1. ABSTRACT

- **Title**

Use of Erythropoiesis Stimulating Agents (ESAs) in Patients Receiving Myelosuppressive Chemotherapy in Europe and the UK

- **Keywords**

Darbepoetin alfa, erythropoiesis stimulating agent, non-myeloid malignancy, haemoglobin,

- **Rationale and Background:**

Myelosuppressive chemotherapy is a common cause of anaemia in cancer patients and erythropoiesis stimulating agents (ESAs), including darbepoetin alfa, are used to reverse chemotherapy induced anaemia (CIA) and reduce the need for red blood cell (RBC) transfusions. An increased risk of mortality has been reported in clinical studies of patients with cancer receiving chemotherapy when Hb levels were targeted above 12 g/dL.

Amgen Study 20070782 was a phase 3, randomised, double-blind, placebo-controlled, non-inferiority trial conducted in patients with CIA receiving multi-cycle chemotherapy for advanced-stage non-small-cell lung cancer, to address safety concerns related to darbepoetin alfa. In Study 20070782, darbepoetin alfa demonstrated no increased risk of mortality or disease progression as compared to placebo. However, real-world use may differ from use in clinical trials, and thereby introduce risks not observed in the trial. Therefore, European Medicines Agency (EMA) requested further evaluation of ESA use in a European setting and determine if and how it might differ from Study 20070782. The observational study reported here was performed to characterise the use of ESAs in cancer patients receiving myelosuppressive chemotherapy in Europe and the United Kingdom (UK), in order to determine whether ESAs are prescribed in accordance with the labelling instructions and to further characterise the important potential risk of mortality and/or tumour progression or recurrence in patients with cancer or a history of cancer.

- **Research Question and Objectives**

Primary objective

1. Describe the baseline haemoglobin (Hb) levels at initiation of treatment with ESA in patients receiving myelosuppressive chemotherapy

Secondary objectives

1. Describe the baseline demographic and clinical characteristics of patients initiating treatment with an ESA and receiving myelosuppressive chemotherapy
2. Describe the duration of ESA prescription in subjects receiving myelosuppressive chemotherapy
3. Describe the dose distribution of treatment with ESA in patients receiving myelosuppressive chemotherapy at (a) first prescription of an ESA and (b) subsequent ESA prescriptions (where available). Dose was categorised by long acting and short-acting ESAs to avoid dose conversion
4. Describe Hb levels during treatment with ESAs in patients receiving myelosuppressive chemotherapy

5. Describe the number of patients with a "rapid" rise in Hb level (considered to be more than 2 g/dL in any 4-week period), and whether patients with a rapid rise in Hb have a subsequent ESA dose reduction or therapy interruption

- **Study Design**

This is a retrospective medical chart review multi-centre observational study that documented real-world ESA-related measures in participants with non-myeloid malignancies treated with chemotherapy at university hospitals, community hospitals, private practice and community-based clinics typical of those that treat participants for whom ESAs were indicated.

- **Setting**

This study was planned to be conducted in 24 sites in 6 countries. Participants were followed from the index date (ie, ESA treatment initiation date) until 9 weeks post-index date or until 1 of the following criteria was met: ESA treatment end date, death, or date of consent/enrolment, whichever comes first. Follow-up was extended for selected analyses by excluding the ESA treatment end date from the censoring criteria. Baseline data on the participant's medical condition prior to use of ESA included data from medical records prior to January 2015.

- **Subjects and Study Size, Including Dropouts**

This study included participants who were ≥18 years old with a documented non-myeloid malignancy diagnosed within 12 months before ESA initiation and prior to chemotherapy. They must have received myelosuppressive chemotherapy and at least 1 ESA dose, with ≥9 weeks between ESA initiation and enrolment. Availability of medical records, a recent Hb measurement, and appropriate consent or notification were also required**.**

- **Data Source(s) and Methods**

Source data were extracted from patients medical records and charts (electronic and/or paper based) as well as pathology and pharmacy databases. Study site staff entered data into the electronic case report form retrospectively for each participant following enrolment into the study. Each participant was assigned a unique identification number at the time of the first data entry. Only data that were previously obtained in accordance with normal clinical practice and testing were available for each participant and no additional testing or interventions were required for study participation.

- **Variables**

Outcome Variables: Baseline Hb levels were presented in units of g/dL and reported as continuous or categorical variables as per Summary of Product Characteristics (SmPC) (≤ 10 g/dL), and as per Study 20070782 (≤ 11 g/dL).

Exposure Variables: The main exposures for the study were treatment with ESAs – either darbepoetin alfa or epoetin (any type). Information on use of an ESA treatment was determined by the presence of 1 or more prescriptions for an ESA as recorded in the electronic medical records, including time of each prescription, dose and type of ESA.

Other Covariates: Demographics, clinical characteristics at index, chemotherapy, comorbidities, and RBC transfusions.

- **Results**

A total of 762 participants were enrolled across 28 sites in 6 countries whose treatment was received between 06 January 2015 to 12 September 2024. The Full Analysis Set

had 398 (52.2%) males and 364 (47.8%) females. The largest proportion of participants (43.7%) were aged 18 to 65 years, followed by 34.8% in the 66 to 75 age group, and 19.7% aged between 76 to 85 years.

Primary Objective: In the Full Analysis Set (N=762), 97.8% (95% Confidence Interval [CI]: 96.5–98.7) of participants had baseline Hb levels ≤11 g/dL, and 83.9% (95% CI: 81.1 - 86.4) had Hb ≤10 g/dL. The mean baseline Hb was 9.20 g/dL (standard deviation [SD]: 0.97; 95% CI: 9.14 - 9.27). The baseline Hb level median and quartiles (Q1 - Q3) were 9.2 g/dL (8.60 - 9.80) with observed values ranging from 5.0 to 12.9 g/dL. By malignancy type, participants with gastrointestinal malignancies showed the highest proportion with baseline Hb ≤11 g/dL (99.3%), whilst those with reproductive system malignancies had the lowest (94.5%). For baseline Hb ≤10 g/dL, the lowest proportion was also seen in reproductive system malignancies (66.7%). Across countries, nearly all participants had baseline Hb ≤11 g/dL, with country specific rates ranging from 96.1% to 100%. The proportion with baseline Hb ≤10 g/dL ranged from 79.3% to 95.5%.

Secondary Objectives:

- **Baseline demographic and clinical characteristics**: In the Full Analysis Set, the gender distribution was nearly even, with 52.2% males and 47.8% females. The most common cancer type was haematologic malignancies (48.4%), followed by respiratory (23.2%), gastrointestinal (17.6%), and reproductive system malignancies (7.2%). Regarding disease stage, 47.0% participants had metastatic disease and 46.1% had non-metastatic disease. ECOG performance scores were generally favourable: 23.5% participants were grade 0 and 30.8% were grade 1. ESA treatment types were almost evenly distributed between long-acting (52.4%) and short-acting (47.6%). Adjuvant therapy was received by 27.8% participants and neo-adjuvant therapy by 14.3% participants. A total of 194 participants received at least 1 RBC transfusion within 93 days before index, with a mean of 2.7 (SD: 2.79) transfusions and a mean of 3.9 units were transfused (SD: 3.98).
- **Duration of ESA prescription**: Overall, 525 (68.9%) participants had an ESA prescription in effect 3 weeks after the index date. At 4 weeks, this proportion of participants declined to 426 (55.9%) which further decreased to 351 (46.1%) at 6 weeks. By 9 weeks, only 190 (24.9%) participants remained on ESA therapy.

  During the follow-up period, participants in the Full Analysis Set received a mean of 1.7 ESA prescriptions (SD: 1.53), with a median of 1.0 (interquartile range [Q1–Q3]: 1.0–2.0).
- **Dose distribution**: Weekly administration was the most frequently recorded dosing interval: 449 (91.3%) of short-acting ESA prescriptions and 487 (62.0%) of long-acting ESA prescriptions. Administration recorded as a single dose (once) was more prevalent in the long-acting ESA group, representing 150 (19.1%) of records, compared to 29 (5.9%) for short-acting ESAs.

  In the Full Analysis Set, the mean (SD) starting dose was 282.8 µg (164.94) for long-acting ESAs and 30,214.1 IU (7,878.98) for short-acting ESAs. The median (Q1 - Q3) dose for long-acting ESAs was 150.0 µg (150.0 - 500.0) whilst for short-acting ESAs was 30,000.0 IU (30000.0 - 30000.0).

  Most participants had no dose modifications. In the Full Analysis Set, 712 (93.4%) participants had no dose modifications and 50 (6.6%) participants experienced at least 1 ESA dose modification during follow-up. Of these, 24 (48.0%) participants had dose escalations, 20 (40.0%) had dose reductions, 9 (18.0%) underwent a transition from maintenance to titration frequency, and 5 (10.0%) participants transitioned from titration to maintenance.

- **Hb levels during treatment**: Overall, 748 (98.2%) participants in the Full Analysis Set had at least 1 repeated Hb measurement during the 9-week follow-up period after the index date.

  Median Hb levels were evaluated at Weeks 3, 4, 6, and 9 in 3 analysis sets. Across all sets and time points, the majority of participants had Hb values either within or below the target range (>10 g/dL to ≤12 g/dL), with relatively few exceeding this threshold. In the Full Analysis Repeated Hb Set, 93.5% of participants at week 3 and 82.9% at week 9 had Hb ≤12 g/dL. Whilst the proportion of participants with Hb >12 g/dL increased over time (reaching 17.1% in the Full Analysis Repeated Hb Set, 18.4% in the transfusion-excluded set, and 15.7% in the follow-up 2 subset by week 9), the absolute number of participants remained low (44, 34, and 17, respectively). Across all 3 analysis sets, the number of participants with available Hb values decreased over time. In the follow-up 2 subset which only included participants continuing ESAs, the participant counts were 33 to 42% of those across time periods in the Full Analysis Repeated Hb set indicating that almost two-thirds of participants at each evaluation time point had discontinued ESA during the follow-up period.. Median Hb levels showed a gradual increase over time.

- **"Rapid" rise in Hb levels during ESA treatment**: A total of 274 participants (38.0%) in the Full Analysis Follow-up Set (N = 721) experienced an increase in Hb of ≥ 2 g/dL within any four-week interval. Of these 274, 9 (3.3%) had a subsequent ESA dose reduction. Among the minority of participants with a baseline Hb >10 g/dL (N = 117), those at greater risk of exceeding the target threshold of 12 g/dL, 23 participants (19.7% of this subgroup and 3.2% of the total population) had such an increase. A total of 246 participants (34.1% of the 721) were continuing ESAs during interval follow-up. Among the group with a baseline Hb >10 g/dL, those most likely with a ≥ 2 g/dL rise to exceed the target Hb of 12 g/dL, the number of participants continuing ESAs with a ≥ 2 g/dL rise was 6 participants (0.8% of the 721).

- **Discussion**

  A total of 762 participants were enrolled in this multinational, observational study between January 2015 and September 2024 across 6 countries: France, Spain, Belgium, Italy, the United Kingdom, and Germany. At baseline, Hb levels were consistently within treatment guidelines for ESA initiation. In the Full Analysis Set, 97.8% of participants had Hb levels ≤11 g/dL and 83.9% had Hb ≤10 g/dL. Country-level data similarly demonstrated high adherence to Hb thresholds, with Hb ≤11 g/dL observed in ≥96% of participants across all countries and Hb ≤10 g/dL ranging from 79.3% to 95.5%. Weekly dosing was the most common dosing frequency prescribed for both ESA types, recorded in 91.3% of short-acting and 62.0% of long-acting ESA prescriptions. Long-acting ESAs were more often associated with extended dosing intervals, including single-dose, every 2 weeks, and every 3 weeks, whereas such intervals were rarely observed with short-acting ESAs. Approximately two thirds of participants discontinued ESAs during follow-up. Across population sets, most participants had no dose modifications (93.4% and 94.5% in the Full Analysis Set and Prior RBC Transfusion Excluded Set, respectively). There was a substantial reduction in the number of participants with available Hb measurements by week 9 following the trend of discontinuation of ESA treatment during the follow-up period; however, most participants with continuing follow-up with Hb measurements had also discontinued ESAs. Specifically, only 6 of 721 participants (0.8%) had both a ≥2 g/dL rise and continued ESA use that could plausibly result in Hb >12 g/dL, underscoring the low clinical impact of these

observations. Although approximately 15.7% to 18.4% of participants across population sets had Hb levels >12 g/dL at week 9, the absolute number of participants remaining on ESA therapy was low. Across different population sets, majority of participants who had a ≥2 g/dL Hb increase within any 4-week interval had baseline Hb of ≤10 g/dL. However, ESA dose reductions following such increases were rare, ranging from 1.2% to 3.5% across populations.

In Study 20070782, darbepoetin alfa demonstrated no increased risk of mortality or disease progression as compared to placebo when ESA was used in accordance with the SmPC to maintain Hb levels within the labelled target. However, real-world use of ESA may differ from the SmPC guidance used in clinical trials. Results from this observational study demonstrated that ESA use in real-world clinical practice was largely consistent with current regulatory guidance and labelling for haemoglobin thresholds and targets. These results along with the results of Study 20070782 served to characterise and address the important potential risk of mortality and/or tumour progression or recurrence in patients with cancer or a history of cancer.

Conclusion*:*

The findings from the Study 20070782, reinforce the importance of managing ESA therapy in alignment with the haemoglobin thresholds specified in the SmPC.

In this current study, conducted across the European Union and the United Kingdom, 86% of ESA prescriptions for CIA were issued to participants with Hb <10 g/dL, and 97% to those with Hb <11 g/dL. The demographic characteristics and baseline comorbidity profiles of these participants were comparable to those enrolled in a large, randomised controlled trial of 2,600 participants assessing overall survival and progression-free survival in individuals with advanced non-small cell lung cancer (NSCLC) and baseline Hb <11 g/dL.

The majority of participants had ESA prescription durations between 1 and 4 weeks, with weekly administration being the most frequently recorded dosing interval. Most participants received treatment without any dose modification. The number of participants with ESA prescriptions decreased steadily over the 9-week follow-up consistent with expected discontinuation patterns. During treatment, most participants maintained Hb levels at or below the target threshold (≤12 g/dL). Although approximately 15% of participants had Hb >12 g/dL at week 9, the absolute number of participants remaining on ESA therapy at that time point was low (17 of 257). Among participants with baseline Hb ≤10 g/dL, a higher incidence of rapid Hb rise (≥ 2 g/dL in any 4-week period) was observed compared with those whose baseline Hb > 10 g/dL.

Overall, this observational study demonstrated that ESA use in real-world clinical practice was largely consistent with current regulatory guidance concerning initiation thresholds, haemoglobin targets. The majority of prescriptions were initiated in participants with baseline Hb <10 g/dL, treatment durations were short, and most participants maintained haemoglobin levels at or below the recommended threshold of 12 g/dL. The limited need for dose adjustments, expected discontinuation patterns, and low incidence of excessive Hb rise further support that ESA use is generally consistent with current regulatory recommendations in routine clinical settings.

The results of this study indicated that ESAs were prescribed in the EU and the UK according to regulatory guidance and labelling. The Hb levels (g/dL) at ESA initiation were lower and more conservative in the real-world Study 20190404, with a mean of 9.2 and median (Q1 - Q3) of 9.2 (8.6 - 9.8), compared with the clinical trial Study

20070782, which reported a mean of 10.1 and median (Q1 - Q3) of 10.1 (9.3 - 10.9). The third quartile of achieved Hb level in those receiving darbepoetin alfa in Study 20070782 at week 13 and 16 were 12.1 and 12.0, respectively, indicating that at least 25% of subjects exceeded a target of 12.0 g/dL. Although the time periods after ESA initiation are not directly comparable, the proportions exceeding a target of 12 g/dL in 20190404 were also consistently lower, ranging from 6.5% to 17.1% over 3 to 9 weeks.

These results, together with findings from Study 20070782, address the important potential risk of mortality and/or tumour progression or recurrence in patients with cancer or a history of cancer and further inform the characterisation of the benefit-risk profile of ESA therapy.

- **Marketing Authorisation Holder:** Amgen Inc.
- **Names and Affiliations of Principal Investigators:** A list of all collaborating institutions and investigators will be made available upon request.