POST-AUTHORISATION SAFETY STUDY INFORMATION

Title	A Post-authorisation, Non-interventional, Retrospective, Drug Utilisation Study to Describe the Pattern of Lenalidomide Use in Patients with Myelodysplastic Syndromes (MDS)
Version Identifier of the Final Study Report	CC-5013-MDS-012 - Version 1.0
Date of Last Version of the Final Study Report	Not applicable
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(s)	Bristol Myers Squibb Pharma EEIG
Joint PASS	No
Research Question and Objectives	The primary research question was to describe the pattern of lenalidomide use within routine clinical practice to treat myelodysplastic syndromes (MDS) in countries within the European Union (EU). Included countries were those in which Revlimid® (lenalidomide) is marketed for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with an isolated deletion involving the long arm of chromosome 5 (del[5q]), a cytogenetic abnormality, when other therapeutic options were insufficient or inadequate and where these patients had access to the drug post-EU approval for the MDS indication. **Primary Objective** To describe the pattern of lenalidomide use in routine clinical practice of MDS patients in the countries included in this study. **Secondary Objectives** To 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 leukaemia (AML) • Haematological and non-haematological adverse events including infections, bleeding, and thromboembolic events • Major cardiac events and second primary malignancies (SPM) other than AML (AML is considered as disease progression in MDS patients) • Evaluation of risk factors collected in the routine clinical practice 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)
Countries of Study	Implementation of this retrospective drug utilisation study is a condition of the EU marketing authorisation for lenalidomide in the approved indication for MDS (Revlimid®, European Commission Decision, Annex IID). This retrospective drug utilisation study includes countries within the EU for 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. To represent an appropriate patient population and in order to meet the primary drug utilisation objective and the secondary safety objectives, this study included results from selected data sources across 10 countries within the EU (Austria, Czech Republic, Denmark, France, Germany, Greece, Netherlands, Poland, Portugal, and Spain) and the United Kingdom. Additionally, the company-sponsored Connect® Myeloid Disease Registry (United States [US] cohort registry) was used to address the secondary safety objectives (but not the primary drug utilisation objective, due to a different approved MDS indication in the US).

Author	[redacted]

MARKETING AUTHORISATION HOLDER(S)

Marketing Authorisation Holder(s)	Bristol Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Ireland
MAH Contact Person	[redacted]

1 ABSTRACT

Title

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

Keywords

Lenalidomide, myelodysplastic syndromes, acute myeloid leukaemia, PASS, registry study

Rationale and Background

Revlimid® (lenalidomide) is a drug belonging to a proprietary series of drugs with immunomodulatory and other properties. It is currently registered in 82 countries worldwide, including the European Union (EU), for the treatment of the following: multiple myeloma (MM) in combination with dexamethasone in adult patients who had received at least one previous therapy, adult patients with previously untreated MM who are not eligible for transplant, and adult patients with relapsed or refractory mantle cell lymphoma or follicular lymphoma. Lenalidomide is also licensed in more than 20 countries outside of the EU, 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 involving the long arm of chromosome 5-(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 del(5q) cytogenetic abnormality when other therapeutic options are insufficient or inadequate (variation EMEA/H/C/717/II/056). The European Commission (EC) decision to approve Revlimid® (lenalidomide) 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; Category 1; 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 lenalidomide use in MDS both within and outside of the EU-approved indication.

This lenalidomide retrospective study also aimed to gather additional safety information among MDS patients treated with lenalidomide outside of the EU-approved indication, including the risk of progression to acute myeloid leukaemia (AML) in a routine clinical practice setting.

Research Question and Objectives

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

This study also collected 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 lenalidomide use in routine clinical practice of MDS patients in the countries concerned

Secondary Objective

- 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
  - Haematological and non-haematological 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 MDS patients)
  - Evaluation of risk factors collected in the routine clinical practice setting associated with progression to AML among MDS patients treated with lenalidomide (dependent on both sufficient patient numbers and availability of data within the selected data sources)

Study Design

This was a post-authorisation, non-interventional, retrospective, drug utilisation study. Retrospective data were collected from MDS patients treated with Revlimid® (lenalidomide) to assess patterns of use in routine clinical practice. Further information was gathered regarding the safety of lenalidomide both within and outside of the EU-approved indication.

Setting

This study collected data from 10 EU countries and the UK, in which Revlimid® (lenalidomide) was marketed in the MDS indication and where MDS patients had access to lenalidomide post EU approval for the MDS indication.

Subjects and Study Size, Including Dropouts

Retrospective data were collected from 523 MDS patients from EU countries and the United Kingdom (UK) who were treated with lenalidomide and eligible for the study ("overall EU and UK population"), and from 44 patients from the company sponsored US Connect® Myeloid Disease Registry (US cohort registry) who were treated with lenalidomide and eligible for the study. Data were collected for both on- and off-label cohorts from date of first lenalidomide dose (baseline) until the date of death or last follow-up (whichever occurred first), including patients lost to follow-up or who discontinued Revlimid® (lenalidomide) for any reason.

Variables and Data Sources

Variables considered in this analysis as baseline, exposure, and outcome variables included demographic and clinical variables, lenalidomide therapy and other treatment variables, and outcome variables for safety. The sources of data for the primary drug utilisation objective in this study included the EUMDS (European myelodysplastic syndromes) Registry, the Spanish Registry of MDS (Registro español de síndromes mielodisplásicos [RESMD]), the Düsseldorf MDS Registry, and the French Registry of MDS (Groupe Francophone des Myélodysplasies [GFM]). The secondary safety objectives were assessed using data sourced from the company-sponsored Connect® Myeloid Disease Registry (US cohort registry) in addition to the sources for the primary objective.

Results

In the overall EU and UK population, 30.0% of MDS patients treated with lenalidomide were treated on-label, 66.0% were treated off-label, and 4.0% had unknown label status. The primary reasons for off-label treatment across all registries were due to patients not being red blood cell (RBC) transfusion-dependent at initiation of lenalidomide (48.4%) and not having del(5q) aberration (45.5%). Of those treated on-label, 10.2% had progression to AML, whereas 13.0% who were treated off-label had progression to AML. The most frequently reported adverse events (AEs) across all registries were neutropenia (38.9% among on-label patients and 33.3% among off-label patients) and thrombocytopenia (36.9% among on-label patients and 28.1% among off-label patients). The most frequently reported infections were non-specific infections (6.4% of on-label patients; 2.3% of off-label patients). Of the major cardiac events, the most frequently reported were non-specific major cardiac events (2.5% of on-label patients; 0.3% of off-label patients). No bleeding events were reported in the on-label patients. Haemorrhage, not specified, was the most frequently reported (0.6%) in off-label patients. Of the venous thromboembolic events (VTE), the most frequently reported were non-specific VTE (1.3% of on-label patients) and deep leg vein thrombosis (0.9% of off-label patients).

SMPs, other than AML, included haematological malignancies (0.6% in both on-label and off-label patients), non-melanoma skin cancers (0.3%–0.6%), and solid tumours (1.7%–7.0%). Among MDS patients treated on-label, 33.8% died during lenalidomide treatment while 21.7% of MDS patients treated off-label died during lenalidomide treatment. The primary causes of death reported for both on- and off-label patients were due to AML (3.2%–6.1%), infection (4.5%-4.6%), or unknown (4.3%–19.1%). Multivariable adjusted models to evaluate risk factors for progression to secondary AML could not be performed due to an insufficient number of patients in each cohort.

In the US Connect® Myeloid Disease Registry cohort, the most common serious adverse events (SAEs) reported for ≥ 5% of MDS patients were haematological (anaemia, pancytopenia, febrile neutropenia), followed by pneumonia, dyspnoea and respiratory failure. SPM of other solid tumour malignancy/leiomyosarcoma was reported in 2.3% of patients. Among the patients treated with lenalidomide in the US registry, 63.6% died, of which the primary causes of death were attributed to disease progression (50.0%) and respiratory failure (10.7%).

Discussion

This non-interventional PASS was conducted using data from 523 patients with transfusion-dependent IPSS low- or int-1-risk MDS with isolated del(5q) or any other type of MDS treated with lenalidomide in routine clinical practice across 10 EU countries and the UK. The analytical dataset for this study was first transferred to the sponsor on 08-Nov-2018 (study start date) and become fully available on 23-Jan-2024 (end of data collection). This study enabled the MAH to ascertain patterns of usage for treatment of MDS with lenalidomide in routine clinical practice. In addition, the current analysis of the results outlines AML progression and survival in patients both within and outside of the EU-approved indication.

The results of this PASS show a lower proportion of patients treated on-label compared to off-label in overall population among the haematology-specialised centres included in the European registries. Progression to AML was 10.2% among patients treated on-label and 13.0% among patients treated off-label. Among all haematological and non-haematological AEs collected, neutropenia and thrombocytopenia were the most frequently reported. Within the categories of SPMs other than AML, haematological malignancies and non-melanoma skin cancers were < 1.0% in both on-label and off-label patients, however, solid tumours occurred in 7.0% of on-label patients and 1.7% of off-label patients across the European registries. The total number of MDS patients who died during lenalidomide treatment was 33.8% among on-label patients and 21.7% among off-label patients. The primary causes of death (AML progression, infection, or unknown) each accounted for < 10% of those who died in the combined on- and off-label cohorts. These results are consistent with those identified from the US Connect® Myeloid Disease Registry cohort (analysed separately). Based on the safety findings from this study, no new safety concerns have been identified in the overall population, on-label, or off-label cohorts, as defined in this study. There is no change to the current benefit-risk profile of lenalidomide.

Marketing Authorisation Holder(s)

Bristol Myers Squibb Pharma EEIG Plaza 254

Blanchardstown Corporate Park 2, Dublin 15, D15 T867

Ireland

Names and Affiliations of Principal Investigators

Not applicable.