1. ABSTRACT

- **Title**

Utilization of Romiplostim in Myelodysplastic Syndromes (MDS) within the Medicare Population: A Study Based on Data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare Linked Database – Original Analysis & Follow-up Analysis

- **Rationale and Background**

Nplate® (romiplostim) is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia (ITP). It is not indicated for treatment of thrombocytopenia due to myelodysplastic syndromes (MDS) or any other cause of thrombocytopenia other than chronic ITP. On 25 June 2014, Amgen received an Information Request from the Food and Drug Administration (FDA) to examine off-label use of romiplostim with a particular interest in use among patients who have MDS. Through discussions between Amgen and the FDA, it was agreed upon that the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database would be an appropriate source of data to examine this question. Amgen conducted these analyses and submitted the report to the Agency on 20 November 2015. On 27 April 2018, the Agency requested that Amgen re-run the analysis based on the most recent release of SEER-Medicare data. This current report reflects results of both the original and updated analyses, which are referred to as the Original Analysis and Follow-up Analysis, respectively, throughout the report.

- **Research Objectives**

To estimate the proportion of all romiplostim users who have a diagnosis of MDS registered in SEER.

To estimate the proportion of SEER-registered MDS patients who are romiplostim users.

- **Study Design**

This study is a retrospective cohort study.

- **Setting**

Patients included in the study represent United States Medicare beneficiaries residing in the SEER catchment areas with a primary diagnosis of MDS and a 5% random sample of Medicare beneficiaries who do not have MDS.

- **Patients and Study Size**

In both the Original Analysis and Follow-up Analysis, patients were included if they were aged ≥65 years at cancer diagnosis for the SEER sample and in the year of analysis for the 5% non-MDS sample; had continuous Medicare Part A and Part B coverage during the time periods of the analysis; and had no Health Maintenance Organization benefits. In the Original Analysis, patients diagnosed with MDS in any year from 2001 to 2011 were included in the MDS cohort; and patients with no diagnosis of MDS in any year (through 2011) were included in the non-MDS cohort. For the Follow-up Analysis, patients diagnosed with MDS in any year from 2005 to 2015 were included in the MDS cohort; and patients with no diagnosis of MDS in any year (through 2015) were included in the non-MDS cohort.

In the Original Analysis, the calculation of the proportion of romiplostim users with MDS among users in the years 2010 and/or 2011 was estimated based on 8,297,220 patients without MDS (after correction to account for the non-sampled patients [that is, the observed count was divided by 0.05 because it represents a 5% sample of all non-MDS

patients living in the SEER catchment areas]) and 8,731 patients diagnosed with MDS (no correction necessary because all MDS patients in the SEER catchment areas are represented). In the Follow-up Analysis, the calculation of the proportion of romiplostim users with MDS among users in the years 2012 and/or 2013 was estimated based on the corrected count of 7,805,120 patients without MDS and 9,775 patients diagnosed with MDS. Also in the Follow-up Analysis, the calculation of the proportion of romiplostim users with MDS among users in the years 2014 and/or 2015 was estimated based on the corrected count of 8,077,920 patients without MDS and 9,920 patients diagnosed with MDS.

In the Original Analysis, the proportion of MDS patients with romiplostim use was estimated among 10,251 MDS patients. In the Follow-up Analysis, the proportion of MDS patients with romiplostim use was estimated among 16,417 MDS patients.

- **Variables and Data Sources**

The study utilized the SEER-Medicare linked database available from the National Cancer Institute (NCI), which includes Medicare beneficiaries residing in the SEER catchment areas with a primary diagnosis of MDS (MDS cohort). In addition, a random 5% sample of Medicare beneficiaries who did not have MDS (non-MDS cohort), also available from the NCI, was utilized.

Key variables of interest included romiplostim exposure and a SEER-registered diagnosis of MDS.

- **Results**

Proportion of romiplostim users with MDS

In the Original Analysis, among all users of romiplostim estimated from Medicare claims in 2010 (n=556) and in 2011 (n=701), the percentage who had a diagnosis of MDS registered in SEER was 2.9% (95% confidence interval [CI]: 2.8 – 3.1) and 3.0% (95% CI: 3.0 – 3.2), respectively. Among romiplostim users in 2010 and/or 2011 (n=1,011), the percentage who had a diagnosis of MDS registered in SEER was 3.1% (95% CI: 3.0 – 3.2).

In the Follow-up Analysis, among all users of romiplostim estimated from Medicare claims in 2012 (n=670), 2013 (n=632), 2014 (n=837), and 2015 (n=819), the percentage who had a diagnosis of MDS registered in SEER was 4.4% (95% CI: 4.2 – 4.6), 5.1% (95% CI: 4.9 – 5.3), 4.4% (95% CI: 4.2 – 4.6), and 4.8% (95% CI: 4.6 – 5.0), respectively. Among romiplostim users in 2012 and/or 2013 (n=910), the percentage who had a diagnosis of MDS registered in SEER was 5.5% (95% CI: 5.3 – 5.7). Among romiplostim users in 2014 and/or 2015 (n=1,142), the percentage who had a diagnosis of MDS registered in SEER was 5.4% (95% CI: 5.2 – 5.6).

Proportion of MDS patients with romiplostim use

In the Original Analysis, among patients who had a diagnosis of MDS registered in SEER from 2001 through 2011, the percentage who had at least one claim for romiplostim in any given year ranged from 0.2% to <1.4%, depending on the year of MDS diagnosis (2001-2009, 2010, and 2011 MDS cohorts were analyzed separately) and the year examined for romiplostim use (2010, 2011, or 2012).

In the Follow-up Analysis, among patients who had a diagnosis of MDS registered in SEER from 2005 through 2015, the percentage who had at least one claim for romiplostim in any given year ranged from 0.3% to 0.8%, depending on the year of MDS diagnosis (2005 – 2013, 2012, 2013, 2014, and 2015 MDS cohorts were analyzed separately) and the year examined for romiplostim use (2012, 2013, 2014, 2015, or 2016).

- **Discussion**

Results of the Original Analysis indicated that among elderly fee-for-service Medicare beneficiaries living in the SEER catchment areas, the proportion of romiplostim users who had MDS was very small and the proportion of MDS patients who used romiplostim was even smaller.

Compared to these findings, results of the Follow-up Analysis indicate that the proportion of all romiplostim users who have MDS may have slightly increased. However, viewing off-label use solely in this manner would be misleading. In the Original Analysis, MDS patients represented 0.11% of the entire sample population (8,731 / 8,305,951). In the Follow-up Analysis, MDS patients represented a higher proportion of the base population – 0.13% (9,775 / 7,814,895) for use examined in 2012 and/or 2013 and 0.12% (9,920 / 8,087,840) for use examined in 2014 and/or 2015. This suggests that there is a true increase in the incidence of MDS and/or there is better detection since it first became reportable to SEER in 2001. Additionally, the proportion of romiplostim users who have MDS over time is relative to the uptake of romiplostim in other indications, including ITP. Similarly, changes in the absolute uptake and relative uptake by indication of other treatments used to treat thrombocytopenia, such as eltrombopag, could also lead to changes in the absolute and relative uptake of romiplostim by indication. Taken as a whole, these factors could lead to an increase in the absolute number of MDS patients with romiplostim use and an increase in their representation in the overall population over time without any actual increases in the proportion of MDS patients who use romiplostim.

Therefore, the proportion of MDS patients who use romiplostim is also an important measure. Compared to the Original Analysis, the estimates of the Follow-up Analysis are more precise as they are based on a larger MDS cohort, and importantly, they suggest that this proportion remains very low. In the Original Analysis, the estimated proportion of MDS patients with romiplostim use ranged from 0.2% to <1.4%. In the Follow-up Analysis, a tighter range of estimates for this proportion was observed, 0.3% to 0.8%, which falls within the observed range from the Original Analysis.

Based on the combination of results from Original Analysis and Follow-up Analysis, among elderly fee-for-service Medicare beneficiaries living in the SEER catchment areas, although the relative proportion of romiplostim users who have MDS may be higher in recent years, the proportion of MDS patients who use romiplostim has been stable and remains very small.

- **Marketing Authorization Holder**

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