Summary Table of Study Protocol

Title	Use of Erythropoiesis Stimulating Agents (ESAs) in Patients Receiving Myelosuppressive Chemotherapy in Europe and the UK
Protocol version identifier	20190404 Amendment **6**
Date of last version of the protocol	**24 October 2023**
EU Post Authorisation Study (PAS) Register No	EU PAS 497**7**5**7**
Active Substance	Darbepoetin alfa
Medicinal Product	Aranesp®
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	The aims of this study are to observe if the pattern of use of darbepoetin is consistent with the EU label (EPAR), to characterise the use of ESAs in cancer patients undergoing myelosuppressive chemotherapy in Europe and the UK, and to observe if and how ESA utilisation is consistent with that observed in Study 20070782. The primary objective is to describe baseline haemoglobin (Hb) levels at initiation of treatment with an ESA in patients receiving myelosuppressive chemotherapy. Secondary objectives are to describe patient characteristics, the duration of ESA prescription, ESA dose and dose changes during treatment, and Hb levels during treatment.
Country(ies) of Study	France, Germany, Italy, Spain, the United Kingdom, and Belgium.
Authors	PPD DPhil Centre for Observational Research, Amgen Ltd.

Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen
MAH Contact	PPD PPD

Investigator's Agreement

I have read the attached protocol entitled Use of Erythropoiesis Stimulating Agents (ESAs) in patients Receiving Myelosuppressive Chemotherapy in Europe and the UK, dated **23 April 2024**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

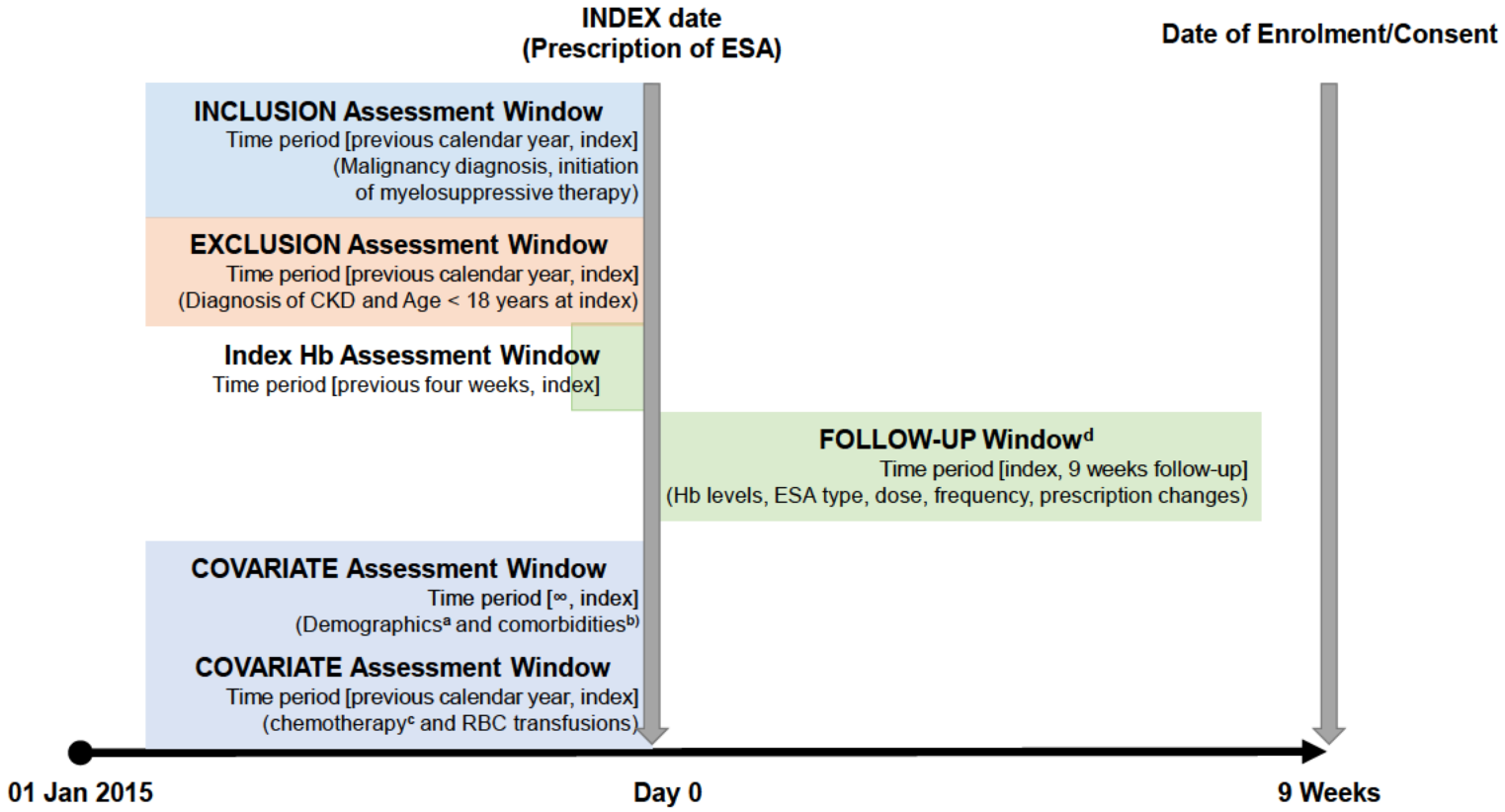
_____ _____
Name of Investigator Date (DD Month YYYY)

_____
Title and Role of Investigator

_____
Institution Name

_____
Address and Telephone Number of Institution

Study Design Scheme



a. Demographics: age and sex index
b. Comorbidities: diabetes, hypertension, cardiovascular disease, liver disease, COPD
c. Chemotherapy: type of chemotherapy, and date of treatment
d. Follow up for 9 weeks or one of the following criteria is met: ESA treatment end date, death, date of enrolment, date of consent, whichever comes first.

ESA = Erythropoietin stimulating agents
CKD = Chronic kidney disease
Hb = haemoglobin

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2. List of Abbreviations

Abbreviation	Definition
CIA	Chemotherapy induced anaemia
CRC	Colorectal cancer
eCRF	Electronic case report form
EMA	European medicines agency
EMR/HER	Electronic medical record/electronic health record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ECOG	Eastern Cooperative Oncology Group
EPAR	European public assessment report
ESA	Erythropoiesis stimulating agent
EU	European Union
Hb	Haemoglobin
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
OS	Overall survival
PASS	Post-authorisation safety study
PFS	Progression free survival
PMC	Post marketing commitment
PRAC	Pharmacovigilance Risk Assessment Committee
RBC	Red blood cell
SmPC	Summary of product characteristics
SOP	Standard operating procedure

3. Responsible Parties

PPD Centre for Observational Research, Amgen Ltd.

PPD EMEA Data Science Hub, IQVIA

4. Milestones

Milestones	*Planned date* *
Finalisation of the protocol	**November** 2022
Registration in the EU PAS register	**November** 2022
Feasibility and study start up	February 2022
Start of data collection	January 2023
End of data collection	September 2024
Final report of study results	September 2025

* Depending on the Pharmacovigilance Risk Assessment Committee (PRAC) conclusion

5. Abstract

- *Study Title*:

  Use of erythropoiesis stimulating agents (ESAs) in patients receiving myelosuppressive chemotherapy in Europe and the UK.

- *Study Background and Rationale*:

  Myelosuppressive chemotherapy is a common cause of anaemia in cancer patients and ESAs, including darbepoetin alfa, are used to reverse the chemotherapy-induced anaemia (CIA) and reduce the need for red blood cell (RBC) transfusions. However, safety concerns regarding increased mortality or tumour progression with ESAs have been raised by some clinical trials and this is a potential risk of darbepoetin that requires further investigation.

  Part of this investigation was the conduct of Study 20070782 - a phase 3, randomized, double-blind, placebo-controlled, noninferiority study in patients with chemotherapy-induced anaemia receiving multi-cycle chemotherapy for the treatment of advanced stage non-small-cell lung cancer (NSCLC).

  Study 20070782 demonstrated no increased risk of mortality or progression as compared to placebo. However, real-world use may differ from the use in clinical trials, and thereby introduce risks not observed in the trial. Therefore, Amgen proposes to evaluate the ESA's use in a European setting and **determine** if and how it might differ from the RCT.

  Similar to the US investigation (**FDA** post-marketing **requirement Study** 20170210), Amgen proposes to characterize the use of ESAs in cancer patients undergoing myelosuppressive chemotherapy in Europe in order to determine if the pattern of use of darbepoetin is consistent with the EU label (EPAR). Amgen also aims to characterize the use of ESAs in cancer patients undergoing myelosuppressive chemotherapy in Europe and the UK, to determine if and how ESA utilisation is consistent with that observed in Study 20070782. Any findings of a substantial prevalence of use inconsistent with Study 20070782, may warrant the initiation of a study to assess mortality risk associated with this alternate pattern of use.

- *Research Question and Objectives*:

  The aim of this study is to describe the real-world use of ESAs in cancer patients with non-myeloid malignancies receiving myelosuppressive chemotherapy in Europe, specifically to determine whether ESAs are being used according to the product label and consistent with Study 20070782.

Objectives	**Endpoints**
Primary	
Describe the baseline Hb levels at initiation of treatment with ESA in patients receiving myelosuppressive chemotherapy	Hb level in g/dL at initiation of ESA, further categorised in 2 alternative ways, as per product label and clinical trial criteria • Hb ≤ 10 g/dL • Hb ≤ 11 g/dL
Secondary	
Describe the baseline demographic and clinical characteristics of patients initiating treatment with an ESA and receiving myelosuppressive chemotherapy	Demographic characteristics (age and sex), comorbidities, type of malignancy, type of chemotherapy treatment received, red blood cell (RBC) transfusions
Describe the duration of ESA prescription in subjects receiving myelosuppressive chemotherapy	Average prescription length of ESA, number of patients prescribed ESA at weeks 3, 4, 6, and 9
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)	Prescribed dose, dose frequency, dose modifications.
Describe Hb levels during treatment with ESA in patients receiving myelosuppressive chemotherapy	Hb level during ESA treatment: • Below target level (≤ 10 g/dL) • Target range (> 10 to ≤ 12 g/dL) • Above target level (> 12 g/dL)
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	Change in Hb level during ESA treatment, categorised: • More than 2 g/dL rise in any 4-week period • More than 2 g/dL rise in any 4-week period that did not have a subsequent ESA dose reduction or therapy interruption

- *Hypothesis/Estimation*

  This is an estimation study and no hypotheses will be tested.

- *Study Design/Type*:

  Retrospective medical chart review.

- *Study Population or Data Resource*

  The study will include patients diagnosed with any non-myeloid malignancy who initiate treatment with an ESA while receiving chemotherapy and were not previously treated with an ESA.

  This multi-centre observational study will be conducted in **6** countries: France, Germany, Italy, Spain, the United Kingdom, and Belgium.

  Study site staff will enter data into the electronic case report form (eCRF) retrospectively for each patient following enrolment into the study, based on data collected from routine clinical visits.

- *Summary of Patient Eligibility Criteria*

  Patients will be included in the study if they meet all the following criteria:

  - At least 1 recorded primary diagnosis for a non-myeloid malignancy within 1 year before index date (ie, ESA treatment initiation) preceding the first chemotherapy administration
  - At least 1 administration for a myelosuppressive chemotherapy drug (any line of therapy) before index date
  - At least 1 administration of an ESA during the study period
  - A minimum of a 9-week period between ESA treatment initiation and enrolment/consent
  - Aged ≥ 18 years at index date
  - Medical records (including diagnosis, demographics) are available for review and data extraction
  - At least 1 Hb recording before index date (the most proximal laboratory value available within 4 weeks prior to index date will be collected).
  - Have provided written informed consent or appropriate parties have been notified of participation (alive or deceased), where required for access to medical charts, according to local laws and regulation requirements.

  Patients will be excluded from the study if they meet any of the following criteria:

  - A diagnosis of chronic or acute kidney disease-induced anaemia within 1 year before index date.
  - A diagnosis of myelodysplastic syndrome within 1 year before index date.
  - ESA administration prior to the index date
  - Index ESA administration before 1 January 2015

- *Follow-up*

  - ESA treatment initiation (based on prescription date) will be considered the index date.
  - All ESA treatment episodes will be collected from the index date until 9 weeks post-index date or if 1 of the following criteria is met: ESA treatment end date, death, or date of consent/enrolment, whichever comes first.

- *Variables*
  - *Outcome Variables*
    Baseline Hb levels will be 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 will be treatment with ESAs – either darbepoetin alfa or epoetin (any type). Information on use of an ESA treatment will be determined by the presence of 1 or more prescriptions for an ESA as recorded in the electronic medical records (EMR), including time of each prescription, dose and type of ESA.
  - *Other Covariates*
    Baseline patient characteristics will include age, sex, type of malignancy (eg, categorized into all non-myeloid malignancies, all lung cancers, NSCLC only, breast cancer, colorectal cancer or lymphoma), type and date of chemotherapy, comorbidities, and RBC transfusions (if available).
- *Study Sample Size*

  The study is estimated to include **approximately 24** sites and aims to recruit 1625 patients who received an ESA during myelosuppressive chemotherapy. There will be no cap on the number of **sites included or sites included per country, nor the number of** patients recruited per site, country or year, but patient recruitment will be reviewed regularly to minimise recruitment bias.
- *Data Analysis*

  For the primary objective, the number and proportion (%) of patients receiving myelosuppressive chemotherapy with a baseline Hb level of ≤ 10 g/dL (as per SmPC criteria), and ≤ 11 g/dL (as per Study 20070782 inclusion criteria) prior to or at initiation of ESA treatment will be summarised with descriptive statistics overall and stratified by ESA type, type of malignancy, and country. Point estimates for the proportions, mean, and median will be presented with 95% confidence intervals (CI) for proportion and mean estimates and first and third quartiles for median estimates.

  Patient demographics (age, sex), clinical characteristics (malignancy characteristics, type of chemotherapy treatment received, presence of comorbidities and previous receipt of RBC transfusions), type of ESA, and country will be summarized with descriptive statistics overall and by ESA type, where appropriate.

  The number of weeks of treatment with an ESA and dose frequency (as indicated in the prescription) will be summarized with descriptive statistics overall and stratified by ESA type, type of malignancy, and country.

  The starting dose will be summarized with descriptive statistics by ESA type. The number and proportion (%) of patients with at least 1 dose modification will be reported overall, and (where available) by type of dose modification (eg, dose reduction, dose escalation, therapy interruption).

  The number and proportion (%) of patients with 1 or more repeated Hb measures after baseline will be reported. The mean, median, minimum and maximum Hb values across all measures available after baseline for each patient will be calculated. The number and proportion (%) of patients with median and maximum Hb levels below the target level (≤ 10 g/dL), in the target range (> 10 to ≤ 12 g/dL)

and above the target level (> 12 g/dL) will be reported. Rapid increases in Hb level may increase the risk of thrombotic events. Therefore, the number and proportion (%) of subjects with a rise in Hb level of more than 2 g/dL in any 4-week period will be reported. Guidance from the SmPC is to regularly monitor Hb levels and reduce or interrupt the ESA dose if a rapid increase occurs, therefore the number and proportion (%) of subjects with a rise in Hb level of more than 2 g/dL in any 4-week period that had a subsequent ESA dose reduction or therapy interruption in their medical notes will be reported.

6. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	28 July 2020	See summary changes		
2	23 December 2020	See summary changes		
3	27 January 2022	See summary changes		
4	28 June 2022	See summary changes		
5	24 October 2023	See summary changes		
6	**23 April 2024**	**See summary changes**		

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Anaemia is a reduction of haemoglobin (Hb) concentration below normal levels of 12 g/dL. It is a common complication in patients with cancer (Aapro et al, 2018). Between 30% and 60% of patients with non-haematological and haematological malignancies, will develop anaemia, and the incidence of anaemia is even higher in patients treated with myelosuppressive chemotherapy (> 60%) (Ludwig et al, 2004).

Treatment options for the management of CIA include adjustments to the cancer treatment regimen, RBC transfusions, ESAs, and iron supplementation either alone or in combination with ESAs (Aapro et al, 2018). Most chemotherapy patients who develop anaemia do not receive any treatment, but patients with a moderate or severe anaemia may be given RBC transfusions. The major aims of anaemia treatment are the reduction of symptoms, particularly fatigue, and an improved quality of life.

Amgen's darbepoetin alfa (Aranesp®) is indicated in the EU for treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy. Aranesp® should be administered only to patients with a Hb concentration ≤ 10 g/dL and used to achieve a target Hb of not greater than 12 g/dL.

In 2008, a class safety review was initiated because clinical trial data showed a consistent unexplained excess mortality and/or tumour progression in cancer patients

with anaemia treated with ESAs. As a consequence, the SmPC was updated and it was considered that routine pharmacovigilance measures (eg, its use according to the label) would be adequate to mitigate this risk (Aranesp SmPC).

Baseline Hb level at ESA initiation is considered an important determinant of safety outcomes during chemotherapy treatment, including mortality, tumour progression, and thrombotic events. The most recent Cochrane review of the use of ESAs for patients with cancer, found that overall survival was shorter and on-study mortality was higher in subjects initiated on an ESA in comparison to those who were not initiated on an ESA who had a baseline Hb level of > 12 g/dL, but not in those with a baseline Hb of < 10 g/dL or 10 to 12 g/dL (Tonia et al, 2012). Study 20070782 was a phase 3 randomised, controlled study that investigated darbepoetin alfa vs placebo in NSCLC subjects receiving chemotherapy, designed to address the potential risk of increased mortality and adverse tumour outcomes with ESAs in the oncology setting. The study reached its primary and secondary endpoints of non-inferiority for overall survival (OS) and progression-free survival (PFS) over placebo. The baseline Hb level at darbepoetin alfa initiation was < 11 g/dL in 96% of subjects and was < 10 g/dL in 52% of subjects.

Real-world use may differ from recommended use and thereby might introduce risks not observed in Study 20070782. Amgen has conducted several prospective European studies describing Hb levels in subjects receiving darbepoetin alfa and other ESAs (Berbec et al, 2018, Smakal et al, 2018, Aerts et al, 2012, clinicaltrials.gov identifier: NCT01444456). In an analysis of subjects with solid tumours who received darbepoetin alfa in European clinical practice between 2008 and 2010, darbepoetin alfa was initiated at a Hb level < 10 g/dL in 50% of breast cancer, 57% of colorectal cancer (CRC), 60% of ovarian, and 57% of lung cancer subjects (Aerts et al, 2012). The Hb level at ESA initiation was between 9 and 11 g/dL in 80% of breast cancer, 76% of CRC, 76% of ovarian, and 77% of lung cancer patients. A study in multiple European countries to evaluate quality of life in CIA patients treated with ESAs between 2011 and 2013 found that baseline Hb was ≤ 10 g/dL in 97% of patients (clinicaltrials.gov a). A study of darbepoetin alfa use for CIA in Central and Eastern Europe between 2012 and 2016 found that 73% had Hb < 10 g/dL at baseline (Smakal, 2018). A study of darbepoetin alfa use for CIA in Romania between 2011 and 2015 found that 81% had Hb between 9 and 11 g/dL at baseline (Berbec et al, 2018). Similarly, several other European observational studies also reported low baseline Hb values among patients treated with an ESA in routine clinical practice (Trotta et al, 2017; Steinmetz et al, 2016; Ray-Coquard et al, 2012), suggesting that patients are indeed treated according to the label. Real-world ESA utilisation in chemotherapy patients remains low and is higher among more severe patients (Tang et al, 2018; Aerts et al, 2012; Ludwig et al, 2004). A significant decline in oncological ESA use has been observed in US data between 2006

and 2013, following regulatory and reimbursement changes (Gawade et al, 2017). The same study also documented a pattern of ESA use largely consistent with US product labelling.

7.2 Rationale

Myelosuppressive chemotherapy is a common cause of anaemia in cancer patients and ESAs, including darbepoetin alfa are used to reverse the CIA and reduce the need for RBC transfusions. However, safety concerns regarding increased mortality or tumour progression with ESAs have been raised by some clinical trials and this is a potential risk in the risk management plan of darbepoetin alfa that requires further investigation.

Part of this investigation was the conduct of Study 20070782 - a phase 3, randomized, double-blind, placebo-controlled, noninferiority study in subjects with chemotherapy-induced anaemia receiving multi-cycle chemotherapy for the treatment of advanced stage NSCLC.

Study 20070782 demonstrated no increased risk of mortality or progression as compared to placebo. However, real-world use may differ from the use in clinical studies, and thereby introduce risks not observed in controlled studies. Therefore, Amgen proposes to evaluate ESA use in a European setting and **determine** if and how it might differ from the randomized controlled trial.

Amgen agreed to perform a real-world drug utilisation study as an EMA post-marketing requirement. Similarly, to the US investigation (PMC Study 20170210), Amgen proposes to characterize the use of ESAs in cancer patients undergoing myelosuppressive chemotherapy in Europe and the UK, to observe whether the drug utilisation is different from that observed in Study 20070782 and if this might impact the applicability of trial results to real-world data. A second aim is to determine if the pattern of use is consistent with the European and UK label. This study will be added as a Category 3 post authorisation safety study (PASS) to the pharmacovigilance plan.

Any findings of a substantial prevalence of use inconsistent with Study 20070782, may warrant the initiation of a study to assess mortality risk associated with this alternate pattern of use.

7.3 Feasibility and Futility Considerations

The intention was to perform a retrospective study cohort using existing European and UK real-world databases. For this purpose, a feasibility assessment of 17 databases, including medical claims, hospital-based EMR sites and registries, from 8 European

countries (EU3 + the Nordics + Portugal) was conducted. Databases were assessed for adequacy of capturing key data (including Hb levels, supportive care therapy including type and dose of ESA, chemotherapy regimens, and tumour types) as well as data access and generalisability. The conclusion of the feasibility assessment was that this design is not optimal due to: low absolute number of patients treated with ESAs of interest in the relevant time period in the databases, a lack of adequate capture of laboratory values as Hb values (eg, claims data/registries), or barriers to access (ie, hospital sites' willingness to provide EMR/EHR data) that hinder the possibility to provide a sufficiently large/representative sample of ESA use in oncology settings in Europe and the UK. By contrast, a chart abstraction from EMR/EHR data of patients with ESAs from a respective sample of European countries was considered to be a design that fulfils efficiency criteria, while making it possible to collect all required information on the essential variables.

7.4 Statistical Inference (Estimation or Hypothesis)

The number and proportion (%) of patients with a baseline Hb level of (i) ≤ 10 g/dL (as per SmPC) and (ii) ≤ 11 g/dL (as per Study 20070782) prior to or at initiation of ESA treatment will be summarized with descriptive statistics overall and stratified by ESA type, type of malignancy, and country.

8. Research Question and Objectives

The aim of this study is to describe the real-world use of ESAs in cancer patients with non-myeloid malignancies receiving myelosuppressive chemotherapy in Europe and the UK, specifically to establish whether ESAs are being used according to the product label and consistent with Study 20070782.

8.1 Primary

- Describe the baseline Hb levels at initiation of treatment with ESA in patients receiving myelosuppressive chemotherapy

8.2 Secondary

- Describe the baseline demographic and clinical characteristics of patients initiating treatment with an ESA and receiving myelosuppressive chemotherapy
- Describe the duration of ESA prescription in subjects receiving myelosuppressive chemotherapy
- 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 will be categorized by long-acting and short-acting ESAs to avoid dose conversion.

- Describe Hb levels during treatment with ESAs in patients receiving myelosuppressive chemotherapy.
- 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.

9. Research Methods

9.1 Study Design

This study will be a retrospective multi-centre observational study conducted in **6** countries: France, Germany, Italy, Spain, the United Kingdom, and Belgium . It will document real-world ESA-related measures in patients with non-myeloid malignancies treated with chemotherapy at university hospitals, community hospitals, private practice and community-based clinics typical of those that treat patients for whom ESAs are indicated.

9.2 Setting and Study Population

9.2.1 Study Period

The study period is anticipated to include data spanning from January 2015 (based on updated guidance by the National Institute for Health and Care Excellence [NICE] at the end of 2014; NICE 2014) until last patient enrolled. Erythropoiesis Stimulating Agents treatment initiation (the prescription date) will be considered the study index date. Patients will be followed from the index date until 9 weeks post-index date or if 1 of the following criteria is met: ESA treatment end date, death, or date of consent/enrolment, whichever comes first. Baseline data to provide details on the patient's medical condition prior to use of ESA may include data from medical records prior to January 2015.

9.2.2 Selection and Number of Sites

This study aims to enrol**l** patients from **approximately 24** sites drawn from **countries within the EU** and the United Kingdom. If the number of potential patients from the final list of selected sites falls below the planned sample size, additional sites within the **countries** already identified may be included. Sites will be approached based on physicians who prescribe ESAs and target where possible Oncologists and Haematologists who are prescribing ESAs.

9.2.3 Subject/Patient/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

Patients will be included in the study if they meet all the following criteria:

- At least 1 recorded primary diagnosis for any non-myeloid malignancy within 1 year before index date (ie, ESA treatment initiation) preceding the first chemotherapy administration
- At least 1 administration for a myelosuppressive chemotherapy drug (any line of therapy) before index date
- At least 1 administration of an ESA during the study period
- A minimum of a 9-week period between ESA treatment initiation and enrolment/consent
- Aged ≥ 18 years at index date
- Medical records (including diagnosis, demographics) are available for review and data extraction
- At least 1 Hb recording on or before the index date (the most proximal laboratory value available within 4 weeks prior to index date will be collected).
- Have provided written informed consent or appropriate parties have been notified of participation (alive or deceased), where required for access to medical charts, according to local laws and regulation requirements.

9.2.3.2 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- A diagnosis of chronic or acute kidney disease-induced anaemia 1 year before index date
- A diagnosis of myelodysplastic syndrome within 1 year before index date
- ESA administration prior to the index date
- Index ESA administration before 1 January 2015

9.2.4 Matching

Not applicable.

9.2.5 Baseline Period

The baseline period is considered 1 year before index date. Collection of comorbidities and associated ongoing concomitant medications may include data prior to this period.

9.2.6 Study Follow-up

All information relating to an individual patient will be collected retrospectively using medical records. All ESA treatment episodes will be collected from the index date until 9 weeks post-index date or if 1 of the following criteria is met: ESA treatment end date, death, or date of consent/enrolment, whichever comes first.

9.3 Variables

9.3.1 Exposure Assessment

The main exposure for the study will be treatment with ESAs – either darbepoetin alfa or epoetin (any type). Information on use of an ESA treatment will be determined by the presence of 1 or more prescriptions for an ESA as recorded in the EMR, including time of each administration (if available), dose and type of ESA.

- Date of ESA prescriptions
- Type of ESA
- Frequency of ESA administration (where available)
- Dose of ESA
    - Recorded dose at each prescription
    - Dose modifications: recorded as raw values and categorised and reported as nominal categorical variables: dose increase/dose decrease/interruption.
- Total duration of ESA prescription will be calculated and expressed in number of weeks on treatment, and by number with prescription duration of 3, 4, 6, and 9 weeks.

9.3.2 Outcome Assessment

Primary outcome

The most proximal Hb value within 4 weeks preceding (and including) the date of first ESA administration will be used to define the Hb level at index. The proportion of patients with the Hb value at index ≤ 10g/dL (as per SmPC), and ≤ 11 g/dL (as per Study 20070782) is the primary outcome.

There is no pre-specified threshold for determining an acceptable minimal clinical difference between Study 20080782 and this study. The results will be contextualized against Study 20070782 and other literature on ESA use.

Secondary outcome

For Hb levels during treatment, all available measurements during ESA treatment will be collected per patient.

Hb values achieved at pre-specified time points during treatment (ie, 3 weeks, 4 weeks, 6 weeks, and 9 weeks) will be reported. These time points are in line with recommended dosing intervals of the SmPC and Study 20070782.

The baseline demographic and clinical characteristics of patients initiating treatment with an ESA and receiving myelosuppressive chemotherapy will be described as the number and proportion (%) for each of the covariates listed in Section 9.3.3.

The duration of prescription will be collected for each ESA prescription. The mean duration of prescription will be described, and the number and proportion (%) of patients with an ESA prescription at 3, 4, 6, and 9 weeks will be described.

9.3.3 Covariate Assessment

- Demographics
  - Age, assessed at index as categorical in 5-year age bands: 18-20, 21-25, 26-30, 31-35, 36-40, 41-45, 46-50, 51-55, 56-60, 61-65, 66-70, 71-75, 76-80, 81-85, > 85
  - Sex
  - Country
- Clinical characteristics at index
  - Type of currently treated malignancy
  - Year of diagnosis for currently treated malignancy
  - Disease stage at diagnosis (nonmetastatic and metastatic)
  - Eastern Cooperative Oncology Group (ECOG) status
- Chemotherapy
  - Timing of administration
  - Drug(s) regimen
- Comorbidities
  - Hypertension
  - Acute liver disease
  - Chronic liver disease
  - Epilepsy
  - Sickle cell anaemia
  - Diabetes (1 and 2)
  - Thromboembolic events
  - Cardiac disease
  - Chronic pulmonary disease
  - Cerebrovascular disease
  - Peripheral vascular disease
  - Red cell aplasia
  - Chronic inflammatory disease (eg, rheumatoid arthritis, inflammatory bowel disease)
  - HIV or AIDS
  - Hepatitis B or C
- RBC transfusions
  - Count of RBC transfusions and number of units at baseline (in the last 3 months before index date)
  - Count of RBC transfusions during treatment

9.3.4 Validity and Reliability

The data collected for this study will be recorded in electronic case report forms (eCRFs) from routine clinical practice for the documentation and decision-making for a patient's care. Due to this, it is expected that the data collected will be routinely available in the medical records as the data include treatment(s) and evaluations involved in standard medical practice. By its nature, medical chart review is open to inter-observer variability in interpretation and abstraction of medical records. In addition, not all outcomes may appear in the charts. The problems of medical chart review are well recognized and various strategies have been proposed to increase validity and reliability of the data.

The eCRF will be structured in a way that allows sites to specifically indicate when requested data are missing or unknown. Sites participating in the study will be fully trained, in data entry and use of the study-specific data base and eCRFs. In addition, a number of quality control checks will be conducted at different time points on the collected data as described in Sections 9.6 and 9.8.

9.4 Data Sources

Source data will include patient medical records and charts (both electronic and/or paper based) as well as pathology and pharmacy databases. Study site staff will enter data into the eCRF retrospectively for each patient following enrolment into the study, based on data collected from routine clinical visits. Data for each patient will be recorded in accordance with normal clinical practice and no additional assessments or tests considered as interventional will be required.

9.5 Study Size

The planned sample size is estimated at 1625 patients who received an ESA during myelosuppressive chemotherapy, and at an estimated **24** study sites across the **6** countries. Recruitment will be competitive, with no limit on the number of **sites activated per country, or** patients recruited per site, country, or year, however patient recruitment will be reviewed regularly to minimise recruitment bias. Characteristics of recruited patients will regularly be compared, where data allows, against non-recruited site data, or published regional, and national data. Comparisons will include the distribution of cancer diagnoses and sociodemographic characteristics. The number of patients approached compared to the number consented per site will be regularly reviewed. The distribution of recruitment within and between countries will also be regularly reviewed. Where discrepancies arise, assertive outreach to site and country investigators will aim to encourage widened recruitment and site selection. Previous

European prospective studies describing Hb levels in patients receiving darbepoetin alfa and other ESAs enrolled between 150 and 1,800 patients (Aerts et al, 2012, Smakal et al, 2018, Berbec et al, 2018). In an analysis of patients with solid tumours who received darbepoetin alfa in European clinical practice between 2008 and 2010, darbepoetin alfa was initiated at a Hb level < 10 g/dL in 50% of breast cancer, 57% of CRC, 60% of ovarian, and 57% of lung cancer patients (Aerts et al, 2012). The Hb level at ESA initiation was between 9 and < 11 g/dL in 80% of breast cancer, 76% of CRC, 76% of ovarian, and 77% of lung cancer patients. A study in multiple European countries to evaluate quality of life in CIA patients treated with ESAs between 2011 and 2013 found that baseline Hb was ≤ 10 g/dL in 97% of patients (clinicaltrials.gov a). A study of darbepoetin alfa use for CIA in Central and Eastern Europe between 2012 and 2016 found that 73% had Hb < 10 g/dL at baseline (Smakal, 2018). A study of darbepoetin alfa use for CIA in Romania between 2011 and 2015 found that 81% had Hb between 9 and 11 g/dL at baseline (Berbec et al, 2018).

The table below provides estimates for the half-width of the 95% CI surrounding a range of proportions (columns) and sample size (rows) expected. One half the width of the 95% CI for proportions is calculated using an exact method proposed by Clopper **and** Pearson (Clopper and Pearson, 1934). The sample size is expected to provide adequate precision for estimation of the primary objective, but not for comparisons between initiation groups.

Table 1. Half Width of the 95% CI for Various Estimated Proportions of (eg, Hb ≤ 10 g/dL), by Sample Size (n)

	Proportion				
Sample size	0.5	0.6	0.7	0.8	0.9
40	0.161982	0.159041	0.149845	0.132978	0.104356
60	0.131938	0.129486	0.121816	0.10773	0.083733
80	0.113952	0.111807	0.105093	0.092755	0.071697
100	0.101679	0.099748	0.093704	0.082594	0.063609
200	0.071342	0.069959	0.06563	0.057666	0.044027
300	0.058002	0.056869	0.053319	0.046787	0.035591
400	**0.050092**	**0.049108**	**0.046028**	**0.040357**	**0.030636**
500	**0.044714**	**0.043833**	**0.041074**	**0.035996**	**0.027287**
600	**0.040756**	**0.039951**	**0.037431**	**0.032790**	**0.024831**
700	**0.037687**	**0.036942**	**0.034606**	**0.030307**	**0.022933**

800	**0.035218**	**0.034520**	**0.032335**	**0.028312**	**0.021410**
900	**0.033176**	**0.032518**	**0.030457**	**0.026662**	**0.020152**
1000	**0.031451**	**0.030826**	**0.028870**	**0.025269**	**0.019091**
1100	**0.029968**	**0.029373**	**0.027507**	**0.024073**	**0.018181**
1200	0.028677	0.028106	0.02632	0.023031	0.017389
1300	0.027538	0.02699	0.025274	0.022113	0.016691
1400	0.026525	0.025997	0.024342	0.021297	0.01607
1500	0.025615	0.025105	0.023507	0.020564	0.015514
1600	0.024793	0.024299	0.022751	0.019901	0.015011
1700	0.024045	0.023565	0.022063	0.019299	0.014554
1800	0.02336	0.022894	0.021435	0.018747	0.014136

9.6 Data Management

All data will be collected by site investigators identified by the **Clinical Research Organisation** (CRO **([**IQVIA**]**). Data are abstracted by site staff from source data into an electronic database. Protocol-specific training and eCRF completion instructions will be provided to all site staff delegated to abstract patient data.

Each patient will be assigned a unique identification number at the time of the first data entry. This unique identification number will be used to link data to subsequent retrospective data entries. The data will be abstracted by site staff from patient's medical records using an electronic abstraction form that will provide an integrated, transparent tool to facilitate and record centre recruitment, case identification, patient selection, and study progress at the centre and patient level. The electronic database will include eCRFs designed to capture the variables and outcomes of interest. The data collected for this study will be derived from medical records that are kept per routine clinical practice for the documentation and decision-making for a patient's care.

9.6.1 Obtaining Data Files

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's "audit trail."
- To ensure the quality of clinical data across all patients and sites, automated logic checks related to data entry will be implemented. In addition, clinical data management review will be performed on patient data received. During this review, patient data is checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process,

data queries and/or site notifications are created in the electronic database for site resolution and closed by the reviewer.

- The physician signs only the Physician Verification Form for this EDC study. This signature indicates that the physician inspected or reviewed the data on the eCRF, the data queries, and site notifications, and agrees with the content.

Protocol-specific training on the eCRFs will be provided to all study site abstractors in advance of the study data collection period to ensure clarity on the questions and the data to be captured are accurate.

9.6.2 Linking Data Files

Not applicable.

9.6.3 Review and Verification of Data Quality

The clinical monitor or designee is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data, and adherence to local regulations on the conduct of research. The clinical monitor or designee is to have access to patient medical records and other study-related records needed to verify the entries on the eCRFs where allowed, in accordance with the local laws and regulations.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Analysis

An interim analysis will be conducted by the CRO (IQVIA) when the study reaches 600 participants. The aim of the interim analysis is to describe the study population, report interim findings on the primary outcomes, the proportion of patients with Hb values at index ≤ 10g/dL (as per SmPC), and ≤ 11 g/dL (as per Study 20070782), and to determine the probability that the results found in the interim analysis would be different if conducted with a larger sample size. The results of the interim analysis will be valuable in examining the prescribing practices at various index Hb values currently observed in Study 20190404 and comparing those with results from similar studies (eg, Study 20170210) to assist with future interpretation and assessment of results from Study 20190404. The interim analysis sample size of 600 has been selected as it provides a similar level of precision in the highest predicted proportion of patients with Hb ≤ 10 g/dL (at a 0.9 proportion), as would the aimed 1625 patient sample at the lowest predicted proportion of patients with Hb ≤ 10 g/dL (at a 0.5 proportion, Table 1).

All variables will be presented as stated in the primary analysis (see Section 9.7.2). Categorical variables will be presented as counts and percentages of the total. Continuous variables will be described using the mean, standard deviation, median, first quartile, third quartile, minimum and maximum. Point estimates will be accompanied by 95% CIs. No imputation method will be used for missing data. Patients with missing age, sex, information about malignancy diagnosis, ESA treatment (start date), chemotherapy treatment, and Hb value recorded at baseline will be excluded during the selection procedure (see Section 9.2.3). For the other variables, missingness will be quantified and reported as the number and percentage of missing observations for each variable.

Patient demographics and clinical characteristics will be presented overall. The primary outcomes, the proportion of patients with Hb values at index ≤ 10g/dL (as per SmPC), and ≤ 11 g/dL (as per Study 20070782), will be presented overall. No subgroup analyses will be reported in the interim analysis.

In addition, Bayesian posterior probabilities and predicted probabilities may be calculated to describe the distribution of proportion of patients with a Hb value at index ≤ 10g/dL and the probability of that proportion being above a given threshold.

9.7.1.2 Primary Analysis

All protocol-specified data analysis will be conducted by the CRO (IQVIA). The primary analysis will be conducted **at the end of the** data collection **period**.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

Categorical variables will be presented as counts and percentages of the total. Continuous variables will be described using the mean, standard deviation, median, first quartile, third quartile, minimum and maximum. Point estimates will be accompanied by 95% CIs.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

No imputation method will be used for missing data. Patients with missing age, **sex**, information about malignancy diagnosis, ESA treatment (start date), chemotherapy treatment, and Hb value recorded at baseline will be excluded during the selection procedure (see Section 9.2.3.1).

For the other variables, missingness will be quantified and reported as the number and percentage of missing observations for each variable.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrolment

Study enrolment will be tabulated by country, by type of primary tumour, and by type of ESA.

9.7.2.3.2 Description of Subject/Patient Characteristics

Patient demographics (age, sex), clinical characteristics (malignancy characteristics, type of chemotherapy treatment received, presence of comorbidities and previous receipt of RBC transfusions), type of ESA, and country will be summarized with descriptive statistics overall and by ESA type, where appropriate.

9.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

Primary endpoint

The number and proportion (%) of patients receiving myelosuppressive chemotherapy with a baseline Hb level of ≤ 10 g/dL (as per SmPC), and ≤ 11 g/dL (as per Study 20070782) prior to or at initiation of ESA treatment will be summarised with descriptive statistics overall and stratified by ESA type, type of malignancy, and country.

The variable will be expressed both as continuous (mean, SD, median, min and max) and categorical (≤ 10 g/dL vs > 10 g/dL and ≤ 11 g/dL vs > 11 g/dL), in accordance with **the** SmPC and Study 20070782 categorization.

Secondary endpoints

The baseline demographic and clinical characteristics of patients initiating treatment with an ESA and receiving myelosuppressive chemotherapy will be described as the number and proportion (%) for categorical variables, or as means, SD, median, min and max for continuous variables, for each of the covariates listed in Section 9.3.3, and stratified by ESA type, type of malignancy, and country.

The frequency of ESA treatment, the number of ESA prescriptions, and the duration of ESA prescriptions will be summarized with descriptive statistics overall and stratified by ESA type, type of malignancy, and country. The number and proportion (%) of patients prescribed an ESA for 3, 4, 6, and 9 weeks will be reported.

The starting dose will be summarized with descriptive statistics by ESA type. The number and proportion (%) of patients with at least 1 dose modification will be reported

overall, and (where available) by type of dose modification (eg, dose reduction, dose escalation, therapy interruption).

The number and proportion (%) of patients with 1 or more repeated Hb measures after baseline will be reported.

Hb values reached at pre-specified time points during treatment (ie, 3 weeks, 4 weeks, 6 weeks, and 9 weeks) will be described.

Hb values during treatment will be described in terms of:

- Mean, standard deviation, median, interquartile range, minimum, maximum values.
- The proportion of patients reaching the target Hb level, expressed as:
  - Below target level (≤ 10 g/dL)
  - Target range (> 10 to ≤ 12 g/dL)
  - Above target level (> 12 g/dL)
- The proportion of patients at week 9 who:
  - Had a rise in Hb of more than 2 g/dL in any 4-week period
  - Had a rise in Hb of more than 2 g/dL in any 4-week period that did not have a subsequent ESA dose reduction or therapy interruption

Handling of multiple measurements per patients:

All Hb values as recorded within ± 6 days around each time point of interest (3, 4, 6, and 9 weeks) will be used to inform on the values to be reported for this study. The mean and median value for each patient will be calculated for each time point. For example, at 3 weeks (day 21), the mean and median of all Hb values recorded in days 15-27 will be calculated.

9.7.2.5 Sensitivity Analysis

For the calculation of Hb values both at baseline and during treatment, we will perform a sensitivity analysis that excludes values from patients with RBC transfusions in the last 28 days from the recorded Hb value, in line with Study 20070782.

9.7.2.5.1 Subgroup Analysis

The primary and secondary objectives will be reported according to the following subgroups:

- Type of ESA (darbepoetin alfa or epoetin)
- Type of primary tumour (all lung [and NSCLC separately], breast cancer total, adjuvant-treated breast cancer, metastatic breast cancer, colorectal cancer, or lymphoma). Patients diagnosed with other non-myeloid tumour types will not be evaluated as specific subgroups
- Country: Belgium, France, Germany, Italy, Spain, **and** the United Kingdom

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Safety data will not be collected or analysed in this study.

9.8 Quality Control

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or correction on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the patient eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, and correspondence. The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Documents to be maintained for the study are as follows:

- Patient files containing the completed eCRF, informed consent forms, as applicable, and patient identification list
- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available. Retention of study documents will be governed by the contractual agreement with Amgen.

Amgen retains all data, programs and outputs generated for the study. At study close, data are uploaded from the electronic clinical database and stored in accordance with Amgen Standard Operating Procedures (SOPs). Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

9.9 Limitations of the Research Methods

A potential limitation to this study is an inability to recruit a sufficient sample who meet the inclusion criteria, and who are both contactable in order to consent and proceed to give informed consent. To minimize this risk, the study has identified a pool of 195 potential study sites and will increase site recruitment as is necessary to capture an adequate study population. A further limitation is introducing selection bias through recruitment of sites and patients who are able and willing to give informed consent. These limitations are discussed in more details in Section 9.9.1.3.

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

Misclassification of either diagnosis or exposure may occur and is discussed below in Section 9.9.1.2 Information bias.

Data are collected retrospectively directly from medical records which are limited by the completeness and accuracy of the underlying data. Data that are not recorded in the EMR/EHR, that are miscoded in the EMR/EHR, or that fail to accurately describe clinical diagnoses all have the potential to introduce bias. Hb measurements might be erroneously measured and recorded; this potential error cannot be avoided; however, it is expected to be minimal and randomly distributed across patients.

9.9.1.2 Information Bias

As in all pharmacoepidemiological studies, there is potential for misclassification bias. However, the exposure is to a specialist product with a narrow indication, therefore it is expected that the misclassification of the disease will be minimal.

Checks of treatment doses against the expected values will be made.

9.9.1.3 Selection Bias

The biggest threat to validity is the potential selection bias, through the selection of study sites and the recruitment of patients.

The selection of study sites will not be completely at random; research-focused study sites, those with capacity to conduct the data collection, and those that are likely to

prescribe the product according to the guidelines are more likely to respond, and therefore a degree of selection bias is unavoidable.

Patients if mandated by local legislation, are required to give informed consent for their data to be collected. The proposed study is a retrospective chart review and selection bias may be introduced during the consenting procedure. Patients who are not contactable to give informed consent may differ from those who are contactable in terms of time of treatment (those who were treated earlier in the included study period may be more difficult to contact), demographic characteristics, and treatment outcome. Bias may also be introduced through the process of informed consent, whereby those willing to give informed consent may be systematically different from those who do not due to treatment outcome (either dissatisfaction with care or due to death).

Selection of sites

- Characteristics of study sites who agree to participate and provide data for the study will be compared to those of non-responding study sites (who refused to participate or were not reachable).
- Sites will be selected based on their capacity to include eligible patients so as to achieve the target sample size. It is expected that some smaller centres will not have **the** capacity to participate in the study and some centres may not be willing to participate. All efforts will be made to select sites representative of specific settings (eg, geographic regions).

Selection of patients

To avoid selection bias when selecting patients, the following measures will be in place:

- The inclusion criteria will be kept minimal to maximise generalisability.
- Patient characteristics will be compared with other published studies on ESA utilisation.

9.9.1.4 Confounding

This is not an aetiological study therefore confounding is not applicable.

9.9.2 External Validity of Study Design

As the dataset will be a subset of eligible cancer patients with non-myeloid malignancies, it is probable that non-participating sites differ slightly in terms of geography, demographics, socioeconomics and clinical practice. The demographic and clinical profile of included patients will be compared to similar populations of interest, that is cancer patients exposed to myelosuppressive chemotherapy who are initiated on ESAs in each included country, through comparison to published data where data allows.

9.9.3 Limitations Due to Missing Data and/or Incomplete Data

Only patients with data available on the key variables will be included and analysed. This might bias the results towards a more positive view than the real-world use, if the data is not missing at random.

Data is collected retrospectively from medical charts and therefore data completeness relies on accurate recording in these medical charts at the time of treatment. There may be missing data for variables where the missingness is related to non-documentation, resulting in non-recorded key information such as patient comorbidities. Source data will be collected and compared from a wide range of sources, including both oncology, hospital, pharmacy, and pathology databases (where available) to minimize this type of missing data.

Data may also be missing for secondary outcomes such as Hb levels at the 3-, 4-, 6-, 8-, and 9-week follow-ups. Regular Hb monitoring during ESA treatment is recommended within the SmPC, and we expect there to be high levels of completion. However, discontinuation of ESAs during the follow-up period or missing data will reduce the precision of our estimates for these secondary outcomes.

Erroneous entries might occur during the abstraction process; however, it is expected for these to be non-differential. Logical checks and clinical data management review will be used in the data collection form, to minimize this type of error.

As many variables are requested to be collected for each patient, there is a risk of incomplete completion of questionnaire and increased prevalence of missing data. It is expected to be non-differential and decrease the precision around estimate but not the direction of the estimate.

10. Protection of Human Subjects/Patients

This study will comply with all relevant ethical and regulatory requirements in each country and data collection will be conducted in accordance with the relevant local laws.

The responsible physician is also responsible for sending the following documents to Amgen or its representative for review before study initiation occurs:

- Signed and dated protocol signature page (Responsible Physician's Agreement)
- Copy of the Central Ethics Board approval of the protocol, waiver for requirement of informed consent where applicable
- Up-to-date curriculum vitae of responsible physician and all co/sub-physicians
- Signed confidentiality agreement

- Signed study contract

The responsible physician will be charged with maintaining correct and comprehensive documentation, while the Amgen or designated CRO monitor/designee is tasked to ensure that the responsible physician is following the correct study protocol.

10.1 Informed Consent

Where required by local laws and regulations, living patients will provide informed consent before any data is collected for the purpose of this study. A template informed consent form will be provided for the investigator or designee to prepare the local informed consent document to be used at his or her site. Where required by local laws and regulations, agreement to participate will be sought from appropriate parties for the inclusion of a deceased patient's data. Updates to the sample informed consent form are to be communicated formally in writing from the IQVIA Study Manager to the investigator or designee. The written informed consent form is to be prepared in the native language(s) of the participating country.

Before a patient's participation in the study, the investigator or designee will explain to the patient, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study.

The acquisition of informed consent is to be documented in the patient's medical records, and the informed consent is to be provided and dated by the patient [or a legally acceptable representative] and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the patient or the patient's legally authorized representative.

If local regulations do not require an informed consent to be signed but mandate that the patient be notified about the study, the investigator or designee should document the notification process in the patient's medical record.

10.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB/IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen or delegate before the study can be executed. The investigator must submit and, where necessary, obtain

approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The investigator is to notify the IRB/IEC or other relevant ethical review board of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures. The investigator is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the investigator's Reports, where applicable by local regulations and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

10.3 Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained for documents submitted to Amgen.

Patients will be assigned a unique identifier by the CRO (IQVIA). Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations and/or ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agencies, and the IRB/IEC direct access to review the patient's original medical records for verification data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

10.4 Patient Decision to Withdraw

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the patient does not wish to or is unable to continue further study participation. Patient data that are publicly available data can be included after withdrawal of consent. As per local regulations, upon withdrawal of consent, the patient has the right to request removal of their data that was collected and

not have it further processed. The investigator is to discuss with the patient appropriate steps for withdrawal of their consent from the study.

11. Collection, Recording, and Reporting of Safety Information and Product Complaints

11.1 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from medical charts, and pharmacy and phlebotomy data and no safety data will be collected.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. When Amgen amends the protocol and distributes the protocol amendment to the sites, written agreement from the investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval for all protocol amendments that Amgen provides to the site. The investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen or their delegate.

Amgen reserves the right to terminate the study at any time. The EMA must be consulted and should give approval for study termination before Amgen provides notification to sites. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the contractual agreement. The investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

For any major amendments happening outside the EMA review cycle, the PRAC will be informed and the protocol resubmitted.

13. Plans for Disseminating and Communicating Study Results

The results of the study will be submitted to PRAC in a final study report.

This study will be registered on the ENCePP website before the start of data collection, and the study summary results will be posted on this public website no later than 12 months after study termination (defined as 'database lock'). The results for this study will be submitted for publication.

13.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and decision, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. References

Aapro M, Beguin Y, Bokemeyer C, et al. Management of Anaemia and Iron Deficiency in Patients With Cancer: ESMO Clinical Practice Guidelines | ESMO. Ann Oncol 2018 [Internet]. 2018 [cited 2019 Dec 12];29(Suppl 4). Available from: https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Anaemia-and-Iron-Deficiency-in-Patients-With-Cancer

Aerts JG, Swieboda-Sadlej A, Karanikiotis C, et al. Use of darbepoetin alfa in European clinical practice for the management of chemotherapy-induced anaemia in four tumour types: final data from the CHOICE study. Curr Med Res Opin. 2012 Jul;28(7):1089–1099.

Aranesp Summary of Product Characteristics [Internet]. 2006. Available from: https://www.ema.europa.eu/en/documents/product-information/aranesp-epar-product-information_en.pdf

Berbec NM, Stanculeanu DL, Badelita NS, et al. APPLY: A prospective observational study of clinical practice patterns of darbepoetin alfa use in patients with chemotherapy-induced anemia in Romania. Memo. 2018;11(2):144–151.

ClinicalTrials.gov [Internet]. Bethesda (MD) -. Anemia Treatment for Advanced Non-Small Cell Lung Cancer (NSCLC) Patients Receiving Chemotherapy -20070782 [Internet]. 2019 [cited 2019 Dec 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT00858364

ClinicalTrials.gov [Internet]. Bethesda (MD) -. Assessment of Quality of Life in Patients with Symptomatic Chemotherapy-induced Anaemia - Full Text View - ClinicalTrials.gov [Internet]. 2019 [cited 2019 Dec 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT01444456

Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 26 (1934):404-416.

Gawade PL, Berlin JA, Henry DH, et al. Changes in the use of erythropoiesis-stimulating agents (ESAs) and red blood cell transfusion in patients with cancer amidst regulatory and reimbursement changes. Pharmacoepidemiol Drug Saf. 2017 Nov;26(11):1357–1366.

Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer Oxf Engl 1990. 2004 Oct;40(15):2293–2306.

National Institute for Health and Social Care Excellence. Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy [Technological appraisal guidance TA323]. 2014. Available from: https://www.nice.org.uk/guidance/ta323

Ray-Coquard I, Morère J-F, Scotté F, Cals L, Antoine E-C. Management of anemia in advanced breast and lung cancer patients in daily practice: results of a French survey. Adv Ther. 2012 Feb;29(2):124–133.

Smakal M. ARTIST: Evaluation of the current management of hemoglobin (Hb) levels in cancer patients with symptomatic chemotherapy-induced anemia (CIA) treated with darbepoetin alfa (DA). Eur J Cancer 92 Suppl 3 2018 S17–S160.

Steinmetz T, Schröder J, Plath M, et al. Antianemic Treatment of Cancer Patients in German Routine Practice: Data from a Prospective Cohort Study-The Tumor Anemia Registry. Anemia. 2016;2016:8057650.

Tang WY, Vlahiotis A, Fung S, Arantes L, Chambers R. Current burden of chemotherapy induced anemia and patterns of erythropoiesis-stimulating agents utilization. J Clin Oncol. 2018 May 20;36(15_suppl):e18765–e18765.

Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database of Systemic Reviews. PubMed. 2012 Dec;12(12):CD003407.

Trotta F, Belleudi V, Fusco D, et al. Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: a population-based cohort study in Italy. BMJ Open. 2017 Mar 10;7(3):e011637.

15. Appendices

Appendix A. List of Stand-alone Documents

None.

Appendix B. ENCePP Checklist for Study Protocols (Revision 4)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

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, 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). 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).

Study title: Use of Erythropoiesis Stimulating Agents (ESAs) in Patients Receiving Myelosuppressive Chemotherapy in Europe

EU PAS Register® number: EU PAS 497757
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	4
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
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)	☒	☐	☐	7.1 & 7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.3.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7.4

[1] 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.
[2] Date from which the analytical dataset is completely available.

Comments:

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
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☐	☐	☒	
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)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1
	4.2.2 Age and sex	☒	☐	☐	9.2.3
	4.2.3 Country of origin	☒	☐	☐	9.2.2
	4.2.4 Disease/indication	☒	☐	☐	9.2.3
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.6
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.2

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)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.4
5.3	Is exposure categorised according to time windows?	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	9.3.1
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?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.4
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:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	9.9.1.3
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.1.2

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)	☒	☐	☐	9.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	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)	☐	☒	☐	
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical [ATC] Classification System)	☐	☒	☐	
9.3.2 Outcomes? (eg, International Classification of Diseases [ICD], Medical Dictionary for Regulatory Activities [MedDRA])	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

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?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2.2
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

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?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

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?	☒	☐	☐	9.9.1.3
12.1.2 Information bias?	☒	☐	☐	9.9.1.2
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).	☐	☐	☒	
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?	☐	☐	☒	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	10.2
13.3 Have data protection requirements been described?	☐	☒	☐	10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	6

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)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: PPD

Date:

Signature: