, this study will be limited to EU countries where lenalidomide became fully reimbursed for the MDS indication and the extent of data per country will be related to time since the EU-approval for the MDS indication and availability of data. The only exception is that eligible patients from the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) will be included regardless of start date of treatment for the assessment of the secondary safety objectives. The sample size of at least 460 patients is based on the proportion of off-label patients for describing the pattern of use of lenalidomide.

Feasibility assessments indicated that off-label use of lenalidomide in MDS in the EU is infrequent (5% to 22% with a large margin of error at either end). However, the second interim descriptive report submitted to PRAC on 27-Mar-2020 (EMEA/H/C/000717/ANX/041.8) showed a higher level of off-label use. The proportion of MDS patients treated in an off-label setting was high, with 57.0% of MDS patients treated off-label (n = 212) versus 40.1% of MDS patients treated on-label (n = 149), and 2.9% of patients with an unknown label status (n = 11). Assuming that the final percentage of off-label patients will be around 50%, a sample size of at least 460 patients will yield a 95% CI = (45.4%, 54.6%).

Assuming a proportion of around 50%, around 230 patients in the study will be off-label. Assuming the proportion of patients progressing to AML will be similar to those on-label, ie, 17%, 230 off-label patients will yield a 95% CI = (12.3%, 22.4%).

Milestones:

- Start of data collection: Q1 2018 (refers to study start)
- First interim descriptive report: 29-Mar-2019 (date of submission to PRAC, EMEA/H/C/000717/ANX/041.7)
- Second interim descriptive report: 27-Mar-2020 (date of submission to PRAC, EMEA/H/C/000717/ANX/041.8)
- Estimated end of data collection: Q2 2023 (to be confirmed once registries have updated their databases)
- Study progress reports: on request from PRAC/National Competent Authorities (NCAs)
  - Periodic Safety Update Reports (PSURs): As per PSUR cycle
  - Other study progress reports: on request from the PRAC/NCAs
- Final report of study results: Q2 2024

3 AMENDMENTS AND UPDATES

The following four updates to the original protocol were generated following input from the Pharmacovigilance Risk Assessment Committee (PRAC):

- Protocol Amendment No. 1 (Version 5.0) – dated 26-Oct-2017
- Protocol Amendment No. 1 (Version 4.0) – dated 07-Jul- 2017
- Protocol Amendment No. 1 (Version 3.0) – dated 14-Dec-2016
- Protocol Amendment No. 2 (Version 1.0) – dated 31-May-2021
- Protocol Amendment No. 3 (Version 1.0) – dated 21-Jul-2022

This protocol Amendment No. 3 (Version 2.0) – dated 10-Aug-2022 describes changes to the proposed sample size in light of a lower availability of patient data in the registries than expected, with minimal impact on the range of the confidence intervals. In addition, the date of eligibility

for patient data was changed from the date of reimbursement to the date of EU-approval for the MDS indication in the interest of further patient numbers. A clarification on the exclusion criteria was also included. Planned dates for milestones were adjusted for data collection and all dependent milestones to ensure that the final data transfer would not be collected before this amendment was approved.

4 MILESTONES

Milestones for this study are summarised in Table 2.

Table 2: Milestones

Milestone	Planned Date
Start of data collection[a]	Q1 2018[a]
First interim descriptive report	29-Mar-2019 (date of submission to PRAC, EMEA/H/C/000717/ANX/041.7)
Second interim descriptive report	27-Mar-2020 (date of submission to PRAC, EMEA/H/C/000717/ANX/041.8)
Estimated end of data collection	Q2 2023 (to be confirmed once registries have updated their databases)
Study progress report(s)	
PSUR	As per PSUR cycle
Other study progress reports	On request from PRAC/NCAs
Final report of study results	Q2 2024

EMEA = European Medicines Agency; NCA = National Competent Authority; PRAC = Pharmacovigilance Risk Assessment Committee; PSUR = Periodic Safety Update Report; Q1 = first quarter; Q4 = fourth quarter.

[a] Refers to study start

5 RATIONALE AND BACKGROUND

5.1 Rationale

Revlimid (lenalidomide) is a drug belonging to the proprietary series of drugs with immunomodulatory and other properties, and is currently registered in several countries worldwide, including the EU, for the treatment of multiple myeloma in combination with dexamethasone in adult patients who had received at least one previous therapy, for the treatment of adult patients with previously untreated MM who are not eligible for transplant, and for the treatment of adult patients with relapsed or refractory mantle cell lymphoma. Lenalidomide also is licensed in more than 20 countries including the United States (US), Australia, Japan, New Zealand, Israel, and Switzerland for the treatment of transfusion-dependent anaemia due to International Prognostic Scoring System (IPSS) low- or intermediate-1 (int-1)-risk MDS with deletion 5q (del(5q)), with or without additional cytogenetic abnormalities. In the EU, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive Opinion on 25-Apr- 2013 for the use of Revlimid in the "treatment of transfusion-dependent anaemia due to low- or int-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other

therapeutic options are insufficient or inadequate," variation EMEA/H/C/717/II/056. The European Commission (EC) Decision was adopted on 13-Jun-2013 based on a condition to the EU marketing authorisation for the Marketing Authorisation Holder (MAH) to implement a non-interventional post-authorization safety study (PASS) (Revlimid, Annex IID to the EC Decision). As per the condition to the marketing authorisation, the MAH implemented this retrospective study to describe the post-marketing pattern of use of lenalidomide in MDS, both within and outside of the EU approved indication.

This lenalidomide retrospective study will also aim to gather additional safety information among MDS patients treated with lenalidomide outside the EU approved indication including the risk of progression to acute myeloid leukemia (AML) in a routine-care setting, depending on both sufficient patient numbers and availability of data within the selected data sources.

5.2 Background

The target population of lenalidomide in MDS with del(5q) has for a long time been erroneously identified with the so-called "del(5q) syndrome," first described by Van den Berghe in 1974 (Van den Berghe, 1974), and characterized by refractory macrocytic anemia, normal or elevated platelet counts associated with erythroid hypoplasia, dyserythropoiesis, modest excess of myeloblasts, hypolobulated megakaryocytes, and del(5q) in the presence of an otherwise normal karyotype. This syndrome is prevalent in females and has a low propensity to evolve into AML. In a case-series from the Düsseldorf MDS Registry, the cumulative incidence of AML among patients with the del(5q) syndrome was reported to be 8% (Germing, 2000). In contrast to patients with the "del(5q) syndrome," patients with IPSS low-/int-1–risk MDS with del(5q) also have well-defined additional risk factors such as additional cytogenetic abnormalities (Schanz, 2012), excess blasts (5% to 10%), severe anemia, and transfusion dependency (Malcovati, 2006; Malcovati, 2011). Depending on the presence of additional risk factors, the survival of these patients can be as low as 7 months.

Patients with del(5q) and complex karyotype have a very high risk of leukemic progression when compared to patients with isolated del(5q) or del(5q) + 1 additional cytogenetic abnormality. In a series of 541 patients with MDS and del(5q), patients with isolated del(5q) had a time to 25% probability of AML transformation of 65 months compared to the same rate of AML transformation of 14.9 months for patients with del(5q) + 1 additional cytogenetic abnormality and of only 4.7 months for patients with a complex karyotype (Mallo, 2011).

Data from the most complete series of untreated IPSS low- or int-1–risk MDS patients with del(5q) with survival data available was published by the Düsseldorf MDS group, who describe the natural history of the disease in a cohort of 381 patients included in the disease registry and treated only with supportive care (Germing, 2012). Patients with transfusion dependence had a 2-year cumulative risk of AML of 4.9% and a 5-year AML risk of 17.6%, higher than the figure previously reported by the same group for the "del(5q) syndrome."

In the seminal Phase 2, uncontrolled study (MDS-003) conducted in patients with low- or int-1–risk MDS del(5q) and transfusion dependence (median of 6 red blood cell [RBC] transfusions in the 8 weeks preceding study entry), patients were treated with lenalidomide at the

initial dose of 10 mg/day for 21 days (46 patients) or 28 days (102 patients) of each 28-day cycle (List, 2006). Seventy-six percent of 148 patients included in the study had a significant improvement of transfusion dependence and 67% of patients became transfusion independent. The median time to response to lenalidomide was rapid (4.6 weeks) and sustained; the median duration of transfusion independence was not achieved at the time of the primary publication, after a median follow-up of 104 weeks. The median increase in hemoglobin levels compared to baseline values was 5.4 g/dL. Thrombocytopenia and an increased transfusion need at study inclusion were predictive factors of no response.

Eighty-five patients were evaluable for the cytogenetic response (at least 20 cells in metaphase available both at study entry and after 24 weeks); of them 45% had a complete cytogenetic response, and 28% a partial cytogenetic response (decrease ≥ 50% of the initial del(5q) clone size) (List, 2006).

A recent randomized, placebo-controlled, double-blind, Phase 3 study (MDS-004) compared 2 different initial regimens of lenalidomide (respectively 10 mg/day for 21/28 days and 5 mg/day continuously, in 28-day cycles) with placebo (Fenaux, 2011). After 16 weeks of double-blind treatment, patients who did not have at least a minor erythroid response (50% or greater reduction in transfusion numbers, compared to baseline) could interrupt the double-blind phase and continue the treatment with active drug in an open-label phase. The vast majority of patients initially allocated to placebo (except for 11 patients) crossed over to the active drug after 16 weeks. For all patients, the double-blind phase was interrupted after 52 weeks, and the study continued as open-label for up to 156 weeks (3 years). The primary endpoint was the transfusion independence maintained for at least 26 weeks (according to the International Working Group [IWG] criteria [Cheson, 2006]), and secondary endpoints were rate of erythroid response, cytogenetic response, overall survival (OS), rate of progression to AML, safety, and Health--related Quality of Life (HRQoL).

During the double-blind phase, 56.1% and 42.6% of patients allocated to lenalidomide 10 mg and 5 mg, respectively, compared with 5.9% of placebo patients met the primary endpoint of transfusion independence, maintained for at least 26 weeks (Fenaux, 2011). Responding patients had rapid (more than 80% of responding patients responded during Cycles 1 and 2) and long-lasting responses (the median duration of response was not yet achieved at the time of primary data publication). Similar to what had been observed in the previous Phase 2 trial (List, 2006), both lenalidomide treatment and platelets levels (platelets ≥ 150×10^9/L) were independently associated with the achievement of transfusion independence (Fenaux, 2011). Cytogenetic response was 50% and 25% for patients treated with lenalidomide 10 mg and 5 mg, respectively, and the respective rate of complete cytogenetic response was 29.4% and 15.6%. Quality of life measured with the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire at Week 12 was significantly improved compared with baseline values in patients who received lenalidomide compared to those who received placebo.

The study confirmed the tolerability profile of lenalidomide in MDS with del(5q) (Fenaux, 2011). The most frequently reported adverse events (AEs) (Grade 3 and 4 according to the National

Cancer Institute (NCI) Common Toxicity Criteria [CTC]) were deep vein thrombosis (6 cases), neutropenia, and thrombocytopenia and were more common during Cycles 1 and 2.

Overall, 52 patients (24.2%) had progression to AML; of these 4/11 (36.4%) were randomized to placebo, 17/56 (30.4%) initially randomized to placebo then crossed over to lenalidomide after 16 weeks, 16/67 (23.2%) were treated in the 5 mg arm, and 15/67 (21.7%) were treated in the 10 mg arm (Fenaux, 2011). The 2-year cumulative risk of AML progression in the combined lenalidomide arms was 16.8% (95% confidence interval [CI] = 9.8 to 23.7). Responding patients (transfusion independence maintained for 8 weeks or more) had a significantly lower cumulative risk of progression to AML. Median survival was 42.2 months, 35.5 months, and 44.4 months, respectively, for placebo, lenalidomide 5 mg, and lenalidomide 10 mg; transfusion independence for 8 or more weeks was associated with a 42% reduction in the risk of progression to AML and 47% reduction in the risk of death.

Lenalidomide and Risk of AML Progression in Patients with Transfusion-dependent IPSS Low- or Int-1–Risk MDS Del(5q)

A retrospective analysis was published (Kuendgen, 2012a) comparing the risk of progression to AML and OS in patients treated with lenalidomide (from Studies MDS-003 and MDS-004 combined (Fenaux, 2011; List, 2006) with that of similar patients from the Düsseldorf MDS Registry (previously described) who never received lenalidomide (Germing, 2012). The comparative study included only patients with transfusion-dependent anemia without concomitant thrombocytopenia (< 50,000/μL) or neutropenia (< 500/μL) to have comparable populations. Overall, the 2 cohorts included 295 lenalidomide-treated and 125 untreated patients.

To account for differences in person-time at risk in these 2 cohorts due to different starting points for follow-up (from diagnosis in the untreated cohort versus inclusion in the study for the treated cohort), *left truncation* was considered appropriate and adopted for all analyses in this study. The 2 cohorts were well balanced, except for a higher transfusion need for treated versus untreated patients (median of 6 versus 2 units of RBC/8 weeks); higher transfusion dependence is a well-known risk factor for progression to AML and reduced survival (Malcovati, 2006).

Based upon the competing-risk estimator with left truncation, the 2-year cumulative incidence of progression to AML was 6.9% and 12.1% for the cohort of treated versus untreated patients, respectively; the respective 5-year cumulative incidence was 22.8% and 19.9% (Kuendgen, 2012a). Two-year survival was 89.9% versus 74.4% in treated versus untreated patients. After adjustment for covariates, the risk of progression to AML was similar in the 2 cohorts (hazard ratio [HR] = 0.969), while the risk of death was significantly reduced in the lenalidomide-treated cohort (HR = 0.597, p = 0.012). The authors concluded that the treatment of patients with low- or int-1–risk MDS and del(5q) with lenalidomide did not increase the risk of progression to AML, but it possibly conferred a survival benefit in RBC transfusion-dependent patients with del(5q) low- or int-1–risk MDS.

A similar study previously compared the time to AML progression and survival in 95 low- or int-1–risk MDS del(5q) patients treated within the French ATU (Authorisation Temporaire d'Utilisation) cohort to 99 similar patients of the GFM (French MDS Group) who never received

lenalidomide (Adès, 2012). Two matched-pair cohorts were generated using a propensity score model to have comparable groups with similar baseline characteristics; again, to account for different timepoints of study entry in the 2 cohorts, this study also used the "left truncation" model. The 4-year estimated cumulative incidence of AML was 9% in patients treated with lenalidomide and 15.8% in controls who did not receive lenalidomide (p = 0.16).

Median survival after diagnosis was 150 months in the 71 patients treated with lenalidomide compared to 78 months in the 71 matched controls (HR = 0.47; 95% CI = 0.23 to 1.01; p = 0.06) (Adès, 2012). The 4-year survival after treatment onset was 67% in patients treated with lenalidomide and 73% in untreated patients (p = 0.15). Based on study results, the authors concluded there was no significant difference in AML progression and survival from diagnosis between the cohort treated with lenalidomide and the control cohort.

Thus, the data available so far suggest there is no increased risk of AML progression in patients with MDS del(5q) treated with lenalidomide compared to patients who never received the drug. However, due to the retrospective nature of those studies and the existing confounding factors, as well as the lack of a prospective, long-term, placebo-controlled, randomized clinical trial, it was not possible to understand whether the incidence of progression to AML reported in clinical trials was solely part of the natural history of the disease or if there also was a causal relationship between the administration of lenalidomide and progression to AML.

The MAH is, therefore, conducting a post-authorisation prospective disease registry in transfusion-dependent, IPSS low- or int-1-risk MDS with isolated del(5q) (Study MDS-010). The primary objective will be to ascertain if the true rate of AML progression in these patients treated with lenalidomide in the routine-care setting is similar to what has been previously reported in clinical trials and in existing disease registries and to detect any significant difference in progression to AML according to baseline risk factors compared to what was previously reported.

However, since the PRAC was also interested to know the pattern of use of lenalidomide in MDS both within and outside the EU approved indication in MDS, this additional specific retrospective drug-utilisation study has been designed. This study will collect retrospective information on the indication(s) of use of lenalidomide in MDS and will also enable a description of the safety of the drug outside EU the approved indication in MDS (ie, in patients with any type of MDS other than transfusion-dependent International Prognostic Scoring System [IPSS] low- or intermediate-1 [int-1]-risk MDS with isolated del(5q)).

With these two non-interventional MDS post-authorisation safety studies, the MAH is meeting its obligation as outlined in the condition to Marketing Authorisation in Annex IID of the Revlimid Product Information – "to gather safety data on the use of lenalidomide in MDS patients and monitor off-label use".

6 RESEARCH QUESTION AND OBJECTIVES

6.1 Research Question

The primary research question of this retrospective drug-utilisation study is to describe the pattern of use of lenalidomide in the clinical routine practice of MDS in countries of the EU in which

Revlimid (lenalidomide) is marketed for *the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate* and where these patients have access to the drug post EU-approval for the MDS indication.

The study will also allow the collection of further information regarding the safety of lenalidomide within and outside of the EU approved indication (ie, in patients with any type of MDS other than transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q)).

6.2 Research Objectives

6.2.1 Primary Objective

- To describe the pattern of use of lenalidomide in the clinical routine practice of MDS patients in the countries concerned

6.2.2 Secondary Objectives

- To further describe the safety of lenalidomide both within the EU approved indication [on-label cohort] and outside of the EU approved indication (ie, in patients with any type of MDS other than transfusion-dependent International Prognostic Scoring System [IPSS] low- or intermediate-1 [int-1]-risk MDS with isolated del(5q)) [off-label cohort], in terms of:
  - progression to AML
  - hematological and non-hematological adverse events, including infections, bleeding, thromboembolic events
  - major cardiac events and second primary malignancies (SPM) other than AML (which is considered as disease progression in patients with MDS)
  - evaluation of risk factors collected in the routine-care setting associated with progression to AML among MDS patients treated with lenalidomide within and outside of the EU approved indication, dependent on both sufficient patient numbers and availability of data within the selected data sources

7 RESEARCH METHODS

7.1 Study Design and Selection Criteria

7.1.1 Study Design

This is a post-authorisation, non-interventional, retrospective, drug-utilisation study. This study will be run in countries in the EU in which Revlimid (lenalidomide) will have been marketed in the new indication and where MDS patients will have access to the drug post EU-approval for the MDS indication. The only exception is that eligible patients from the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) will be included regardless of start date of treatment to assess the secondary safety objectives (but not the primary drug-utilisation objective due to a different MDS indication approved in the US [see Section 7.4 for the US MDS approved indication]). Results from the selected data sources that represent at least 10 EU

countries, which have lenalidomide reimbursement, will be included. More EU countries will potentially be included, once they gain reimbursement.

This retrospective drug-utilisation study will include patients with MDS treated with lenalidomide, irrespective if within or outside the approved indication in the EU (eg, patients commencing lenalidomide treatment for transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q) or with additional cytogenetic abnormalities, or IPSS risk categories int-2 or high, or patients with MDS without del(5q) will also be recorded). Both prevalent and incident MDS cases, defined as follows, are eligible for the inclusion into the retrospective drug-utilisation study:

Prevalent patients: patients whose initial MDS diagnosis is **prior** to the date of EU-approval for the MDS indication, but whose initiation of lenalidomide treatment occurs on or after the date of EU-approval for the MDS indication.

Incident patients: patients whose initial MDS diagnosis and initiation of treatment with lenalidomide is **after** the date of EU-approval for the MDS indication.

The sources of data for this study are described in Section 7.4.

The study is planned to collect retrospective data from subjects with MDS treated with lenalidomide according to the inclusion criteria, until at least 460 patients are included.

An interim descriptive report was prepared 1 year after study start. Within the interim descriptive report, available data on eligible patients regarding the pattern of use of lenalidomide within and outside the EU approved indication, namely the distribution of MDS patients according to predefined categories (eg, transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q), or with additional cytogenetic abnormalities, or IPSS risk categories int-2 or high, or patients with MDS without del(5q)) was presented. On 29-Mar-2019, the first interim descriptive report was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) in order to discuss if the data collected on lenalidomide use, across different groups of MDS patients, are sufficient to allow successful completion of this study. The Assessment Report adopted by the CHMP on 27-Jun-2019 included a request to submit another interim descriptive report in Quarter (Q)1 2020. On 27-Mar-2020, the second interim descriptive report was submitted to PRAC (EMEA/H/C/000717/ANX/041.8). The final Assessment Report, adopted by the CHMP on 10-Dec-2020, concluded that the post-authorisation measure for the second interim report was fulfilled with no further action required.

The final data analysis will occur after at least 460 patients have been included and will be based on data from all eligible patients available at that time.

Data will be collected for both on- and off-label patients, to cover the period from date of first lenalidomide dose (baseline) until the date of death or last follow-up available at the time of the retrospective data collection (whichever occurs first) including for patients lost to follow-up or who discontinue the drug for any reason. Data collected at baseline will include those data that could have been generated earlier but are relevant at the baseline date (for example, information related to diagnosis).

Time to progression to AML or time to any other kind of event will be counted from the date of first lenalidomide dose (baseline).

7.1.2 Selection Criteria

7.1.2.1 Inclusion Criteria

- Patients with MDS commencing their treatment with lenalidomide after the granting of Regulatory approval for use in the treatment of MDS in the EU (EC Decision, 13-Jun-2013) and a subsequent positive reimbursement decision in the countries concerned, irrespective if the initial MDS diagnosis occurred before (prevalent patients) or after (incident patients) such date with the exception of eligible patients from the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) who will be included regardless of start date of treatment
- Laboratory confirmation (morphological and cytogenetic) of MDS
- Patients with confirmed date of MDS diagnosis and lenalidomide treatment initiation
- Obtaining appropriate permission from the selected data sources to utilise the data

7.1.2.2 Exclusion Criteria

- Patients receiving lenalidomide prior to regulatory approval for use in the treatment of MDS in the EU (EC Decision, 13-Jun-2013) in the countries concerned
- Patients treated with lenalidomide in an interventional therapeutic clinical trial for MDS

7.2 Setting

7.2.1 Study Population and Cohorts

Overall population: Those MDS patients who have received at least one dose of lenalidomide and who started their treatment after lenalidomide has obtained EU Regulatory approval for the MDS indication and in countries that granted a subsequent positive reimbursement decision with the exception of eligible patients from the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) who will be included regardless of start date of treatment.

This population will include both prevalent (patients whose initial MDS diagnosis is **prior** to the date of EU-approval for the MDS indication, but whose initiation of lenalidomide treatment occurs on or after the date of EU-approval for the MDS indication) and incident patients (patients whose initial MDS diagnosis and initiation of treatment with lenalidomide is **after** the date of EU-approval for the MDS indication).

MDS licensed indication cohort (ie, on-label cohort): All patients with transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q) in the EU who started their treatment after lenalidomide has obtained EU Regulatory approval for the MDS indication and in countries that gave a subsequent positive reimbursement decision.

Other MDS indication cohort (ie, off-label cohort): All patients with any type of MDS other than transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q) in the EU who

started their treatment after lenalidomide has obtained EU Regulatory approval for the MDS indication and in countries that gave a subsequent positive reimbursement decision with the exception of eligible patients from the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) who will be included regardless of start date of treatment.

7.3 Variables

Variables to be considered in this analysis as baseline, exposure, treatment, and outcome variables are described in Table 3 (demographic and clinical variables), Table 4 (lenalidomide therapy and other treatment variables), and Table 5 (outcome variables for safety).

The following data variables will be collected from the registries according to local medical practice and availability of data.

Table 3: Demographics and Clinical Variables for Both On- and Off-label Cohorts

Variables[a]	
Demographics	
Age	Age
Sex	Male/female
Country	Country
Clinical Variables (Baseline Characteristics)	
Date of MDS Diagnosis	Date of initial MDS diagnosis
Date of First Dose of Lenalidomide	Date of first record of lenalidomide treatment initiation
Cytogenetic Abnormalities[b]	Karyotype information, method of diagnosis
Prior invasive malignancy	Yes/No and date/type of previous malignancy, previous therapy (yes/no/unknown for surgery, radiation, chemotherapy)
Bone Marrow and Peripheral Blood Morphology	Bone marrow blast count (%) – at baseline and until disease progression; other bone marrow findings according to the WHO classification: dysplasia by lineage, ringed sideroblasts/erythroid precursors, and Auer rods at baseline
Transfusion Burden	Transfusion burden (units/8 weeks); before lenalidomide treatment initiation and until PD or last follow-up date
Hemoglobin Level	Hemoglobin level; at baseline and every 6 months until PD or last follow-up date
Ferritin level	Ferritin level; at baseline
Platelet Count	Platelet count; at baseline and every 6 months until PD or last follow-up date
Neutrophil Count	Neutrophil count; at baseline and every 6 months until PD or last follow-up date
Endogenous EPO Level	EPO level; at baseline
Risk Classification	Classification as per IPSS

Table 3: Demographics and Clinical Variables for Both On- and Off-label Cohorts

Variables[a]	
Relevant Medical History	Prior history of cardiovascular events (eg, angina/coronary artery disease, MI, CHF, arrhythmia, hypertension, peripheral arterial disease, cerebrovascular event); thromboembolic events (VTEs); pulmonary, hepatic, pancreatic or renal disease; diabetes; prior invasive malignancy, prior NMSC; past life-threatening illness in other organ system.
Comorbidities	Current cardiovascular or cerebrovascular disease, chronic VTE, current pulmonary, hepatic, pancreatic or renal disease, diabetes, current life-threatening illness in other organ system

CHF = congestive heart failure; EPO = erythropoietin; EU = European Union; IPSS = International Prognostic Scoring System; IPSS-R = revised IPSS; MDS = myelodysplastic syndromes; MI = myocardial infarction; NMSC = non-melanoma skin cancer; PD = progression of disease; VTE = venous thromboembolic event; WHO = World Health Organization,

[a] As far as available in data sources and as per clinical practice

[b] Cytogenetic risks will be categorized as described in the new cytogenetic scoring system (Schanz, 2012) that has been integrated into the IPSS-R (Greenberg, 2012).

Table 4: Therapy and Other Treatment Variables for Both On- and Off-label Cohorts

Variables[a]	
Lenalidomide Treatment	Indication of use, starting dose, dose adjustments, dose interruptions
Other MDS medications	Current use (yes, no); dose, response, duration of use
Prior ESA Treatment	Prior use (yes, no); prior response (yes/no), most recent treatment, duration of treatment
Other Prior MDS Treatments	Prior use (yes, no); prior response (yes/no), most recent treatment, duration of treatment
Concurrent ESA Use	Current use (yes, no); dose, response, duration of use
Concomitant Medications	Concomitant medications, duration of treatment
RBC transfusion	Yes/no, number of units over last 8 weeks (baseline and until PD)

Con = concomitant; ESA = erythropoiesis-stimulating agent; MDS = myelodysplastic syndromes; Meds = medications; PD = progression of disease; RBC = red blood cell.

[a] As far as available in data sources and as per clinical practice

Table 5: Outcome Variables for Safety for Both On- and Off-label Cohorts

Variables[a]	
Progression to AML[b]	Yes/no, date of event, and method of documentation
Death	Date and cause of death, and method of documentation
Adverse Events	Date of event (incidence) (using case definitions from NCI CTCAE where feasible) of hematologic and non-hematologic adverse events, including but not limited to neutropenia, thrombocytopenia, VTEs, infections, bleeding, and major cardiac events
SPM (Invasive [hematologic and solid tumors] and NMSC)[c]	Yes/no, date of event, and method of documentation

AML = acute myeloid leukemia; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; NMSC = non-melanoma skin cancer; SPM = second primary malignancy; VTE = venous thromboembolic event.

[a] As far as available in data sources and as per clinical practice

[b] Vardiman, 2009.

[c] Not including AML, which is considered disease progression in patients with myelodysplastic syndromes.

7.4 Data Sources

Celgene assessed the feasibility of this protocol using various potential data sources across the EU for the identification of off-label prescriptions and existence of longitudinal data to measure long-term outcomes of patients with MDS, including progression to AML. The sources of data for the primary drug-utilisation objective and the secondary safety objectives in this study will include, but will not be limited to:

- the existing academic EUMDS Registry
- the Spanish Registry of MDS or RE SMD (registro español de síndromes mielodisplásicos), coordinated by the Spanish Group of MDS [GESMD] who aims to promote and develop primary research on MDS, bringing together all those involved in research, diagnosis and management of patients with MDS.
- the Düsseldorf MDS Registry, who aims, as best possible, to biologically characterize MDS, anticipate the course of the disease, and find the most suitable therapies as a benefit for all MDS patients
- the online French Registry of MDS, coordinated by the French MDS group [GFM]), a non-profit organization that includes most French haematology centres, several of them registered as centres of excellence of the International MDS Foundation
- the Danish National Acute Leukemia Registry.

Additionally, the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) will be used to address the secondary safety objectives (but not the primary drug-utilisation objective due to a different MDS indication approved in the US, which is for the treatment of patients with *transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes [MDS] associated with a deletion 5q abnormality with or without additional*

cytogenetic abnormalities). The company-sponsored Connect® Myeloid Disease Registry is a non-interventional, prospective, longitudinal, observational, multicenter, US cohort registry study of patients with confirmed cases of newly diagnosed MDS, idiopathic cytopenia of undetermined significance, and AML.

A limitation of the selected EU data sources is that they collect data only from specific countries or patient catchment areas, hence they cannot provide complete representation of the actual real-world European drug-utilisation patterns. However, the EUMDS Registry captures high quality data from 17 EU countries, and it will be used to mitigate this limitation. Of these 17 countries in the selected data sources, results will be included from at least 10 EU countries that have lenalidomide reimbursement for the MDS indication. More EU countries will potentially be included, once they gain reimbursement for the MDS indication. In addition, the Spanish Registry of MDS, the Düsseldorf MDS Registry, the online French Registry of MDS, and the Danish National Acute Leukemia Registry will provide a comprehensive coverage of MDS patients in these four countries to complement the data in the EUMDS Registry. Adjustments will be made for any patients in the four national registries that overlap with patients in the EUMDS Registry.

Operational definition of variables will be consistent regardless of the data source.

To protect privacy and according to the local regulations, analysis of study endpoints will be conducted using aggregated data (majority of analyses) or performed by the local registries (Kaplan-Meier and multivariate analyses). To do the analyses which are based on aggregated data, datasets limited to the necessary variables will be compiled from pseudonymized datasets provided to the sponsor by each registry, and processed in accordance with the applicable regulations regarding privacy protection.

7.5 Study Size

The study population will be composed of at least 460 patients with MDS treated with lenalidomide after the granting of Regulatory approval of Revlimid (lenalidomide) for use in the treatment of MDS in the EU (EC Decision, 13-Jun-2013) in the countries concerned. The final data analysis will include all patients eligible for this study at the end of data collection.

An interim descriptive report was prepared 1 year after study start. Within the interim descriptive report, available data on eligible patients regarding the pattern of use of lenalidomide within and outside the EU approved indication, namely the distribution of MDS patients according to predefined categories (eg, transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q), or with additional cytogenetic abnormalities, or IPSS risk categories int-2 or high, or patients with MDS without del(5q)) was presented. On 29-Mar-2019, the first interim descriptive report was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) in order to discuss if the data collected on lenalidomide use, across different groups of MDS patients, are sufficient to allow successful completion of this study. The Assessment Report adopted by the CHMP on 27-Jun-2019 included a request to submit another interim descriptive report in Quarter (Q)1 2020. On 27-Mar-2020, the second interim descriptive report was submitted to PRAC (EMEA/H/C/000717/ANX/041.8). The final Assessment Report, adopted by the CHMP on

10-Dec-2020, concluded that the post-authorisation measure for the second interim report was fulfilled with no further action required.

The data on patients treated with lenalidomide for MDS will only be available within a country following EU-approval of the product for the MDS indication and once available in the selected data source. Therefore, this study will be limited to countries that gave a subsequent decision to fully reimburse lenalidomide for the MDS indication and the extent of data per country will be related to time since the EU-approval for the MDS indication and availability of data with the exception of eligible patients from the company-sponsored Connect® Myeloid Disease Registry (US Cohort Registry) who will be included regardless of start date of treatment (see Section 7.4 [Data Sources]).

This retrospective drug-utilisation study will include patients with MDS treated with lenalidomide, irrespective if within or outside the approved indication in the EU (eg, patients commencing lenalidomide treatment for transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q), or with additional cytogenetic abnormalities, or IPSS risk categories int-2 or high, or patients with MDS without del(5q) will also be recorded).

The primary objective of the study is to evaluate the proportion of patients outside of the EU approved indication (off-label). Feasibility assessments indicated that off-label use of lenalidomide in MDS in the EU is infrequent (5% to 22% with a large margin of error at either end). However, the second interim descriptive report submitted to PRAC on 27-Mar-2020 (EMEA/H/C/000717/ANX/041.8) showed a higher level of off-label use. The proportion of MDS patients treated in an off-label setting was high, with 57.0% of MDS patients treated off-label (n = 212) versus 40.1% of MDS patients treated on-label (n = 149), and 2.9% of patients with an unknown label status (n = 11). Assuming that the final percentage of off-label patients will be around 50%, a sample size of 460 patients will yield a 95% CI = (45.4%, 54.6). The sample size calculated would not only allow to investigate this assumption, but also will detect smaller percentages if the true proportion would be smaller.

Assuming a proportion of around 50%, around 230 patients in the study will be off-label. Assuming the proportion of patients progressing to AML will be similar to those on-label, ie, 17%, 230 off-label patients will yield a 95% CI = (12.3%, 22.4%).

7.6 Data Management

Study Monitoring and Source Data Verification

The data is in this study will be owned by the data owners including, but not limited to, the data sources described in Section 7.4. All individual data management, data security, and data protection requirements will be the responsibility of the data owners (ie, registries). For all results provided to Celgene, security of the results will be maintained at all times in line with applicable local law and procedures. Access to results will be limited to authorised individuals. Controls, such as document encryption, will be used to ensure the authenticity, integrity, and confidentiality of electronic records when transmitted over open systems (eg, the internet). Adequate back up of the data will be maintained throughout the course of the study.

The management of missing data as potential sources of study biases will be done when analyzing the distribution of available data on eligible patients and the outcomes from longitudinal follow-up, as described in Section 7.9 "Limitations of the Research Method".

The data required for classifying patients as on- or off-label are critical to satisfy the primary objective of this study. An attempt will be made to obtain values when data are missing. However, if data cannot be found to classify lenalidomide patient as on- or off-label, that patient cannot be classified and will be dropped from the primary analysis.

For the analyses of time to progression to AML (Kaplan-Meier and multivariate analyses adjusted for confounding and risk factors) to be performed at the end of study, data owners will be provided with instructions and will be requested to perform this analysis on an individual registry basis. This approach will ensure that all data have appropriate legal and data protection requirements fulfilled. All such data will be pseudonymized by the registries and processed in accordance with local regulations regarding privacy protection.

7.7 Data Analysis

The following analyses will be performed according to the availability of data from the data sources.

An overview of study analyses is included in this section. A detailed Statistical Analysis Plan (SAP) will be developed after approval of the final study protocol. For the aggregated data analyses, detailed statistical framework documents will be provided to all data owners to ensure a consistent approach.

In general, continuous variables will be summarised using descriptive statistics (mean, standard deviation, median, minimum, and maximum), while categorical variables will be summarised using frequency and percentages.

Due to the secondary use of the data, raw data will not be edited in individual listings, but aggregated data will be used according to the data source.

7.7.1 Demographic Data and Baseline Characteristics

Measures to characterize the MDS population exposed to lenalidomide and to study events of interest will include:

- Demographic data and baseline characteristics, which will be described including age, time from diagnosis to treatment, RBC transfusion burden, complete blood counts (CBCs) (white blood cells [WBC], platelets, hemoglobin levels), ferritin level, relevant medical history, co-morbidities, previous treatment of MDS and response to previous treatments, current co-medications

7.7.2 Descriptive Analyses of Lenalidomide Use Patterns in Routine Clinical Practice

The number and percent of MDS patients (both prevalent and incident) who have received at least one dose of lenalidomide will be characterized as in the labeled indication (ie, transfusion-dependent IPSS low- or int-1-risk MDS with an isolated del(5q) cytogenetic

abnormality) or outside of the EU labeled indication (ie, patients with any type of MDS other than transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q)). The rate of patients treated for MDS outside of the EU approved indication (off-label), will be provided with its 95% CI. MDS patients who are outside of the labeled EU indication will be further characterized as to the following:

- IPSS Status (Int-2 or High).
- Presence of additional cytogenetic abnormalities (yes/no) and characterization of type of additional cytogenetic abnormalities based upon the Revised International Prognostic Scoring System (IPSS-R) classification.
- Lack of documentation of transfusion-dependent status or documentation of transfusion burden insufficient to meet accepted criteria for transfusion-dependence.

It is acknowledged that patients who are out of the labeled indication may satisfy more than one of the disqualifying criteria. For the purpose of the current retrospective MDS PASS, transfusion-dependence is defined as requiring ≥ 2 RBC units over an 8-week period prior to the date of the first dose of lenalidomide treatment (due to MDS-related causes and not because of hemorrhage, trauma, or other acute cause).

In addition, patients within and outside the EU labeled indication will be characterized as to other demographic and clinical characteristics (ie, age, gender, duration of MDS, CBCs [WBC, platelets, hemoglobin levels], ferritin level, time from diagnosis to treatment, and RBC transfusion burden), relevant medical history, co-morbidities, previous MDS treatments, and current co-medications.

7.7.3 Safety Analyses

Safety analyses will be based on both the on- and off-label cohorts.

The cumulative incidence of progression to AML will be calculated and stratified according to predictive factors; 95% CIs will be calculated for each of the two cohorts. Aggregated data will be listed by country when possible.

Each registry will be requested to produce Kaplan-Meier curves for on- and off-label patients separately and to calculate the hazard ratio of on- versus off-label patients. They will also be requested to perform multivariate analyses using a Cox model including and on-/off-label indication and prognostic factors as described in the Statistical Analysis Plan on their own individual data. The respective outcomes will be provided by each registry to the study sponsor. Safety for the on- and off-label cohorts will be determined based on the incidence of reported hematological and non-hematological adverse events including SPM other than AML (which is considered as disease progression in patients with MDS). In particular episodes of neutropenia, thrombocytopenia, venous thromboembolic events, infections, bleeding, major cardiac events and SPM will be collected throughout the observational period of a patient in both cohorts as part of the clinical routine.

Due to the secondary use of the data, individual data may not be available. In these conditions, no explorative analyses on confounding or risk factors is foreseen in the protocol, except for progression to AML.

As there is no international standard to define transfusion dependence and there is a risk of error in transfusion coding, an additional sensitivity analysis will be completed to assess the impact of transfusion on the size of the on- and off-label cohorts. This sensitivity analysis will describe the proportion of off-label patients based only on IPSS categories other than low and int-1, and any karyotype other than isolated del(5q).

All safety analyses will be mainly descriptive or explorative in nature.

7.7.4 Interim Descriptive Report

An interim descriptive report was prepared 1 year after study start. Within the interim descriptive report, available data on eligible patients regarding the pattern of use of lenalidomide within and outside the EU approved indication, namely the distribution of MDS patients according to predefined categories (eg, transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q), or with additional cytogenetic abnormalities, or IPSS risk categories int-2 or high, or patients with MDS without del(5q)) was presented. On 29-Mar-2019, the first interim descriptive report was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) in order to discuss if the data collected on lenalidomide use, across different groups of MDS patients, are sufficient to allow successful completion of this study. The Assessment Report adopted by the CHMP on 27-Jun-2019 included a request to submit another interim descriptive report in Quarter (Q)1 2020. On 27-Mar-2020, the second interim descriptive report was submitted to PRAC (EMEA/H/C/000717/ANX/041.8). The final Assessment Report, adopted by the CHMP on 10-Dec-2020, concluded that the post-authorisation measure for the second interim report was fulfilled with no further action required.

7.8 Quality Control

See Section 7.6 for the subsection on Study Monitoring and Source Data Verification.

7.9 Limitations of the Research Methods

A drug-utilisation study of lenalidomide in the commercial setting is an important addition to the pharmacovigilance activities for evaluating the safety and use of lenalidomide. This proposed retrospective drug-utilisation study will help determine the extent of use of lenalidomide in MDS by cohort (on-label, off-label, and overall). This will provide valuable information by which to determine the number and type of patients who are being treated outside of the EU approved indication and the consequences of such lenalidomide prescribing vis-à-vis the safety profile of the drug.

To provide a representative analysis of the European population, the study will include information from at least 10 EU countries that have lenalidomide reimbursement for the MDS indication, including data from the EUMDS Registry (de Swart, 2015). More EU countries will potentially be included, once they gain reimbursement for the MDS indication. As data collection for this study is retrospective and relies on existing data sources, there is a significant risk that there will be

missing information. To address this, a common set of variables and other data elements will be defined and will be the same across all sources. This will also facilitate the pooling of aggregated data for analysis. Pooling of raw data is not feasible because raw data will be held by the data owners (ie, data sources in Section 7.4).

Since this study is retrospective and based on secondary data that were collected in several registries, these registries may differ by their initial purpose, the characteristics of their patient populations and availability of some information. The sponsor will define and standardize the criteria for data use both in the aggregated datasets and in the pseudonymized datasets; however, it is expected that a level of inter-registry heterogeneity will exist, which may be a consideration for the meta-analyses. Consequently, the interpretation of results will be made with caution and consider important differences across the original data sources.

Assessing the safety of lenalidomide in a retrospective study will encounter the same lost-to-follow-up issues common to all follow-up studies. A comparison of baseline and treatment characteristics between patients who are and are not lost to follow-up as they were followed in the registry (or other data sources) will enable this form of selection bias to be evaluated where applicable.

Because worsening MDS and/or AML progression may be associated with worsening symptomatology, patients with deteriorating MDS status may have shorter intervals between visits but an assessment of these time intervals will determine whether a delay in AML diagnosis may be affecting the results.

Specification of del(5q) status (isolated vs. other cytogenetic findings) confirmed through cytogenetic information obtained from the evaluation of bone marrow specimens is a mandated inclusion criterion for this study. The results of bone marrow procedures conducted at the local level are not mandated to be confirmed through central laboratory assessment as is commonly done in clinical trials. There remains a potential for misclassification of del(5q) MDS status if there is variability in the performance quality of individual cytogenetic laboratories. Poor review of cytogenetic materials is more likely to lead to failure to identify additional cytogenetic lesions than to identification of cytogenetic lesions that do not exist. Since patients with a greater number of cytogenetic abnormalities are known to have a greater AML progression risk, misclassification of cytogenetic status would bias upward the estimates of AML cumulative incidence and AML incidence rates. A similar problem could occur if blast counts are underestimated.

Random error related to any form of misclassification will result in loss of precision. A greater concern is that missing data may be related to patient characteristics. This can be evaluated in a number of ways (eg, through evaluating whether a certain magnitude of missingness at the variable or patient level is associated with specific study settings and/or patient types).

7.10 Other Aspects

Not applicable.

8 PROTECTION OF HUMAN SUBJECTS

In accordance with local regulations, the data sources' owners who will provide the patient records for this study will be asked to confirm that all required regulatory and ethical review requirements on data confidentiality have been completed prior to data use. To protect privacy, data will be pseudonymized by the registries and processed in accordance with local regulations regarding privacy protection.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Study MDS-012 is a retrospective drug-utilisation study that is based upon the secondary use of data. Reporting requirements for this non-interventional study are described in Module VI Good Pharmacovigilance Practices, VI.C.1.2.1. Non-interventional Studies. "Real-time" adverse reaction reporting is not required, as described in Good Pharmacovigilance Practices (Module VI) and in the relevant section within Module VIII on the PASS:

- "for non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. Reports of adverse events/reactions should only be summarised in the study report, where applicable"

However, as described in the modules for both the Periodic Safety Update Report (PSUR) (Module VII) and the Risk Management Plan (RMP) (Module V), information on collected adverse events will be included in the study report and reported appropriately in both the PSUR and the RMP. In cases of doubt, the reporting requirement will be clarified with the concerned authorities in EU Member States. Information on adverse events other than MDS disease progression, progression to AML, and SPM other than AML, (which is considered as disease progression in patients with MDS), will be collected using the Common Terminology Criteria for Adverse Events (CTCAE) to identify the incidence, but not the severity, of retrospectively identified adverse events. The CTCAE will be used where feasible to provide a common definitional framework for the adverse events collected as part of this study.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Regular progress report updates as well as final results will be made available to the PRAC as per regulatory requirements via the PSURs. An interim descriptive report was prepared 1 year after study start. On 29-Mar-2019, the first interim descriptive report was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) in order to discuss if the data collected on lenalidomide use, across different groups of MDS patients, are sufficient to allow successful completion of this study. The Assessment Report adopted by the CHMP on 27-Jun-2019 included a request to submit another interim descriptive report in Quarter (Q)1 2020. On 27-Mar-2020, the second interim descriptive report was submitted to PRAC (EMEA/H/C/000717/ANX/041.8).

The final Assessment Report, adopted by the CHMP on 10-Dec-2020, concluded that the post-approval measure for the second interim report was fulfilled with no further action required.

Final data will be appropriately communicated when available, through presentation at major European and global congresses of hematology and/or oncology. Final results of the MDS drug-utilisation study also will be submitted for expedited review and publication to an appropriate scientific and medical journal.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

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

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2020), which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

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

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies [EMA, 2012]). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP) (EMA, 2013).

Study title:
A post-authorisation, non-interventional, retrospective, drug-utilisation study to describe the pattern of use of lenalidomide in patients with myelodysplastic syndromes (MDS)

EU PAS Register® number: ENCEPP/EUPAS22604
Study reference number (if applicable): CC-5013-MDS 012, Amendment 3 (Version 2.0)

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[a]	☒	☐	☐	6
1.1.2 End of data collection[b]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	6

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

Comments:

Section 2: Research question		Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1	Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8.1
2.1.2	The objective(s) of the study?	☒	☐	☐	8.2
2.1.3	The target population? (ie population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.1
2.1.4	Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5	If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

The study is retrospective and purely descriptive in nature. No formal hypothesis has been formulated

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.1
3.3	Does the protocol specify measures of occurrence? (eg,, rate, risk, prevalence)	☒	☐	☐	9.1.1
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9.3

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1.2
	4.2.2 Age and sex	☒	☐	☐	9.3
	4.2.3 Country of origin	☒	☐	☐	9.4
	4.2.4 Disease/indication	☒	☐	☐	9.1.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.1.1
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.1.2, 9.2, 9.4

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Data will be collected retrospectively and from pre-existing data registries. Data quality is expected to be high, although there could also be areas of missing data due to the real-world setting.

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (eg, confounding by indication)	☒	☐	☐	9.9
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

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

Comments:

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

Comments:

No comparisons are being made between groups. For the Swedish and the Danish databases, reference will be taken from the national patient registries for the endpoint/covariates, and from the dispensing registry for exposure.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1, 9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2, 9.7.3
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.9
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2, 9.7.3

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6, 9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Ethics Committee/Institutional Review Board approvals will be obtained by the selected data sources.

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

[redacted]

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.