EUROPEAN UNION RISK MANAGEMENT PLAN

Aranesp® (darbepoetin alfa)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	10.0
Date:	19 March 2025
Supersedes:	Version 9.7, dated 21 March 2022

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	10.0
Data lock point (DLP) of this RMP:	31 October 2024
Date of final sign-off:	19 March 2025
Rationale for submitting an updated RMP:	• Removal of the important potential risk of 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission' • Removal of the additional risk minimization measures (aRMMs) of 'Demonstration device, training checklist, and poster-size instructions for use (IFU) for patients/caregivers with diminished eyesight for Aranesp SureClick® (Pre-filled Pen) self-administration'.

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part II: Safety Specification		
SIII: Clinical Trial Exposure	Updated the clinical trial exposure tables to a data lock point of 31 October 2018	Version 10.0, 19 March 2025
SV: Postauthorization Experience	Updated the postmarketing exposure to a data lock point of 31 October 2024	Version 10.0, 19 March 2025
SVII: Identified and Potential Risks	Removed the important potential risk of 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission'	Version 10.0, 19 March 2025
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	Updated the status and milestone due date of the final report for Study 20190404	Version 10.0, 19 March 2025
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	• Updated the routine pharmacovigilance activities to align with the changes in Part II, Module SVII above • Removed the aRMMs of demonstration device, training checklist, and poster-size IFU for patients/caregivers with diminished eyesight for Aranesp SureClick (pre-filled pen) self-administration • Updated the summary of risk minimization measures to align with the changes above	Version 10.0, 19 March 2025
Part VI: Summary of the Risk Management Plan	Updated to align with the changes in the sections above	Version 10.0, 19 March 2025
Part VII: Annexes		
Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	Updated the status and milestone due date of the final report for Study 20190404	Version 10.0, 19 March 2025
Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	Updated to include the latest protocol amendment for Study 20190404	Version 10.0, 19 March 2025
Annex 6: Details of Proposed Additional Risk Minimization Activities	Removed the details for the aRMMs of demonstration device, training checklist, and poster-size IFU for patients/caregivers with diminished eyesight for Aranesp SureClick (pre-filled pen) self-administration	Version 10.0, 19 March 2025

Other RMP versions under evaluation:	
RMP version number:	None
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	9.7
Approved with procedure:	EMEA/H/C/000332/IB/0160
Date of approval (opinion date):	20 May 2022
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
ADR	adverse drug reaction
aRMM	additional risk minimization measures
CKD, CRF	chronic kidney disease, chronic renal failure (used interchangeably in this document)
DHPC	Direct Healthcare Professional Communication
DLP	data lock point
DOPPS	Dialysis Outcomes and Practice Patterns Study
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EpoR	erythropoietin receptor
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
EU	European Union
HCP	healthcare professional
HIV	human immunodeficiency virus
HR	hazard ratio
IFU	instructions for use
IV	intravenous(ly)
MAH	marketing authorization holder
PBRER	Periodic Benefit-Risk Evaluation Report
PI	Product Information
PIL	Patient Information Leaflet
PL	package leaflet
PRCA	pure red cell aplasia
PSUR	Periodic Safety Update Report
QM	once monthly
QPPV	Qualified Person for Pharmacovigilance
QW	once weekly
Q2W	once every 2 weeks
Q3W	once every 3 weeks
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
rHuEPO	recombinant human erythropoietin

Term/Abbreviation	Explanation
RMP	Risk Management Plan
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
START-CKD	study entitled “Strategies Using Darbepoetin alfa to Avoid Transfusions in chronic kidney disease”
TREAT	study entitled “Trial to Reduce Cardiovascular Events with Aranesp® Therapy” (Solomon et al, 2010; Pfeffer et al, 2009)
US	United States
USRDS	United States Renal Data System

PART I. PRODUCT(S) OVERVIEW

Table 1. Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Darbepoetin alfa
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	B03XA02
Marketing authorization holder (MAH)	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Aranesp® (darbepoetin alfa)
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Hyperglycosylated analogue of recombinant human erythropoietin (rHuEPO)
Summary of mode of action	Darbepoetin alfa binds to the erythropoietin receptor (EpoR) on erythroid progenitor cells and stimulates their proliferation and differentiation into mature red blood cells (RBCs), and also inhibits their apoptosis (Egrie et al, 2003; Macdougall, 2000).
Important information about its composition	Darbepoetin alfa is produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.
Indication(s) in the EEA	
Current:	Treatment of symptomatic anemia associated with chronic renal failure (CRF) in adults and paediatric patients. Treatment of symptomatic anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.
Proposed (if applicable)	Not applicable

Table 1. Product Overview

Dosage in the EEA Current:	<u>Treatment of Symptomatic Anemia in Adult and Pediatric CRF Patients</u> *Adult Patients With CRF* • Correction Phase: The initial dose by subcutaneous (SC) or intravenous (IV) administration is 0.45 μg/kg body weight, as a single injection once weekly (QW). Alternatively, in patients not on dialysis, the following initial doses can also be administered SC as a single injection: 0.75 μg/kg once every 2 weeks (Q2W) or 1.5 μg/kg once monthly (QM). • Maintenance Phase: In dialysis patients, darbepoetin alfa may continue to be administered as a single injection QW or Q2W. Dialysis patients converting from QW to Q2W dosing with darbepoetin alfa should initially receive a dose equivalent to twice the previous QW dose. In patients not on dialysis, darbepoetin alfa may continue to be administered as a single injection QW, Q2W, or QM. *Pediatric Population With CRF* • Correction Phase: For patients ≥ 1 year of age, the initial dose by SC or IV administration is 0.45 μg/kg body weight, as a single injection QW. Alternatively, in patients not on dialysis, an initial dose of 0.75 μg/kg may be administered SC as a single injection Q2W. • Maintenance Phase: For pediatric patients ≥ 1 year of age, darbepoetin alfa may continue to be administered as a single injection QW or Q2W. Patients < 6 years of age may need higher doses for maintenance of hemoglobin than patients above that age. Dialysis patients converting from QW to Q2W dosing with darbepoetin alfa should initially receive a dose equivalent to twice the previous QW dose. In patients ≥ 11 years of age not on dialysis, once the target hemoglobin has been achieved with Q2W dosing, darbepoetin alfa may be administered SC QM using an initial dose equal to twice the previous Q2W dose.

Table 1. Product Overview

Dosage in the EEA (continued) Current (continued):	*Pediatric Population With CRF (continued)* • Maintenance Phase (continued): Patients receiving rHuEPO 2 or 3 times weekly may be converted to QW darbepoetin alfa, and those receiving rHuEPO QW may be converted to Q2W darbepoetin alfa. The initial weekly pediatric dose of darbepoetin alfa (μg/week) can be determined by dividing the total weekly dose of rHuEPO (IU/week) by 240. The initial Q2W of darbepoetin alfa (μg/Q2W) can be determined by dividing the total cumulative dose of rHuEPO administered over a 2-week period by 240. The same route of administration should be used. *Treatment of Symptomatic Chemotherapy-induced Anemia in Cancer Patients* Darbepoetin alfa should be administered by the SC route to patients with anemia (eg, hemoglobin concentration ≤ 10 g/dL [6.2 mmol/L]) in order to increase hemoglobin to not greater than 12 g/dL (7.5 mmol/L). The recommended initial dose is 500 μg (6.75 μg/kg) given once every 3 weeks (Q3W), or QW dosing can be given at 2.25 μg/kg bodyweight.
Proposed (if applicable):	Not applicable
Pharmaceutical form(s) and strength(s) Current:	Darbepoetin alfa is supplied as a sterile, colorless, preservative-free protein solution for IV or SC injection in: • Pre-filled syringes at doses of 10, 15, 20, 30, 40, 50, 60, 80, 100, 130, 150, 300, and 500 μg (concentrations ranging from 25 to 500 μg/mL depending on dose). • SureClick pre-filled pens at doses of 10, 15, 20, 30, 40, 50, 60, 80, 100, 130, 150, 300, and 500 μg (concentrations ranging from 25 to 500 μg/mL depending on dose). • Vials at doses of 25, 40, 60, 100, 200, and 300 μg (concentrations ranging from 25 to 300 μg/mL depending on dose).
Proposed (if applicable):	Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Symptomatic Anemia Associated with CRF in Adults and Pediatric Patients

Incidence	Anemia is a common and important complication of CRF, which develops as kidney function declines and is ubiquitous among patients with end-stage renal disease (ESRD) (United States Renal Data System [USRDS], 2011); therefore, the incidence of anemia among CRF patients can be estimated from the incidence of ESRD. In 2013, the overall unadjusted incidence of renal replacement therapy for ESRD in 34 countries in Europe and bordering the Mediterranean Sea was 112 per million population (Kramer et al, 2016). In 2013, the unadjusted incidence of ESRD per million population was 110 in Australia, 182 in Brazil, 152 in Canada, 165 in Hong Kong, 286 in Japan, 101 in Norway, and 50 in Russia (USRDS, 2015). In the United States (US), the 2013 incidence rate of ESRD was 352 per million (adjusted for age, sex, and race/ethnicity) (USRDS, 2015).
Prevalence	The prevalence of anemia among chronic kidney disease (CKD) adult patients in the United States is estimated at 15.4% (Stauffer and Fan, 2014). The prevalence of anemia has been reported to increase with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5 (Stauffer and Fan, 2014). The crude prevalence of renal replacement therapy in 2013 among ESRD patients in 34 countries in Europe and bordering the Mediterranean Sea was 738 per million population (Kramer et al, 2016). Anemia among nondialysis CKD patients in the United States is common. The prevalence of anemia (hemoglobin < 12 g/dL in men and < 11 g/dL in women) increased from 1% among patients with an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 to 9% at an eGFR of 30 mL/min/1.73 m^2 and to 33% to 67% at an eGFR of 15 mL/min/1.73 m^2 (Hsu et al, 2002). Data describing the prevalence of CRF not on dialysis in Europe are limited (Hallan et al, 2006); however, the total prevalence of CRF not on dialysis was 10% in Norway (Hallan et al, 2006). The crude prevalence of ESRD per million population in 2013 was as follows: Australia (928), Brazil (771), Canada (1193) Hong Kong (1223), Japan (2411), Norway (901), and Russia (241) (USRDS, 2015). The adjusted prevalence of ESRD per million in the United States was 1981 (adjusted for age, sex, and race/ethnicity) (USRDS, 2015). Approximately 14% of individuals in the United States were estimated to have CKD between 2007 and 2012 (USRDS, 2015).

Table 2. Summary of Epidemiology of Symptomatic Anemia Associated with CRF in Adults and Pediatric Patients

Demographics of population in the authorized indication and risk factors for the disease	The identified primary causes for CKD among individuals with and without anemia have been well documented and include (USRDS, 2012): • diabetes • hypertension • glomerulonephritis Chronic renal failure occurs in men and women. The incidence of CRF increases with increasing age. Patients on dialysis with anemia (hemoglobin < 11.0 g/dL) are more likely to be younger, black, diabetic, and recently hospitalized (Collins et al, 2001). Patients on dialysis with anemia may be more likely to be women, although data are conflicting depending on the hemoglobin range studied (Gilbertson et al, 2013; Collins et al, 2001). Patients not on dialysis with anemia are more likely to be female, non-white, and slightly older compared with those without anemia (Vlagopoulos et al, 2005).
Main existing treatment options	Currently, anemia treatments for CKD patients include: • iron supplementation • erythropoiesis-stimulating agents (ESAs): – epoetin alfa, beta, theta, or zeta • and rarely RBC transfusions.
Natural history of the indicated condition in the population, including mortality and morbidity	The anemia of CKD is due primarily to reduced production of erythropoietin by the kidney and to shortened red cell survival (Eschbach, 1991). Anemia is a common feature in many patients with CKD who do not yet require dialysis, with anemia becoming increasingly common as eGFRs decline below 60 mL/min/1.73 m^2 (Astor et al, 2002; Hsu et al, 2002). Epidemiologic data suggest the rate of transition from an eGFR between 15 to 60 mL/min/1.73 m^2 to ESRD may be approximately 1.5% per year, while the rate of transition from an eGFR > 60 to < 60 mL/min/1.73 m^2 is approximately 0.5% per year (Fox et al, 2004; Hsu et al, 2004). In studies of individuals with CRF, anemia has been shown to be independently associated with cardiovascular morbidity, including heart failure (Thorp et al, 2009; Dowling, 2007), left ventricular hypertrophy, as well as adverse cardiovascular outcomes including mortality (Astor et al, 2004; McClellan et al, 2002; Parfrey and Foley, 1999). Cardiovascular morbidity is the primary cause of death among patients on dialysis in the United States and in many other countries (Foley and Hakim, 2009). In the first 4 months of dialysis, the mortality rate per 100 patient-years was 22.1 in the United Kingdom, 33.0 in the United States, 17.0 in Japan, 22.8 in France, 28.3 in Italy, 28.4 in Sweden, and 25.4 in Australia/New Zealand (Robinson et al, 2014). Anemia may also be a risk factor for progression of kidney disease to ESRD (Astor et al, 2006; Levin et al, 2006).

Table 2. Summary of Epidemiology of Symptomatic Anemia Associated with CRF in Adults and Pediatric Patients

Important comorbidities	• Diabetes (USRDS, 2014; Dialysis Outcomes and Practice Patterns Study [DOPPS], 2012). • Cardiovascular disease (DOPPS, 2012; McCullough et al, 2008; Schiffrin et al, 2007; Kundhal and Lok, 2005; Locatelli et al, 2004; Goodkin et al, 2003; Manjunath et al, 2003; Chavers et al, 2002). • Hypertension (USRDS, 2013; DOPPS, 2012). • Cerebrovascular disorders (USRDS, 2014; Gilbertson et al, 2013; DOPPS, 2012; Foley et al, 2003; Seliger et al, 2003; Kawamura et al, 1998). • Patients with CRF are often prescribed therapies for comorbidities such as hypertension (eg, beta blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics), diabetes (eg, insulin), coronary artery disease (statins, nitrates, aspirin, and antiarrhythmics), and other complications of CRF such as secondary hyperparathyroidism and hyperphosphatemia (eg, phosphate binders and vitamin D).

Table 3. Summary of Epidemiology of Symptomatic Anemia in Adult Cancer Patients With Non-Myeloid Malignancies Receiving Chemotherapy

Incidence	Anemia is common in patients with cancer and is an important contributor to the morbidity associated with malignancy. In oncology clinical trials, the incidence of National Cancer Institute common toxicity criteria grade 1 to 4 and grade 3 to 4 anemia after chemotherapy was reported to be as high as 90% and 30%, respectively, depending on tumor type and chemotherapy regimen (Chau et al, 2003; Scheithauer et al, 2003; Hitt et al, 2002; Louvet et al, 2002; Schiller et al, 2002). Other data sources have reported the overall incidence of anemia during chemo- or radiotherapy to be 54%, with variations by anemia severity (mild 39%, moderate 14%, and severe 1%) (Scrijvers et al, 2009). Lung cancer patients are reported to have the highest incidence (71%), followed by gynecological cancer patients (65%), with increases dependent on the number of chemotherapy cycles (Scrijvers et al, 2009).
Prevalence	Prevalence of chemotherapy-induced anemia among patients with non-myeloid cancers are limited. A Spanish hospital survey reported 48% of patients with non-myeloid malignancies undergoing systemic therapy had anemia, with approximately 87% of these cases being mild (Steegmann et al, 2013). A similar survey from Italy and Austria reported an overall anemia prevalence of 32% (31% from Italy and 36% from Austria), among patients undergoing myelosuppressive chemotherapy (Merlini et al, 2013). The authors further reported that over 50% of the patients had received 3 or fewer chemotherapy cycles highlighting that anemia can occur quite early in the treatment cycle (Merlini et al, 2013).

Table 3. Summary of Epidemiology of Symptomatic Anemia in Adult Cancer Patients With Non-Myeloid Malignancies Receiving Chemotherapy

Demographics of population in the authorized indication and risk factors for the disease	Cancer patients with anemia are more likely to be women than men (Barrett-Lee et al, 2005). The incidence of anemia increases with age (Penninx et al, 2007; Barrett-Lee et al, 2005). Anemia can be caused or exacerbated by chemotherapy, radiotherapy, infection, nutritional deficiency, bleeding, and bone marrow infiltration by tumor cells.
Main existing treatment options	Currently, anemia treatment options include (Xu et al, 2016): • ESAs, such as epoetin alfa, beta, theta, or zeta • RBC transfusions • nutritional supplements • iron supplementation • no treatment
Natural history of the indicated condition in the population, including mortality and morbidity	Studies have suggested a significant association between anemia and disease control in patients with cancers of the head, neck or larynx (Knight et al, 2004). According to a systematic review, 18 observational studies have reported an association between anemia and decreased survival or increased mortality (Knight et al, 2004). A significant correlation between anemia and quality-of-life scores has also been reported in patients not being treated for anemia (Holzner et al, 2002; Lind et al, 2002; Cella, 1997).
Important comorbidities	• Thromboembolic events (Burris, 2006; Castelli and Porro, 2006; Fennerty, 2006; Otten et al, 2004; Joung and Robinson, 2002; Heit et al, 2000). • For patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, darbepoetin alfa is administered in conjunction with standard antineoplastic therapy and supportive care agents.

Part II: Module SII - Nonclinical Part of the Safety Specification

Table 4. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Reproductive toxicity	In studies performed in rats and rabbits no clinically relevant evidence of harmful effects with respect to pregnancy, embryonal/ fetal development, parturition or postnatal development was observed. Placental transfer was minimal. No alteration of fertility was detected.	It is recommended that caution be exercised in the administration of darbepoetin alfa to pregnant women. A decision on whether to abstain from breast-feeding or to abstain from therapy with darbepoetin alfa should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of darbepoetin alfa therapy to the woman. Use in pregnant and lactating women is not considered a safety concern in this RMP. Use of darbepoetin alfa in pregnant or lactating women will continue to be monitored through routine pharmacovigilance and reported in Periodic Benefit-Risk Evaluation Reports/Periodic Safety Update Reports (PBRERs/PSURs).
Carcinogenicity	The carcinogenic potential of darbepoetin alfa has not been evaluated in long-term animal studies. Darbepoetin alfa did not alter the proliferative response of non-hematological cells in vitro or in vivo. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type. Erythropoiesis-stimulating agents do not enhance tumor growth in rodent tumor models with and without radiotherapy (Kirkpatrick et al, 2006; Ning et al, 2005).	Although the nonclinical results to date suggest that ESAs do not directly promote tumor growth, theoretically EpoR may be expressed at a low frequency on tumor cells and ESAs may stimulate tumor progression through indirect mechanisms. Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer is included as an important potential risk (see Table 14).

Table 4. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Carcinogenicity (continued)	Using a panel of human tissues, the in vitro tissue binding profile of darbepoetin alfa was identical to epoetin alfa. Neither molecule bound to human tissues other than those expressing the EpoR. Erythropoietin receptors have been reported to be expressed in normal and malignant non-hematopoietic tissues. Amgen has investigated the expression and function of EpoR in tumors and endothelial cells and has analyzed the potential for ESAs to stimulate tumor progression through direct or indirect mechanisms. The results of these investigations (Elliott et al, 2013; Elliott et al, 2012; Sinclair et al, 2010; Swift et al, 2010; Rossi et al, 2009; Sinclair et al, 2008), together with a critical review of the literature (Elliott and Sinclair, 2012), suggest that ESAs do not directly stimulate tumor cells and that similarly the cytoprotective and other non-hematopoietic effects of ESA treatment reported are not a direct effect of ESAs acting through EpoR on nonerythroid cells.	

Table 4. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Repeat dose toxicity/thrombosis	Studies have found that neither human platelets nor megakaryocytes express surface EpoR or respond to ESAs (Loberg et al, 2011). Investigative studies conducted in rats revealed that mortality and thrombotic events reported in ESA nonclinical toxicology studies were associated with higher ESA dose level, dose frequency and dose duration, and not solely related to a high hematocrit. Identified prothrombotic risk factors in rats given suprapharmacologic doses of ESAs were sequelae from an increased magnitude of erythropoiesis (eg, increasingly immature reticulocytes, functional iron deficiency) and pleotropic cytokines implicated in thrombosis (eg, monocyte protein 1 and 3, macrophage inhibitory protein-2) (Andrews et al, 2014a; Andrews et al, 2014b; Andrews et al, 2014c).	The inactivity of EpoR on platelets or megakaryocytes suggests that ESAs do not directly impact thrombotic pathways and the dose-response toxicity studies in rats indicates that thromboses, while not solely related to high hematocrit, may be due to sequelae from an increased magnitude of erythropoiesis.

Part II: Module SIII - Clinical Trial Exposure

Table 5. Total Subject Exposure to Darbepoetin Alfa in Clinical Trials by Indication and Duration
Safety Analysis Set

	Exposure to Aranesp by Duration					
	≤ 4 weeks n (subj-yrs)	5 to 8 weeks n (subj-yrs)	9 to 13 weeks n (subj-yrs)	14 to 17 weeks n (subj-yrs)	> 17 weeks n (subj-yrs)	Total Subjects n (subj-yrs)
Anemia of cancer (N = 1128)	205 (9.0)	150 (22.5)	407 (92.5)	39 (11.8)	327 (136.0)	1128 (271.9)
Chemotherapy Induced Anemia (N = 13 940)	1780 (70.1)	1455 (188.4)	4794 (1074.6)	3089 (871.2)	2822 (1226.1)	13 940 (3430.5)
Chronic Obstructive Pulmonary (N = 12)	12 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (0.0)
Heart Failure (N = 1471)	102 (4.2)	38 (5.1)	32 (6.7)	36 (10.6)	1263 (2555.0)	1471 (2581.5)
Myelodysplastic Syndrome (N = 342)	15 (0.4)	13 (1.6)	16 (3.4)	12 (3.8)	286 (288.4)	342 (297.6)
Nephrology (N = 19 712)	1141 (32.1)	575 (77.1)	724 (155.9)	518 (155.3)	16 754 (16 282.7)	19 712 (16 703.1)
Normal Volunteer (N = 30)	30 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (2.4)
Surgical (N = 95)	95 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	95 (1.5)
All Indications (N = 36 730)	3380 (119.8)	2231 (294.7)	5973 (1333.0)	3694 (1052.7)	21 452 (20 488.2)	36 730 (23 288.4)

n = number of subjects exposed to darbepoetin alfa; subj-yrs = total subject-yrs of follow-up
Note: Data is from completed studies. A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Note: Data cutoff is 31OCT2018
Program: /userdata/stat/nesp/ERS/2018_11/prod/tables/t-ex-sum-by-dur-allindic-psur-combined-all-2024-l.sas Output: t3-06-001-ex-sum-by-dur-allindic-psur-combined-all-2024-l.rtf (Date generated: 19NOV2024:22:19) Source data: crt.adsl, crt.adminlog, crt.demog

Table 6. Total Subject Exposure to Darbepoetin Alfa in Clinical Trials by Age Group and Gender
Safety Analysis Set

	Male n (subj-yrs)	Female n (subj-yrs)	Total n (subj-yrs)
Anemia of Cancer (N = 1126)			
All Pediatric Subjects	0 (0.0)	0 (0.0)	0 (0.0)
18 - <45 years	11 (2.3)	35 (7.6)	46 (9.9)
45 - <65 years	151 (30.6)	220 (51.4)	371 (82.0)
65 - <75 years	184 (41.5)	168 (47.3)	352 (88.8)
≥75 years	193 (46.7)	164 (43.9)	357 (90.6)
All Adult Subjects	539 (121.0)	587 (150.2)	1126 (271.3)
Total Subjects	539 (121.0)	587 (150.2)	1126 (271.3)
Chemotherapy Induced Anemia (N = 13 940)			
<1 year	0 (0.0)	0 (0.0)	0 (0.0)
1 - <6 years	0 (0.0)	1 (0.1)	1 (0.1)
6 - <12 years	4 (1.0)	2 (0.7)	6 (1.6)
12 - <18 years	7 (1.7)	1 (0.1)	8 (1.8)
All Pediatric Subjects	11 (2.6)	4 (0.9)	15 (3.6)
18 - <45 years	296 (70.3)	976 (249.7)	1272 (320.0)
45 - <65 years	2467 (579.5)	3954 (1029.7)	6421 (1609.2)
65 - <75 years	1918 (445.0)	2110 (531.3)	4028 (976.3)
≥75 years	1073 (248.1)	1131 (273.3)	2204 (521.3)
All Adult Subjects	5754 (1342.9)	8171 (2083.9)	13 925 (3426.9)
Total Subjects	5765 (1345.6)	8175 (2084.9)	13 940 (3430.5)
Chronic Obstructive Pulmonary (N = 12)			
All Pediatric Subjects	0 (0.0)	0 (0.0)	0 (0.0)
18 - <45 years	0 (0.0)	0 (0.0)	0 (0.0)
45 - <65 years	2 (0.0)	0 (0.0)	2 (0.0)
65 - <75 years	4 (0.0)	2 (0.0)	6 (0.0)
≥75 years	4 (0.0)	0 (0.0)	4 (0.0)
All Adult Subjects	10 (0.0)	2 (0.0)	12 (0.0)
Total Subjects	10 (0.0)	2 (0.0)	12 (0.0)

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 6. Total Subject Exposure to Darbepoetin Alfa in Clinical Trials by Age Group and Gender
Safety Analysis Set

	Male n (subj-yrs)	Female n (subj-yrs)	Total n (subj-yrs)
Heart Failure (N = 1471)			
All Pediatric Subjects	0 (0.0)	0 (0.0)	0 (0.0)
18 - <45 years	14 (13.2)	30 (53.7)	44 (66.9)
45 - <65 years	198 (373.9)	166 (310.1)	364 (684.0)
65 - <75 years	300 (493.1)	188 (349.8)	488 (842.9)
≥75 years	354 (575.3)	221 (412.4)	575 (987.8)
All Adult Subjects	866 (1455.5)	605 (1126.0)	1471 (2581.5)
Total Subjects	866 (1455.5)	605 (1126.0)	1471 (2581.5)
Myelodysplastic Syndrome (N = 342)			
All Pediatric Subjects	0 (0.0)	0 (0.0)	0 (0.0)
18 - <45 years	0 (0.0)	1 (0.7)	1 (0.7)
45 - <65 years	28 (23.1)	28 (21.9)	56 (45.0)
65 - <75 years	52 (50.7)	49 (49.2)	101 (99.9)
≥ 75 years	96 (76.8)	88 (75.3)	184 (152.0)
All Adult Subjects	176 (150.6)	166 (147.0)	342 (297.6)
Total Subjects	176 (150.6)	166 (147.0)	342 (297.6)
Nephrology (N = 19708)			
< 1 year	0 (0.0)	0 (0.0)	0 (0.0)
1 - <6 years	7 (2.9)	7 (2.0)	14 (4.9)
6 - <12 years	37 (14.9)	23 (8.7)	60 (23.6)
12 - <18 years	73 (30.2)	50 (19.7)	123 (49.9)
All Pediatric Subjects	117 (47.9)	80 (30.4)	197 (78.3)
18 - <45 years	1390 (954.8)	1013 (750.3)	2403 (1705.1)
45 - <65 years	3595 (2912.7)	3237 (2930.4)	6832 (5843.1)
65 - <75 years	2815 (2422.6)	2810 (2685.2)	5625 (5107.8)
≥75 years	2423 (1991.2)	2228 (1976.0)	4651 (3967.2)
All Adult Subjects	10223 (8281.3)	9288 (8341.9)	19511 (16623.2)
Total Subjects	10340 (8329.2)	9368 (8372.3)	19708 (16701.5)
Normal Volunteer (N = 30)			
All Pediatric Subjects	0 (0.0)	0 (0.0)	0 (0.0)
18 - <45 years	16 (1.3)	4 (0.3)	20 (1.6)
45 - <65 years	4 (0.3)	5 (0.4)	9 (0.7)
65 - <75 years	0 (0.0)	1 (0.1)	1 (0.1)
≥75 years	0 (0.0)	0 (0.0)	0 (0.0)
All Adult Subjects	20 (1.6)	10 (0.8)	30 (2.4)
Total Subjects	20 (1.6)	10 (0.8)	30 (2.4)

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 6. Total Subject Exposure to Darbepoetin Alfa in Clinical Trials by Age Group and Gender
Safety Analysis Set

	Male n (subj-yrs)	Female n (subj-yrs)	Total n (subj-yrs)
Surgical (N = 95)			
All Pediatric Subjects	0 (0.0)	0 (0.0)	0 (0.0)
18 - <45 years	0 (0.0)	8 (0.0)	8 (0.0)
45 - <65 years	8 (0.0)	27 (0.4)	35 (0.4)
65 - <75 years	8 (0.2)	20 (0.6)	28 (0.8)
≥75 years	6 (0.1)	18 (0.2)	24 (0.3)
All Adult Subjects	22 (0.3)	73 (1.2)	95 (1.5)
Total Subjects	22 (0.3)	73 (1.2)	95 (1.5)
All Indications (N = 36 724)			
< 1 year	0 (0.0)	0 (0.0)	0 (0.0)
1 - <6 years	7 (2.9)	8 (2.1)	15 (5.0)
6 - <12 years	41 (15.9)	25 (9.4)	66 (25.2)
12 - <18 years	80 (31.9)	51 (19.8)	131 (51.7)
All Pediatric Subjects	128 (50.6)	84 (31.3)	212 (81.9)
18 - <45 years	1727 (1041.8)	2067 (1062.2)	3794 (2104.1)
45 - <65 years	6453 (3920.2)	7637 (4344.3)	14 090 (8264.4)
65 - <75 years	5281 (3453.2)	5348 (3663.5)	10 629 (7116.6)
≥75 years	4149 (2938.2)	3850 (2781.1)	7999 (5719.3)
All Adult Subjects	17 610 (11 353.4)	18 902 (11 851.0)	36 512 (23 204.4)
Total Subjects	17 738 (11 404.0)	18 986 (11 882.3)	36 724 (23 286.3)

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n = number of subjects exposed to darbepoetin alfa; subj-yrs = total subject-yrs of follow-up
Note: Data is from completed studies. A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.
Age represents age at first dose.
6 subject(s) are missing age and/or sex and have been excluded from the table.
Note: Data cutoff is 31OCT2018
Program: /userdata/stat/nesp/ERS/2018_11/prod/tables/t-ex-sum-by-sex-agecat-allindic-psur-combined-2024-p.sas
Output: t2-04-ex-sum-by-sex-agecat-allindic-psur-combined-2024-p.rtf (Date generated: 19NOV2024:22:45)
Source data: crt.adsl, crt.adminlog, crt.demog

Table 7. Exposure to Darbepoetin Alfa in Clinical Trials by Dose Level and Indication
Safety Analysis Set

	Exposure to Aranesp in Days			Subject Exposure to Aranesp		
	2.25 mcg/kg QW n (mean)	500 mcg Q3W n (mean)	All other doses[a] n (mean)	2.25 mcg/kg QW n (subj-yrs)	500 mcg Q3W n (subj-yrs)	All other doses[a] n (subj-yrs)
Anemia of Cancer (N = 1128)	33 (67.4)	0 (0.0)	1095 (88.7)	33 (6.1)	0 (0.0)	1095 (265.8)
Chemotherapy Induced Anemia (N = 13 940)	1129 (80.9)	2711 (81.2)	10 100 (93.2)	1129 (250.2)	2711 (602.4)	10 100 (2577.8)
Chronic Obstructive Pulmonary (N = 12)	0 (0.0)	0 (0.0)	12 (1.0)	0 (0.0)	0 (0.0)	12 (0.0)
Heart Failure (N = 1471)	0 (0.0)	0 (0.0)	1471 (641.0)	0 (0.0)	0 (0.0)	1471 (2581.5)
Myelodysplastic Syndrome (N = 342)	0 (0.0)	303 (320.3)	39 (298.8)	0 (0.0)	303 (265.7)	39 (31.9)
Nephrology (N = 19 712)	0 (0.0)	0 (0.0)	19 712 (309.5)	0 (0.0)	0 (0.0)	19 712 (16 703.1)
Normal Volunteer (N = 30)	0 (0.0)	0 (0.0)	30 (29.0)	0 (0.0)	0 (0.0)	30 (2.4)
Surgical (N = 95)	0 (0.0)	0 (0.0)	95 (5.9)	0 (0.0)	0 (0.0)	95 (1.5)
All Indications (N = 36 730)	1162 (80.6)	3014 (105.2)	32 554 (248.7)	1162 (256.3)	3014 (868.1)	32 554 (22 164.0)

[a] This includes all other QW doses, Q2W dosing, other Q3W doses, and other dosing paradigms

n = number of subjects exposed to darbepoetin alfa; subj-yrs = total subject-yrs of follow-up.

Note: Data is from completed studies. A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Note: Data cutoff is 31OCT2018

Program: /userdata/stat/nesp/ERS/2018_11/prod/tables/t-ex-sum-by-dose-allindic-combined-all-2024-l.sas

Output: t3-07-001-ex-sum-by-dose-allindic-combined-all-2024-l.rtf (Date generated: 19NOV2024:22:20) Source data: crt.adsl, crt.adminlog, crt.demog

Table 8. Total Subject Exposure to Darbepoetin Alfa in Clinical Trials by Indication and Race/Ethnic Group
Safety Analysis Set

	White or Caucasian n (subj-yrs)	Black or African American n (subj-yrs)	Hispanic or Latino n (subj-yrs)	Asian n (subj-yrs)	American Indian or Alaskan Native n (subj-yrs)	Native Hawaiian or Other Pacific Islander n (subj-yrs)	Other n (subj-yrs)	Missing /Unknown n (subj-yrs)	Total Subjects n (subj-yrs)
Anemia of cancer (N = 1128)	963 (230.3)	107 (27.4)	22 (4.9)	14 (4.2)	0 (0.0)	2 (0.5)	9 (2.2)	11 (2.5)	1128 (271.9)
Chemotherapy Induced Anemia (N = 13940)	11249 (2776.9)	1070 (276.3)	473 (117.4)	945 (205.4)	12 (3.3)	23 (5.8)	132 (35.1)	36 (10.1)	13940 (3430.5)
Chronic Obstructive Pulmonary (N = 12)	12 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (0.0)
Heart Failure (N = 1471)	1068 (1797.9)	116 (223.9)	100 (213.8)	180 (334.9)	3 (5.5)	0 (0.0)	4 (5.5)	0 (0.0)	1471 (2581.5)
Myelodysplastic Syndrome (N = 342)	311 (273.8)	16 (10.4)	8 (7.2)	6 (5.1)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	342 (297.6)
Nephrology (N = 19712)	14838 (12456.3)	3090 (2683.1)	903 (885.3)	401 (372.2)	30 (24.4)	23 (20.7)	288 (210.7)	139 (50.2)	19712 (16703.1)
Normal Volunteer (N = 30)	25 (2.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	30 (2.4)
Surgical (N = 95)	87 (1.4)	5 (0.0)	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	95 (1.5)
All Indications (N = 36730)	28553 (17538.7)	4406 (3221.3)	1507 (1228.7)	1548 (921.9)	45 (33.2)	49 (28.0)	436 (253.7)	186 (62.8)	36730 (23288.4)

n = number of subjects exposed to darbepoetin alfa; subj-yrs = total subject-yrs of follow-up.
Note: Data is from completed studies. A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Note: Data cutoff is 31OCT2018
Program: /userdata/stat/nesp/ERS/2018_11/prod/tables/t-ex-sum-by-race-allindic-psur-combined-all-2024-l.sas
Output: t3-04-001-ex-sum-by-race-allindic-psur-combined-all-2024-l.rtf (Date generated: 19NOV2024:22:55) Source data: crt.adsl, crt.adminlog, crt.demog

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Contraindications			
Uncontrolled hypertension	Darbepoetin alfa is contraindicated in patients with uncontrolled hypertension.	No	Poorly controlled hypertension is a contraindication in the Summary of Product Characteristics (SmPC). Blood pressure should be monitored in all patients, particularly during initiation of therapy. If blood pressure is difficult to control by appropriate measures, the dose can be reduced or withheld accordingly.
Known sensitivity to darbepoetin alfa	Patients with hypersensitivity to darbepoetin alfa, rHuEPO or to any of the excipients should not be administered darbepoetin alfa.	No	Hypersensitivity to darbepoetin alfa is a contraindication in the SmPC. Anaphylactic reaction, angioedema, allergic bronchospasm, skin rash, and urticaria are listed as adverse reactions in the SmPC from clinical studies and postmarketing experience. Consequences of a hypersensitivity reaction can be minimized by ensuring that administration of darbepoetin alfa is attended by appropriate precautions. Darbepoetin alfa should be immediately and permanently discontinued and appropriate therapy administered if a serious allergic or anaphylactic reaction occurs.
Exclusion Criteria Applying to Both Indications			
Systemic hematologic disease	Subjects whose anemia was potentially multifactorial were excluded to allow evaluation of darbepoetin alfa's efficacy in clinical trials for the indicated patient population.	No	The SmPC contains a warning that darbepoetin alfa should be used with caution in patients with sickle cell anemia. However, based on clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion Criteria Applying to Both Indications (continued)			
Recent IV iron therapy	Recent exposure to other anemia therapy would interfere with the ability to assess darbepoetin alfa's efficacy in clinical studies.	No	The SmPC contains guidance that iron status should be monitored in all patients before and during treatment with darbepoetin alfa and that concomitant iron therapy is recommended for patients who are not iron replete.
Recent transfusion	Recent exposure to other anemia therapy would interfere with the ability to assess darbepoetin alfa's efficacy in clinical studies.	No	Transfusions are common in the target anemia population as they may be administered concomitantly with ESAs.
Recent ESA therapy (for studies of anemia correction only in nephrology indication)	Recent exposure to other anemia therapy would interfere with the ability to assess darbepoetin alfa's efficacy in clinical studies.	No	Clinical experience in dose conversion studies support safely switching patients from 1 ESA to another.
Exclusion Criteria Applying to Nephrology Indication			
Known human immunodeficiency virus (HIV) disease	Subjects whose anemia was potentially multifactorial were excluded to allow evaluation of darbepoetin alfa's efficacy in clinical trials for the indicated patient population.	No	Other ESAs, with the same mechanism of action as darbepoetin alfa, include an indication for HIV disease treated with antiretrovirals that cause anemia. Based on the biological plausibility and clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion Criteria Applying to Nephrology Indication (continued)			
Systemic infection treated with antibiotics Recent gastrointestinal bleeding or hospitalization or surgery Systemic immunosuppressive therapy Evidence of severe hyperparathyroidism	Subjects whose anemia was potentially multifactorial were excluded to allow evaluation of darbepoetin alfa's efficacy in clinical trials for the indicated patient population.	No	These conditions commonly occur in the target population. Based on the biological plausibility and clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in these patient populations.
Current malignancy or recent treatment for malignancy (usually 4 weeks)	Subjects whose anemia was potentially multifactorial were excluded to allow evaluation of darbepoetin alfa's efficacy in clinical trials for the indicated patient population.	No	In the clinical setting, the choice of types and lines of cytotoxic chemotherapy is at the discretion of the treating physician. Darbepoetin alfa includes an indication for cancer patients treated with chemotherapy which cause anemia. The SmPC contains a warning on the potential effect of ESAs on tumor growth.
Recent androgen therapy	Recent exposure to other anemia therapy would interfere with the ability to assess darbepoetin alfa's efficacy in clinical studies.	No	In the clinical setting, the choice of types and lines of therapies is at the discretion of the treating physician. Based on the biological plausibility and clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion Criteria Applying to Nephrology Indication (continued)			
Recent grand mal seizure or treatment for grand mal seizure	These subjects were excluded from trials to adequately assess risks of these events after exposure to darbepoetin alfa. Recent history of 1 of these events would have confounded the assessment.	No	This condition is prevalent in the target population and the SmPC includes convulsions as a warning and an identified adverse drug reaction (ADR). Based on clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.
Recent myocardial infarction Recent stroke Advanced heart failure	These subjects were excluded from trials to adequately assess risks of these events after exposure to darbepoetin alfa. Recent history of 1 of these events would have confounded the assessment.	No	These conditions are prevalent in the target population and the SmPC includes warnings for these events when ESAs are administered to hemoglobin targets $>$ 12 g/dL. Based on clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.
Planned kidney transplant	To minimize the dropout rate in clinical studies.	No	For patients anticipating a kidney transplant, ESAs have been administered to avoid transfusions, which can lead to sensitization and a negative impact on graft outcome.
Start of dialysis, for CRF patients not on dialysis	To minimize the dropout rate in clinical studies.	No	Darbepoetin alfa is indicated in this patient population.
Exclusion Criteria Applying to Oncology Indication			
Uncontrolled angina, uncontrolled heart failure, or uncontrolled cardiac arrhythmia Known myocardial infarction	These conditions would interfere with the ability to assess darbepoetin alfa's safety in clinical studies.	No	Determination of patient status for therapy is at the discretion of the treating physician. These conditions are prevalent in the target population. Based on clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion Criteria Applying to Oncology Indication (continued)			
Seropositivity for HIV, diagnosis for acquired immunodeficiency syndrome, positive for hepatitis B surface antigen or seropositive hepatitis C	These conditions would interfere with the ability to assess darbepoetin alfa's safety in clinical studies.	No	Determination of patient status for therapy is at the discretion of the treating physician. Other ESAs, with the same mechanism of action as darbepoetin alfa, include an indication for HIV disease treated with antiretrovirals that cause anemia. Based on the biological plausibility and clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.
History of deep venous thrombosis or embolic event	These conditions would interfere with the ability to assess darbepoetin alfa's safety in clinical studies.	No	Determination of patient status for therapy is at the discretion of the treating physician. This condition is prevalent in the target population and the SmPC includes thromboembolic events as an identified ADR and a warning for these events when hemoglobin levels > 12 g/dL. Based on clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.
Brain metastasis	This condition would interfere with the ability to assess darbepoetin alfa's safety in clinical studies.	No	This exclusion criterion was specific to lung cancer studies only. Darbepoetin alfa is indicated for cancer patients treated with chemotherapy which cause anemia, regardless of tumor type.

Table 9. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion Criteria Applying to Oncology Indication (continued)			
History of seizure disorder or recently taking anti-seizure medication	These conditions would interfere with the ability to assess darbepoetin alfa's safety in clinical studies.	No	Determination of patient status for therapy is at the discretion of the treating physician. This condition is prevalent in the target population and the SmPC includes convulsions as a warning and an identified ADR. Based on clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.
Clinically significant systemic infection or uncontrolled chronic inflammatory disease	These conditions would interfere with the ability to assess darbepoetin alfa's efficacy in clinical studies.	No	Determination of patient status for therapy is at the discretion of the treating physician. Based on the biological plausibility and clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.
Known previous treatment failure to ESAs	These conditions would interfere with the ability to assess darbepoetin alfa's efficacy in clinical studies.	No	Determination of patient status for therapy is at the discretion of the treating physician. Based on the biological plausibility and clinical experience, the safety and efficacy of darbepoetin alfa are not expected to differ in this patient population.
Other reasons for anemia that are not related to cancer	These conditions would interfere with the ability to assess darbepoetin alfa's efficacy in clinical studies.	No	Darbepoetin alfa and other ESAs are indicated for anemia due to other conditions, including CRF.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as adverse reactions with a long latency. For rare ADRs (frequency ≥ 0.01% and < 0.1%), the probability of seeing at least 1 event is between 86.1% and > 99.9% in CRF patients and between 77.8% and > 99.9% in patients with cancer. The clinical development program for the oncology indications is unlikely to detect adverse reactions caused by prolonged or cumulative exposure. However, in the nephrology indication, darbepoetin alfa therapy is often long term. The clinical trial program allowed detection of ADRs caused by prolonged exposure in the CRF population.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 10. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Eleven pregnancies were reported in the clinical study development program, one of which was associated with paternal exposure to darbepoetin alfa.
Breast-feeding women	Not included in the clinical development program.
Patients with relevant comorbidities	
Patients with hepatic impairment	Data not available.
Patients with renal impairment	A total of 19 712 subjects (16 703.1 subject-years) were included in the nephrology clinical development program.
Patients with cardiovascular impairment	Data not available.
Immunocompromised patients	Due to the nature of the product indications, many subjects were immunocompromised.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable
Population with relevant different ethnic origin	Table 8 provides the race/ethnicity of subjects included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	Not included in the clinical development program.

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are reported monthly by country and are converted to a monthly estimate of person-count (when feasible) or person-time using region- and product-specific utilization parameters and algorithms. These parameters include the average number of milligrams per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

SV.1.2 Exposure

Table 11. Estimated Number of Postmarketing Patient-years of Exposure to Darbepoetin Alfa, by Region and Demographic Characteristics

Demographic Characteristic	Cumulative Patient-years of Exposure					
	AU	CA	EUR	US	Other	Total
Overall	268 264	1 208 986	4 746 155	3 150 625	1 020 279	10 394 309
Sex						
Female	153 796	693 112	2 720 971	1 806 253	584 926	5 959 057
Male	114 468	515 874	2 025 184	1 344 372	435 353	4 435 252
Age (years)						
< 18	832	3748	14 713	9767	3163	32 222
18 - 34	2844	12 815	50 309	33 397	10 815	110 180
35 - 49	15 667	70 605	277 175	183 996	59 584	607 028
50 - 64	70 393	317 238	1 245 391	826 724	267 721	2 727 467
65 - 74	55 048	248 084	973 911	646 508	209 361	2 132 912
≥ 75	123 482	556 496	2 184 655	1 450 233	469 634	4 784 500

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 11. Estimated Number of Postmarketing Patient-years of Exposure to Darbepoetin Alfa, by Region and Demographic Characteristics

Demographic Characteristic	Cumulative Patient-years of Exposure					
	AU	CA	EUR	US	Other	Total
Sex/Age (years)						
Female						
< 18	376	1693	6645	4411	1428	14 552
18 - 34	1690	7617	29 901	19 849	6428	65 484
35 - 49	10 757	48 480	190 321	126 340	40 913	416 812
50 - 64	44 425	200 208	785 963	521 743	168 958	1 721 298
65 - 74	31 602	142 419	559 097	371 144	120 189	1 224 450
≥ 75	64 947	292 696	1 149 044	762 766	247 009	2 516 462
Male						
< 18	456	2055	8068	5356	1734	17 670
18 - 34	1154	5199	20 408	13 548	4387	44 696
35 - 49	4909	22 124	86 855	57 656	18 671	190 216
50 - 64	25 968	117 030	459 428	304 980	98 763	1 006 169
65 - 74	23 446	105 665	414 814	275 365	89 172	908 463
≥ 75	58 535	263 801	1 035 611	687 466	222 625	2 268 038

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AU = Australia; CA = Canada; EUR = Europe Union, European Economic Area, United Kingdom, and Switzerland; Other = countries, not otherwise specified, where Amgen is the marketing authorization holder; US = United States
Note: Cutoff date 31 October 2024.
Numbers may not add to the total due to rounding.
Age and sex breakdowns are based on patient characteristics in MarketScan, a US health insurance claims database. Applying these distributions to regions outside the US requires strong assumptions that are not easily testable.

Postauthorization Use From Business Partners

Cumulatively until 31 October 2024, an estimated 3 406 061 patient-years have been treated in Kyowa Kirin Co., Ltd. territories with darbepoetin alfa.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

Use of darbepoetin alfa as a performance enhancing drug for athletes has been reported, although it has been shown that darbepoetin alfa has a much longer detection window in urine than any other available ESA, which is a major disadvantage for illegal use in sports (Lamon et al, 2007). The same effect that improves endurance performance also puts the user at risk (Jelkmann, 2000). The potential for misuse is expected to be less for children than for adults, given the difficulties that a child would have in obtaining a prescription drug without supervision. No potential to cause psychological or physical dependence or symptoms of withdrawal has been identified for darbepoetin alfa.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 12. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
Important Potential Risks		
Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission	Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission, previously classified as an important potential risk has been removed from the list of safety concerns	An evaluation of the important potential risk of 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission' was conducted in PBRER 39, for the reporting period of 01 November 2020 to 31 October 2023, submitted in January 2024. Based on review of the data, as presented in the PBRER 39 Section 16.3.1.6, most events were non-serious. Adverse events reported in these cases were assessed as not considered related to the missed or partial dose, no impact to patient safety was identified, and no new safety concerns have been identified. In addition, these events do not require further characterization and are not expected to have a significant impact on the benefit-risk profile of the product. Therefore, the MAH considers that the risk of 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission' no longer meets the criteria to be classified as an important potential risk. A review of the requests for orders of the demonstration device, associated training checklist, and poster-size IFU was conducted in 2024. Cumulatively through September 2024, there has been a significant decrease in demand for these tools since their inception in 2019 with limited requests for the demonstration device, associated training checklist, and poster-size IFU. Review of the product complaint/adverse event data since the implementation of the aRMM shows a worldwide decrease in user error events reported with the pre-filled pen device as reported in PBRER 39 Section 16.3.1.6. This decrease in user error events and the reporting pattern of product complaint/adverse event are similar in both the EU and non-EU countries which do not have the demonstration device, associated training checklist, and poster-size IFU as regulatory requirements. Therefore, the data do not indicate a correlation between the distribution of the aRMMs and the reduction in user error events, as well as the overall reporting of product complaints or adverse events. Thus, the MAH is removing the risk of 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission' and corresponding aRMMs of demonstration device, associated training checklist, and poster-size IFU from the RMP and Annex IID "Conditions or restrictions with regard to the safe and effective use of the medicinal product". The detailed IFU already included in the Package Leaflet provides sufficient guidance for patients to understand how to correctly use the pre-filled pen device. The risk will continue to be monitored via routine pharmacovigilance.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 13. Important Identified Risk: Antibody-mediated PRCA (Nephrology Indication Only)

Potential mechanisms	Darbepoetin alfa-induced antibody-mediated pure red cell aplasia (PRCA) is due to the production of neutralizing anti-darbepoetin alfa antibodies. These antibodies have been shown to recognize the protein moiety of darbepoetin alfa and to cross-react with all available ESAs, as well as with endogenous erythropoietin. The mechanisms by which darbepoetin alfa can induce an immune reaction with production of neutralizing antibodies in few patients are not understood, but occurrence of such reaction has been shown to be favored by SC administration (Macdougall, 2005; Thorpe and Swanson, 2005; Cournoyer et al, 2004).
Evidence source(s) and strength of evidence	This risk was identified in the postmarketing setting. Most cases of PRCA were reported for patients with CKD. Antibody-mediated PRCA is considered an important identified risk in the nephrology indication and an important potential risk in the oncology indication since only a small number of cases have been identified in cancer patients.
Characterization of the risk	
Frequency	Out of 36 730 subjects who received darbepoetin alfa in clinical studies, 13 cases of antibody-mediated PRCA were reported in nephrology (4 cases) and oncology (9 cases) clinical studies; all cases were assessed as serious. Of these 13 cases, 1 nephrology case was medically adjudicated as meeting the criteria for antibody-mediated PRCA.
Severity	None of the 13 serious clinical study cases were fatal.
Reversibility	Antibody-mediated PRCA should generally not be considered reversible after discontinuation of darbepoetin alfa; some cases have recovered with immunosuppressive therapy.
Long-term outcomes	Long-term outcome of PRCA is dependent on patient comorbidities and on the cause of the event (ie, lymphoproliferative disorders, parvovirus B19 infection, thymoma, or systemic autoimmune disease) and on the development of neutralizing anti-erythropoietin antibodies.
Impact on quality of life	Profound transfusion-dependent anemia is the most common morbidity associated with acquired chronic PRCA.

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 13. Important Identified Risk: Antibody-mediated PRCA (Nephrology Indication Only)

Risk factors and risk groups	PRCA, in association with neutralizing antibodies to endogenous erythropoietin, has been observed in patients treated with ESAs, including darbepoetin alfa. PRCA has been reported predominantly in patients with CKD and in patients with hepatitis C treated with interferon and ribavirin. Most cases have been associated with SC administration of ESAs. No other risk factor has been identified with darbepoetin alfa.
Preventability	Darbepoetin alfa should be discontinued in any patient with evidence of PRCA, and the patient evaluated for the presence of binding and neutralizing antibodies to darbepoetin alfa, endogenous erythropoietin, and any other ESAs administered to the patient. Darbepoetin alfa should not be administered in patients with PRCA secondary to neutralizing antibodies. Patients should not be switched to other ESAs, as antibodies usually cross-react with other ESAs. Darbepoetin alfa is not approved for the treatment of anemia related to treatment for hepatitis C. Most cases of PRCA have been associated with SC administration of ESAs. As a result, IV administration of ESAs in hemodialysis patients appears to be an effective tool for preventing occurrence of this ADR. Proper storage and handling of the drug could also decrease the risk of antibody-mediated PRCA.
Impact on the risk-benefit balance of the product	The risk of antibody-mediated PRCA (nephrology indication only) has been incorporated into the benefit-risk assessment, and the overall benefit-risk balance remains positive. This risk is minimized through product labeling. Antibody testing is an additional pharmacovigilance activity to further characterize this risk.
Public health impact	Darbepoetin alfa is indicated only in a specific and limited population, there would be few patients per year that would experience the event. In addition, with appropriate conservative dosing strategy, the risk of clinical consequences and the overall impact on public health is considered low.

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ADR = adverse drug reaction; CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; IV = intravenous(ly); PRCA = pure red cell aplasia; SC = subcutaneous(ly)

Table 14. Important Potential Risk: Mortality and/or Tumor Progression or Recurrence in Patients With Cancer or a History of Cancer

Potential mechanisms	Erythropoiesis-stimulating agents have been hypothesized to directly promote tumor growth via an interaction with EpoR expressed on tumors or associated vasculature. Erythropoietin receptors have been reported to be expressed in normal and malignant non-hematopoietic tissues. The hypothesis is largely dependent on experiments that used anti-EpoR antibodies to detect EpoR protein in cell lines, cells, and tissues. However, several independent groups have shown that the antibodies used to detect EpoR expression are non-specific and provide false-positive results (Laugsch et al, 2008; Brown et al, 2007; Della Ragione et al, 2007; Kirkeby et al, 2007; Kokhaei et al, 2007; Sturiale et al, 2007; Elliott et al, 2006). In addition, the data suggesting the presence of functional EpoR on the surface of tumor cells, according to results from ESA treated tumor cell lines or tumor-bearing animals, are conflicting and/or confounded (data reviewed by Österborg et al, 2007; Sinclair et al, 2007). Furthermore, the results of further investigations by Amgen (Elliott et al, 2013; Elliott et al, 2012; Sinclair et al, 2010; Swift et al, 2010; Rossi et al, 2009; Sinclair et al, 2008), together with a critical review of the literature (Elliott and Sinclair, 2012), suggest that ESAs do not directly stimulate tumor cells and that similarly the cytoprotective and other non-hematopoietic effects of ESA treatment reported are not a direct effect of ESAs acting through EpoR on nonerythroid cells. In the radiotherapy setting with targeted hemoglobin levels beyond the correction of anemia, a potential mechanism exists for reduced efficacy of local radiotherapy at higher hemoglobin targets (Vaupel et al, 2006).
Evidence source(s) and strength of evidence	This potential risk was identified in the clinical trial setting. Increased mortality or adverse cancer outcomes were observed with ESAs in 8 clinical studies conducted in subjects with cancer. In the nephrology indication, the potential risk of mortality in subjects with a history of malignancy was identified based on a post-hoc subgroup analysis of the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT).
Characterization of the risk	
Frequency	<u>CRF patients</u>: In a post-hoc subgroup analysis of TREAT, more deaths from any cause were observed in those patients who indicated a prior history of malignancy in the darbepoetin group (60 of 188 subjects) compared with placebo (37 of 160 subjects) (hazard ratio [HR]: 1.38 [95% CI: 0.91, 2.07]). <u>Cancer patients</u>: In a combined analysis of patient-level data from 7 randomized, double-blind, placebo-controlled trials, the HR (darbepoetin alfa relative to placebo) was 0.97 (95% CI: 0.85 to 1.1) for overall survival and 1.11 (95% CI: 0.84 to 1.47) for on-study death. For tumor outcome endpoints, the HR (darbepoetin alfa relative to placebo) was 0.93 (95% CI: 0.84 to 1.04) for progression-free survival and 0.92 (95% CI: 0.82 to 1.03) for disease progression. In the combined analysis of on-study death, 110 of 1200 subjects (9.2%) died in the darbepoetin alfa arm and 92 of 912 subjects (10.1%) died in the placebo arm.

Footnotes, including abbreviations, are defined on the last page of this table.

Table 14. Important Potential Risk: Mortality and/or Tumor Progression or Recurrence in Patients With Cancer or a History of Cancer

Characterization of the risk (continued)	
Severity	Not applicable since risk is mortality and tumor progression events.
Reversibility	The majority of tumor progression events do not resolve, and the majority are fatal.
Long-term outcomes	Depending on the type and presentation of the tumor, long-term outcomes are variable, but the majority are fatal.
Impact on quality of life	An increased risk of adverse tumor outcomes could result in increased morbidity and mortality for patients with cancer.
Risk factors and risk groups	There are no data available describing risk factors for death among patients with CRF who have a history of cancer and are receiving ESA therapy. In patients with cancer, adverse tumor outcomes and mortality are closely linked with tumor characteristics including tumor type, stage, responsiveness to therapy, and location of metastatic lesions, and patient factors including age, nutritional status, comorbidity, and immune suppression.
Preventability	Darbepoetin alfa is not indicated for administration beyond the correction of anemia or in patients not receiving chemotherapy. An increased mortality has been observed in clinical studies of patients with cancer receiving chemotherapy to target a hemoglobin level of greater than 12 g/dL. In addition, in a post-hoc subgroup analysis of TREAT study, more deaths from any cause were observed in those CKD patients who indicated a prior history of malignancy and were treated with darbepoetin alfa to target a hemoglobin level of 13 g/dL. Therefore, a potential way to manage this risk would be to treat hemoglobin levels consistent with the targets specified in the SmPC.
Impact on the risk-benefit balance of the product	The potential risk of mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer has been incorporated into the benefit-risk assessment, and the overall benefit-risk balance remains positive. This risk is minimized through product labeling.
Public health impact	Darbepoetin alfa is indicated only in a specific and limited population, there would be few patients per year that would experience the event. In addition, with appropriate conservative dosing strategy, the risk of clinical consequences and the overall impact on public health is considered low.

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CKD = chronic kidney disease; CRF = chronic renal failure; EpoR = erythropoietin receptor; ESA = erythropoiesis-stimulating agent; HR = hazard ratio; SmPC = Summary of Product Characteristics; TREAT = study entitled “Trial to Reduce Cardiovascular Events with Aranesp® Therapy”
(Solomon et al, 2010; Pfeffer et al, 2009)

Table 15. Important Potential Risk: Antibody-mediated PRCA (Oncology Indication Only)

Potential mechanisms	Darbepoetin alfa-induced antibody-mediated PRCA is due to the production of neutralizing anti-darbepoetin alfa antibodies. These antibodies have been shown to recognize the protein moiety of darbepoetin alfa and to cross-react with all available ESAs, as well as with endogenous erythropoietin. The mechanisms by which darbepoetin alfa can induce an immune reaction with production of neutralizing antibodies in few patients are not understood, but occurrence of such reaction has been shown to be favored by SC administration (Macdougall, 2005; Thorpe and Swanson, 2005; Cournoyer et al, 2004).
Evidence source(s) and strength of evidence	This potential risk was identified in the postmarketing setting. Most cases of PRCA were reported for patients with CKD. Antibody-mediated PRCA is considered an important identified risk in the nephrology indication and an important potential risk in the oncology indication since only a small number of cases have been identified in cancer patients.
Characterization of the risk	
Frequency	Out of 36 730 subjects who received darbepoetin alfa in clinical studies, 13 cases of antibody-mediated PRCA were reported in nephrology (4 cases) and oncology (9 cases) clinical studies; all cases were assessed as serious. Of these 13 cases, 1 nephrology case was medically adjudicated as meeting the criteria for antibody-mediated PRCA.
Severity	None of the 13 serious clinical study cases were fatal.
Reversibility	Antibody-mediated PRCA should generally not be considered reversible after discontinuation of darbepoetin alfa; some cases have recovered with immunosuppressive therapy.
Long-term outcomes	Long-term outcome of PRCA is dependent on patient comorbidities and on the cause of the event (ie, lymphoproliferative disorders, parvovirus B19 infection, thymoma, or systemic autoimmune disease) and on the development of neutralizing anti-erythropoietin antibodies.
Impact on quality of life	Profound transfusion-dependent anemia is the most common morbidity associated with acquired chronic PRCA.
Risk factors and risk groups	PRCA, in association with neutralizing antibodies to endogenous erythropoietin, has been observed in patients treated with ESAs, including darbepoetin alfa. PRCA has been reported predominantly in patients with CKD and in patients with hepatitis C treated with interferon and ribavirin. Most cases have been associated with SC administration of ESAs. No other risk factor has been identified with darbepoetin alfa.

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 15. Important Potential Risk: Antibody-mediated PRCA (Oncology Indication Only)

Preventability	As specified in the SmPC, darbepoetin alfa should be discontinued in any patient with evidence of PRCA, and the patient evaluated for the presence of binding and neutralizing antibodies to darbepoetin alfa, endogenous erythropoietin, and any other ESAs administered to the patient. Darbepoetin alfa should not be administered in patients with PRCA secondary to neutralizing antibodies. Patients should not be switched to other ESAs, as antibodies usually cross-react with other ESAs. Darbepoetin alfa is not approved for the treatment of anemia related to treatment for hepatitis C. Proper storage and handling of the drug could also decrease the risk of antibody-mediated PRCA.
Impact on the risk-benefit balance of the product	The potential risk of antibody-mediated PRCA (oncology indication only) has been incorporated into the benefit-risk assessment, and the overall benefit-risk balance remains positive. This risk is minimized through product labeling. Antibody testing is an additional pharmacovigilance activity to further characterize this risk.
Public health impact	Darbepoetin alfa is indicated only in a specific and limited population, there would be few patients per year that would experience the event. In addition, with appropriate conservative dosing strategy, the risk of clinical consequences and the overall impact on public health is considered low.

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CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; PRCA = pure red cell aplasia; SC = subcutaneous(ly); SmPC = Summary of Product Characteristics

SVII.3.2 Presentation of the Missing Information

There is no missing information for darbepoetin alfa.

Part II: Module SVIII - Summary of the Safety Concerns

Table 16. Summary of Safety Concerns

Important identified risks	• Antibody-mediated PRCA (nephrology indication only)
Important potential risks	• Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer • Antibody-mediated PRCA (oncology indication only)
Missing information	• None

PRCA = pure red cell aplasia

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 17 and Table 18.

Table 17. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Pure Red Cell Aplasia	Antibody-mediated PRCA (Nephrology and Oncology Indications)	To further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk

Table 18. Other Forms of Routine Pharmacovigilance Activities

Description of Activity	Safety Concern(s)	Objectives	Milestones
Multidisciplinary review and evaluation of cases, adjudication of potential antibody-mediated PRCA cases using pre-defined criteria, and individual case assessment.	Antibody-mediated PRCA (Nephrology and Oncology Indications)	To further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk, and to build a robust and comprehensive antibody-mediated PRCA case dataset to serve as a reliable source of information.	PBRERs/ PSURs
Pregnancy and lactation follow up forms	Not applicable	To monitor the use of darbepoetin alfa and potential adverse effects in pregnant and lactating women in the clinical trial and postmarketing settings	Not applicable

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned category 1 or 2 studies.

Table 19. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title, and Category Number	Rationale and Study Objectives	Study Design	Study Populations	Milestones
Study 20190404 A retrospective cohort study to assess the use of ESAs in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy in Europe Category 3	To characterize the use of ESAs in cancer patients undergoing myelosuppressive chemotherapy in European clinical practice <u>Safety concerns addressed:</u> Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer	Retrospective cohort study using existing European databases	Patients with non-myeloid malignancy who were administered an ESA during a course of myelosuppressive chemotherapy	Final report: 30 September 2025

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned darbepoetin alfa category 1 or 2 studies.

Table 20. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20190404 A retrospective cohort study to assess the use of ESAs in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy in Europe Ongoing	To characterize the use of ESAs in cancer patients undergoing myelosuppressive chemotherapy in European clinical practice	Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer	Final report	30 September 2025

Table 21. Other Forms of Additional Pharmacovigilance Activities

Description of Activity	Safety Concern(s)	Objectives	Milestones
Antibody testing	Antibody-mediated PRCA (Nephrology and Oncology Indications)	To further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk	PBRERs/PSURs

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 22. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Antibody-mediated PRCA (Nephrology Indication Only)	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for investigation of non-response to therapy with darbepoetin alfa and testing for anti-erythropoietin antibodies is included in SmPC Section 4.4.
Important Potential Risks	
Mortality and/or Tumor Progression or Recurrence in Patients With Cancer or a History of Cancer	Routine risk communication: • SmPC Sections 4.4, 5.1, and 5.3 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Information regarding effect on tumor growth is contained in SmPC Section 4.4.
Antibody-mediated PRCA (Oncology Indication Only)	Routine risk communication: • SmPC Section 4.4 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for investigation of non-response to therapy with darbepoetin alfa and testing for anti-erythropoietin antibodies is included in SmPC Section 4.4.

PL = package leaflet; PRCA = pure red cell aplasia; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimization Measures

Table 23. Removal of Additional Risk Minimization Activities

Additional Risk Minimization Activities Proposed to be Removed	Rationale for the Removal
• Demonstration device • Training checklist • Post-size instructions for use (IFU) for patients/caregivers with diminished eyesight	Background: The important potential risk 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission', and the corresponding aRMMs, demonstration device, training checklist, and poster-size IFU for patients/caregivers with diminished eyesight for Aranesp SureClick (pre-filled pen device) self-administration, were included in the EU RMP and implemented in 2019. Rationale for the removal: An evaluation of the important potential risk of 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission' was conducted in PBRER 39, for the reporting period of 01 November 2020 to 31 October 2023, submitted in January 2024. Based on review of the data, as presented in the PBRER 39 Section 16.3.1.6, most events were non-serious. Adverse events reported in these cases were assessed as not considered related to the missed or partial dose, no impact to patient safety was identified, and no new safety concerns have been identified. In addition, these events do not require further characterization and are not expected to have a significant impact on the benefit-risk profile of the product. Therefore, the MAH considers that the risk of 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission' no longer meets the criteria to be classified as an important potential risk. A review of the requests for orders of the demonstration device, associated training checklist, and poster-size IFU was conducted in 2024. Cumulatively through September 2024, there has been a significant decrease in demand for these tools since their inception in 2019, with limited requests for the demonstration device, associated training checklist, and poster-size IFU. Review of the product complaint/adverse event data since the implementation of the aRMMs shows a worldwide decrease in user error events reported with the pre-filled pen device, as reported in PBRER 39 Section 16.3.1.6. This decrease in user error events and the reporting pattern of product complaint/adverse event are similar in both the EU and non-EU countries which do not have the demonstration device, associated training checklist, and poster-size IFU as regulatory requirements.

Table 23. Removal of Additional Risk Minimization Activities

Additional Risk Minimization Activities Proposed to be Removed	Rationale for the Removal
• Demonstration device • Training checklist • Post-size instructions for use (IFU) for patients/caregivers with diminished eyesight (continued)	Therefore, the data do not indicate a correlation between the distribution for the aRMMs and the reduction in user error events, as well as the overall reporting of product complaints or adverse events. Thus, the MAH is removing the risk 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission' and corresponding aRMM demonstration device, associated training checklist, and poster-size IFU from the RMP and Annex IID 'Conditions or restrictions with regard to the safe and effective use of the medicinal product'. The detailed IFU, already included in the Package Leaflet, provides sufficient guidance for patients to understand how to correctly use the pre-filled pen device. The risk will continue to be monitored through routine pharmacovigilance.

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aRMM = additional risk minimization measure; EU = European Union; IFU = instructions for use; MAH = Marketing Authorization Holder; PBRER = Periodic Benefit-Risk Evaluation Report; RMP = Risk Management Plan

V.3 Summary of Risk Minimization Measures

Table 24. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Antibody-mediated PRCA (Nephrology Indication Only)	Routine risk minimization measures: • SmPC Section 4.4 where advice regarding bone marrow examination and action regarding Aranesp is provided • SmPC Section 4.8 • PL Section 2 • PL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse event follow-up form for adverse reactions (Pure red cell aplasia questionnaire). • Multidisciplinary review and evaluation of cases, adjudication of potential antibody-mediated PRCA cases using pre-defined criteria, and individual case assessment. Additional pharmacovigilance activities: • Antibody testing
Important Potential Risks		
Mortality and/or Tumor Progression or Recurrence in Patients With Cancer or a History of Cancer	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 5.1 • SmPC Section 5.3 • PL Section 2 • PL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Observational Study 20190404
Antibody-mediated PRCA (Oncology Indication Only)	Routine risk minimization measures: • SmPC Section 4.4 where recommendation for bone marrow examination is provided • PL Section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse event follow-up form for adverse reactions (Pure red cell aplasia questionnaire). • Multidisciplinary review and evaluation of cases, adjudication of potential antibody-mediated PRCA cases using pre-defined criteria, and individual case assessment. Additional pharmacovigilance activities: • Antibody testing

PL = package leaflet; PRCA = pure red cell aplasia; SmPC = Summary of Product Characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for darbepoetin alfa is presented below.

Summary of Risk Management Plan for Aranesp® (darbepoetin alfa)

This is a summary of the risk management plan (RMP) for Aranesp. The RMP details important risks of Aranesp, how these risks can be minimized, and how more information will be obtained about Aranesp's risks and uncertainties (missing information).

Aranesp's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Aranesp should be used.

This summary of the RMP for Aranesp should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Aranesp's RMP.

I. The medicine and what it is used for

Aranesp is authorized for the treatment of symptomatic anemia associated with chronic kidney failure (renal failure) in adults and pediatric patients (nephrology indication) and treatment of symptomatic anemia in adult cancer patients with non-bone marrow cancers (non-myeloid malignancies) receiving chemotherapy (oncology indication) (see SmPC for the full indication). It contains darbepoetin alfa as the active substance and it is given by injection either into a vein (intravenous) or under the skin (subcutaneous).

Further information about the evaluation of Aranesp's benefits can be found in Aranesp's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/medicines/human/EPAR/Aranesp.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Aranesp together with measures to minimize such risks and the proposed studies for learning more about Aranesp's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of Important Risks and Missing Information

Important risks of Aranesp are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Aranesp. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Antibody-mediated pure red cell aplasia (nephrology indication only)
Important potential risks	• Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer • Antibody-mediated pure red cell aplasia (oncology indication only)
Missing information	• None

II.B. Summary of Important Risks

Important identified risk: Antibody-mediated pure red cell aplasia (development of antibodies to the hormone that stimulates the production of red blood cells, which causes the body to stop the production of red blood cells) (nephrology indication only)	
Evidence for linking the risk to the medicine	This risk was identified in the postmarketing setting. Most cases of pure red cell aplasia were reported for patients with chronic kidney disease. Antibody-mediated pure red cell aplasia is considered an important identified risk in the nephrology indication and an important potential risk in the oncology indication since only a small number of cases have been identified in cancer patients.
Risk factors and risk groups	Pure red cell aplasia, in association with antibodies to the hormone that stimulates the production of red blood cells, has been observed in patients treated with medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents), including darbepoetin alfa. Pure red cell aplasia has been reported predominantly in patients with chronic kidney disease and in patients with hepatitis C treated with interferon and ribavirin. Most cases have been associated with under-the-skin administration of medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents). No other risk factor has been identified with darbepoetin alfa.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where advice regarding bone marrow examination and action regarding Aranesp is provided • SmPC Section 4.8 • PL Section 2 • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Antibody testing See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Mortality (death) and/or tumor progression or recurrence in patients with cancer or a history of cancer	
Evidence for linking the risk to the medicine	This potential risk was identified in the clinical trial setting. Increased death or adverse cancer outcomes were observed with medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents) in 8 clinical studies conducted in subjects with cancer. In the nephrology indication, the potential risk of death in subjects with a history of malignancy was identified based on a post-hoc subgroup analysis of a randomized, double-blind, placebo-controlled study called the Trial to Reduce Cardiovascular (heart and blood vessel) Events with Aranesp® Therapy (TREAT).
Risk factors and risk groups	There are no data available describing risk factors for death among patients with chronic renal failure who have a history of cancer and are receiving medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agent therapy). In patients with cancer, adverse tumor outcomes and death are closely linked with tumor characteristics including tumor type, stage, responsiveness to therapy, and where the cancer has spread, and patient factors including age, nutritional status, comorbidity, and weakness of the body's immune system (immune suppression).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 5.1 • SmPC Section 5.3 • PL Section 2 • PL Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Observational Study 20190404 See Section II.C of this summary for an overview of the postauthorization development plan

Important potential risk: Antibody-mediated pure red cell aplasia (development of antibodies to the hormone that stimulates the production of red blood cells, which causes the body to stop the production of red blood cells) (oncology indication only)	
Evidence for linking the risk to the medicine	This potential risk was identified in the postmarketing setting. Most cases of pure red cell aplasia were reported for patients with chronic kidney disease. Antibody-mediated pure red cell aplasia is considered an important identified risk in the nephrology indication and an important potential risk in the oncology indication since only a small number of cases have been identified in cancer patients.
Risk factors and risk groups	Pure red cell aplasia, in association with antibodies to the hormone that stimulates the production of red blood cells, has been observed in patients treated with medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents), including darbepoetin alfa. Pure red cell aplasia has been reported predominantly in patients with chronic kidney disease and in patients with hepatitis C treated with interferon and ribavirin. Most cases have been associated with under-the-skin administration of medicines that stimulate the production of red blood cells in the body (erythropoiesis-stimulating agents). No other risk factor has been identified with darbepoetin alfa.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where recommendation for bone marrow examination is provided • PL Section 2 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Antibody testing See Section II.C of this summary for an overview of the postauthorization development plan

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Aranesp.

II.C.2 Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study 20190404 A retrospective cohort study to assess the use of erythropoiesis-stimulating agents in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy in Europe	To characterize the use of erythropoiesis-stimulating agents in cancer patients undergoing myelosuppressive chemotherapy in European clinical practice Safety concerns addressed: Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer

PART VII: ANNEXES

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Annex 1. EudraVigilance Interface

Annex 2. Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Table 25. Annex II: Planned and Ongoing Studies From the Pharmacovigilance Plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Protocol Link Milestone
Category 3 - Required additional pharmacovigilance activities			
Study 20190404 A retrospective cohort study to assess the use of ESAs in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy in Europe Ongoing	To characterize the use of ESAs in cancer patients undergoing myelosuppressive chemotherapy in European clinical practice	Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer	Study 20190404 Final report: 30 September 2025

Table 26. Annex II: Completed Studies From the Pharmacovigilance Plan

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Link to Report
Study 20070782 Controlled clinical study A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term Safety and Efficacy of Darbepoetin Alfa Administered at 500 µg Once-Every-3-Weeks in Anemic Subjects With Advanced Stage Non-small Cell Lung Cancer Receiving Multi-cycle Chemotherapy Category 3	Primary: To demonstrate non-inferiority of overall survival when comparing subjects on darbepoetin alfa treated to a hemoglobin ceiling of 12.0 g/dL to subjects treated with placebo Secondary: • To demonstrate non-inferiority of progression-free survival when comparing subjects on darbepoetin alfa treated to a hemoglobin ceiling of 12.0 g/dL to subjects treated with placebo • To demonstrate superiority in reducing the incidence of RBC transfusions when comparing subjects on darbepoetin alfa treated to a hemoglobin ceiling of 12.0 g/dL to subjects treated with placebo • To assess other safety and efficacy parameters in subjects on darbepoetin alfa treated to a hemoglobin ceiling of 12.0 g/dL compared to subjects treated with placebo	• Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer • Cerebrovascular disorders	21 December 2018

Table 26. Annex II: Completed Studies From the Pharmacovigilance Plan

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Link to Report
Study 20110226: Controlled clinical study START-CKD: Strategies Using Darbepoetin alfa to Avoid Transfusions in CKD Category 3	Primary: To evaluate the incidence of RBC transfusions in CKD subjects not on dialysis using either a hemoglobin-based titration algorithm or a weight-based dose that will not be titrated (fixed dose), and to evaluate the difference in the incidence of RBC transfusions between the 2 groups. Secondary: • To summarize the following for each dosing strategy: – Transfusion burden – Time to first RBC transfusion – Achieved hemoglobin concentration – Cumulative dose of darbepoetin alfa • To describe the difference in each of the above between the 2 dosing strategies. Safety: To describe the safety profile of darbepoetin alfa, including adverse events and the occurrence of adjudicated clinical events of interest.	• Cerebrovascular disorders • Ischemic heart disease, including myocardial infarction	21 December 2018

Annex 3. Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

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Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

Not applicable

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

Not applicable

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.

Final protocols not reviewed or not approved:

Study Number	Version Number	Date of Protocol
20190404	Amendment 6	23 April 2024

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	Stephen Puntis, DPhil Centre for Observational Research, Amgen Ltd.

Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen
MAH Contact	Stephen Puntis spuntis@amgen.com

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

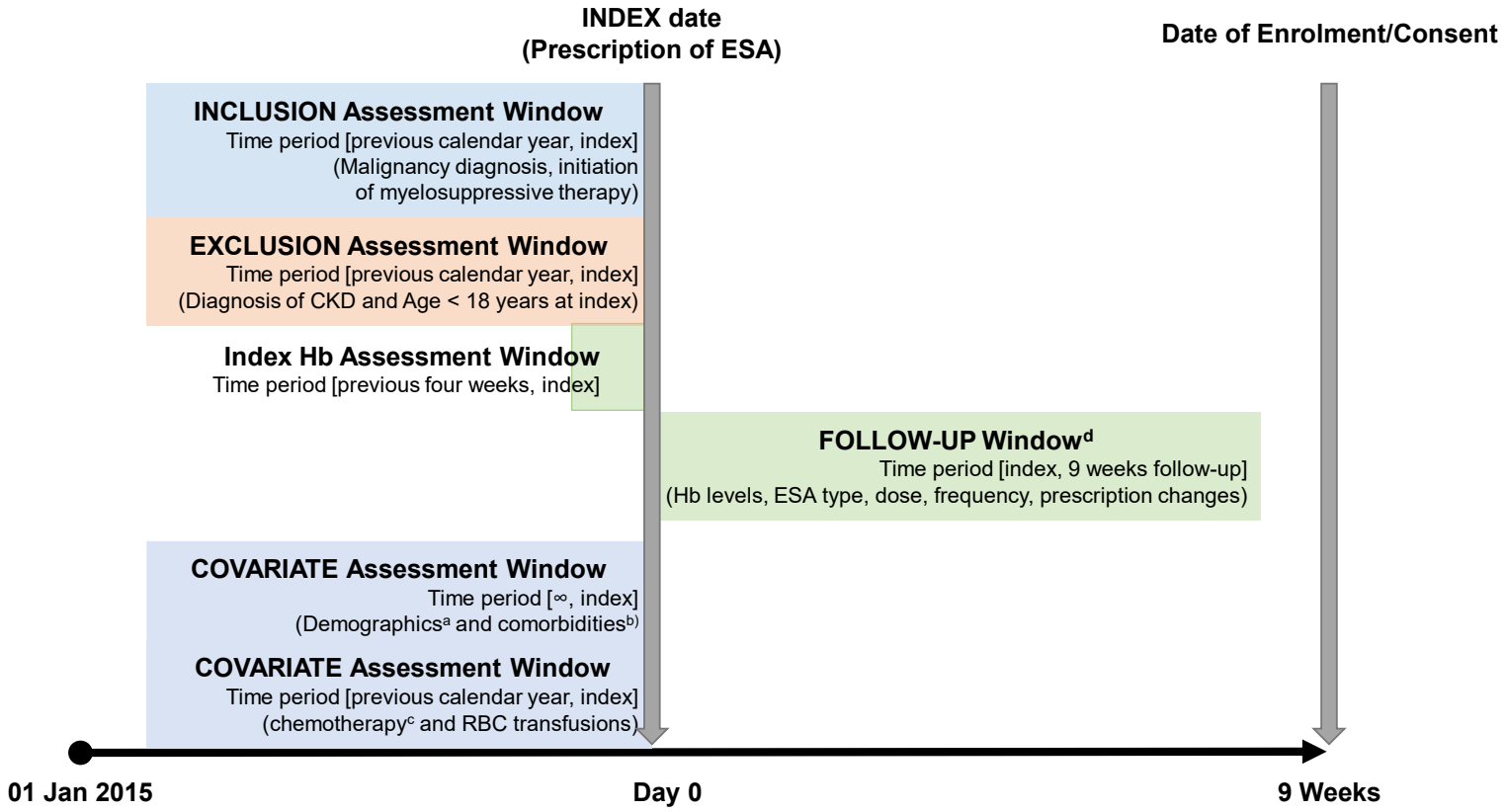
_____ _____
Name of Investigator Date (DD Month YYYY)

_____
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

Stephen Puntis, Centre for Observational Research, Amgen Ltd.

Deborah Layton, 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

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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)	☒	☐	☐	10.1

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: Stephen Puntis

Date:

Signature:

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

1. PATIENT INFORMATION

Patient Initials (Confidential)

Age at Time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: _____lb _____kg

Date of Event (dd/mm/yyyy)

Date of this Report (dd/mm/yyyy)

2. MEDICATION ADMINISTERED

Amgen Drug | Dose | Frequency | Route

Amgen Drug | Dose | Frequency | Route

Other Medications: _____ Co-suspect Medications: _____

3. SIGNS AND SYMPTOMS (Check all that apply)

- ☐ Pallor
- ☐ Syncope
- ☐ Near syncopal event
- ☐ Weakness
- ☐ Fatigue
- ☐ Lethargy
- ☐ Anxiety
- ☐ Dyspnoea
- ☐ Tachycardia

☐ What was the original (primary) etiology of the anemia?

☐ Etiology of PRCA identified (explain)

☐ Decreased response to erythropoietic agents

☐ Sudden loss of effect to erythropoietic agents

☐ Refractory or recalcitrant to other ESA compounds
List compound and dates of administration and outcomes:

☐ Anemia is due to renal insufficiency/failure
☐ Renal disease has worsened recently

☐ Other _____

4. EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please attach baseline labs, if available, and copy of reports)

Diagnostic	Results/Units	Reference Range/ Units	Date	Report Attached Y	N
RBCs					
WBCs with differential					
HCT					
Hgb					
MCV					
MCH					
MCHC					
RDW					
Platelet count					
MPV					
Reticulocyte Count					
Serum Erythropoietin					
Serum Ferritin					
Serum Iron					
Transferrin Saturation					
Anti-epo antibody test/titres					
Coombs Titer					
Vit B12					
Folate					
C-Reactive Protein					
BUN					
Creatinine					
Serum Parathyroid Hormone					
Serum Phosphate					
AST					
ALT					
Serum Albumin					
Carnitine					

Diagnostic	Results/Units	Reference Range/ Units	Date	Report Attached Y	N
Total Bilirubin					
Direct Bilirubin					
Indirect Bilirubin					
Parvovirus B19 Titers/PCR					
Hepatitis test/titers Type: _____					
HIV Antibodies					
Epstein-Barr antibodies					
Aluminum level					
Fecal occult blood test					
Other _____					

5. REPORTS/RELEVANT FINDINGS (Indicate attachments if available)

- ☐ Bone marrow biopsy _____
- ☐ Chest x-ray _____
- ☐ CT scan _____
- ☐ Bone marrow biopsy finding _____
- ☐ Consult report _____
- ☐ Hospital or discharge report _____

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

Amgen
Office Fax:

CONTINUED ON NEXT PAGE

AMGEN®

PURE RED CELL APLASIA
(continued)

AER # **Page 122**

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Do not provide any information by or through which a patient can be identified, other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

1. PATIENT INFORMATION

Patient Initials (Confidential)

Age at Time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: _____lb _____kg

Date of Event (dd/mm/yyyy)

Date of this Report (dd/mm/yyyy)

2. MEDICATION ADMINISTERED

Amgen Drug	Dose	Frequency	Route

Amgen Drug	Dose	Frequency	Route

Other Medications:_____ Co-suspect Medications: _____

6. PATIENT HISTORY/RISK FACTORS (Please provide dates and dosage and attach available reports)

☐ Viral Infections:
- ☐ Hepatitis Type: _____
- ☐ Parvovirus B19
- ☐ Epstein-Barr virus
- ☐ HIV
- ☐ Other (specify) _____

☐ Autoimmune Diseases:
- ☐ Rheumatoid arthritis
- ☐ Systemic lupus erythematosus
- ☐ Other (specify) _____

☐ Neoplastic diseases:
- ☐ Lymphoma
- ☐ Leukemia
- ☐ Myeloma
- ☐ Thymoma

☐ Other (specify) _____

☐ Bone metastases

☐ Myelodysplasia

☐ Myelofibrosis (reticulin or collagen fibrosis)

☐ Osteitis fibrosa

☐ Haemoglobinopathy

☐ Recent intercurrent infection

Previous exposure to other erythropoietin treatment

If yes, please specify drug, (type of ESA, dose, dates of treatment)

_____

_____

☐ Please provide patient's blood transfusion history

_____

_____

☐ Family history of PRCA

_____

_____

☐ Chemotherapy agents exposure

☐ Procainamide

☐ Isoniazid

☐ Aztreonam

☐ Dapsone

☐ Interferons

☐ Lamivudine

☐ Zidovudine

☐ Rifampin

☐ Carbamezapine

☐ Phenytoin

☐ Valproic Acid

☐ Allopurinol

☐ D-Penicillamine

☐ IM Gold

☐ Rituximab

☐ Sulfasalazine

☐ Azathioprine

☐ Cyclosporine

☐ Tacrolimus

☐ Other:
- ☐ Exposure to Aluminum
- ☐ Exposure to myelotoxic or immunsuppressive medication (please specify)

_____

- ☐ Other: _____

Amgen
Office Fax:

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

INITIAL PREGNANCY (MOTHER) AUTHORIZATION AND QUESTIONNAIRE

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To: [reporter_first_name]:[1] [reporter_last_name]:[1]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name]:[1] [reporter_last_name]:[1],

Thank you for reporting your [patient_initials] pregnancy while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire and signed consent form with requested information to the address, email or fax below.

Kindly note the following attachments:

- **AUTHORIZATION FOR RELEASE OF PREGNANCY AND INFANT HEALTH INFORMATION**
- **INITIAL PREGNANCY QUESTIONNAIRE (MOTHER)**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

Authorization for Release of Pregnancy and Infant Health Information

[This is an example of text that can be used to obtain authorization for release of information from a female who initiated an Amgen product during her pregnancy or became pregnant during treatment or after discontinuing treatment with an Amgen investigational or marketed product. It is also applicable to a pregnant woman whose male partner was taking an Amgen product when she became pregnant or initiated an Amgen product during the pregnancy]
Make alterations as directed within each square bracket [ ] that are appropriate to the region/country. This text should be altered only if required by local laws and regulations and following legal review. Discard all directions in the final form, including this one, before sending externally.]

Female Authorization Form to Obtain Pregnancy and Infant Health Information
[Authorization author: select the appropriate statement from the two options below depending on whether the female is the exposed parent or her male partner.]

[Authorization author: specify appropriate Amgen entity, e.g., Amgen Inc., Amgen Ltd., Amgen Canada] has been informed that you have become pregnant (or were already pregnant) during or after discontinuing treatment with *[add Amgen investigational or marketed product name]*.

OR

[Authorization author: specify appropriate Amgen entity, e.g., Amgen Inc., Amgen Ltd., Amgen Canada] has been informed that you have become pregnant (or were already pregnant) while your male partner was taking *[add Amgen investigational or marketed product name]*.

[Authorization author: include this information in all authorizations]
Amgen Inc. and its respective global subsidiaries and affiliates (collectively referred to as "Amgen") collects pregnancy-related health information when a woman becomes pregnant (or was already pregnant), while she, or her male partner, was taking an Amgen investigational or marketed drug product. The information collected will contribute to the body of knowledge that could ultimately help patients and their healthcare providers (HCP) make more informed decisions about taking an Amgen medication during pregnancy.

We would like to collect this information whether or not you and your partner decide, in consultation with your HCP and/or study doctor (if the pregnancy occurred during a study), to continue with this pregnancy. Although Amgen collects information about the pregnancy and birth outcome, Amgen will not be responsible for any expenses relating to this pregnancy or its outcome. We do not provide any payment or compensation to you for providing information and there are no medications or treatments prescribed.

Because we are collecting personal health information, you are required to <<sign an authorization>> *[for regions where signed authorization is required or]* <<provide authorization>> *[for regions where verbal authorization may be acceptable such as the U.S.]* for release of information concerning your pregnancy, and if applicable, the birth and health of your child(ren) born from this pregnancy. The medical information requested may include:

- your current health, your pregnancy and previous pregnancies and birth outcomes.
- your child(ren)s health information from this pregnancy (e.g., any newborn complications) up to 12 months following birth, if applicable.

[Authorization Author: Use this language if follow-up will only be conducted with the HCP]
If you agree to be a part of this pregnancy follow-up activity, Amgen will contact your HCP, and/or a study doctor (if the pregnancy occurred during a study), to request your and your child(ren)s health information. If applicable, additional information will be requested approximately 6 to 8 weeks after the estimated delivery date and when the child(ren) is/are 6 and 12 months of age. Your HCP may also contact other HCPs responsible for your or your child(ren)s medical care to obtain additional information about your health, your pregnancy, and the health of your child(ren).

OR

[Authorization Author: Use this language if (acceptable per local laws and customs) follow-up may be conducted with the HCP and/or the patient (such as the US)]

If you agree to be a part of this pregnancy follow-up activity, Amgen will contact you and/or your HCP, or the study doctor (if the pregnancy occurred during a study), to request your and your child(ren)s health information. If applicable, additional information will be requested approximately 6 to 8 weeks after the estimated delivery date and when the baby is 6 and 12 months of age. Amgen may also contact other HCPs responsible for your or your childs medical care to obtain additional information about your health, your pregnancy, and the health of your child(ren). Contact information (name, phone number, etc.) about you and your child(ren) is not collected unless you have contacted Amgen or given authorization for Amgen to contact you directly. In that case, Amgen will continue to store your contact information. However, your personal identifiable information will not be released to any outside agencies unless required by law.

[Authorization Author: Include this language for all patients/subjects]

Because Amgen medications may be taken by patients throughout the world, Amgen and its service providers have offices in many global locations. Other countries may not provide the same level of protection for your and your child(ren)s personal information as is available in *[patients home country name]*. Regardless of the country in which data is collected and processed, Amgen maintains administrative, technical and physical safeguards to protect information about you and your child(ren).

Regulatory agencies and Amgen business partners who distribute *[add Amgen investigational or marketed product name]* both within and outside *[patients home country name]* *[Authorization Author: Only include the Institutional Review Board and Ethics Committee information if the subject or father of the baby was enrolled in a study]* and the *[specify appropriate name for the party responsible for ethics review and approval e.g., Institutional Review Board (IRB), Ethics*

Committee] may review pregnancy and infant health information that Amgen collects. If you have provided your and/or your child(ren)s name and any other identifying data, this information will not be revealed, unless required by applicable law or regulation.

The information collected may also be used in future scientific research into *[specify therapeutic area]* and any related scientific or educational publications. Neither you nor your child will be identified in any such publications.

Your authorization to provide this information is completely voluntary and gives Amgen and its trusted service providers permission to obtain, store, and analyse information about you and your child(ren). You are free to withdraw authorization at any time. *[The following sentence may be used, depending on applicable laws and regulations for your country/region]:* You may also access information held about you and your child(ren), and you have the right to correct inaccuracies in the information held about you and your child(ren). If you withdraw your authorization, all information capable of identifying you or your child(ren) will be deleted from the Amgen database. Amgen may continue to use such anonymized information collected prior to the date of withdrawal. *[The following may be used, depending on applicable laws and regulations for your country/region]* In such circumstances, since the data can no longer be linked to you, we will be unable to respond to access requests.

If you have any questions at any time, or you wish to withdraw your authorization, or you wish to exercise any rights you have with respect to information collected by Amgen, including on behalf of your child(ren), please notify your doctor or write to Amgen (contact details given below).

Thank you for your willingness to provide Amgen this with important information.

By signing this authorization form, I confirm that I understand the terms above and agree to allow the collection of my and my child(ren)s personal health information.

Mother Full Name *(Printed)*	Signature	Date

Authorization on Behalf of Child

By signing this authorization form, I confirm that I agree that my child(ren) (born from this pregnancy) will take part in this activity and is/are subject to the same terms described above.

Child Full Name (as applicable post birth) *Printed*

[Add additional lines for additional children born from this pregnancy]

Mother Full Name *(Printed)*	Signature	Date

[Authorization Author: Include for Clinical Trials Only]

Healthcare Provider (Investigator) Full Name *(Printed)* (If applicable)	Signature	Date

Study Number: _____ Site Number: _____

Subject Number: _____

[Authorization Author: Please add contact details for forwarding the signed authorization and if applicable for questions]

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER)

You may return completed form to Amgen Office Fax or Email:

[Office Fax or Email]

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other_____ Parent exposed to product? ☐ Mother ☐ Father

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the patient sign the *Authorization for Release of Pregnancy Related Medical Information*? ☐ Yes ☐ No

Section 2 – Mother Current Pregnancy Information

Mother's Initials:

_____

Date of birth: (if permitted to provide by local laws)

_____
Day Month Year

Date of last menstrual period:

_____
Day Month Year

Age: _____ years

Number of fetuses_____

Estimated date of delivery:

_____
Day Month Year

Relevant Laboratory Tests & Procedures

Test Name	Test Date (dd/mm/yr)	Test Result

Section 3 – Mother Prenatal Medication History

Please list all medications (prescription and over-the-counter [include vitamins, herbal medications, etc.) and vaccines, taken by the **mother within 3 months prior to or during pregnancy**.

Amgen Product Used	Dose	Route (e.g. oral, subq)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Weeks of Pregnancy When Drug Taken (e.g. wk 28–wk 32)	Indication for Treatment
Resumed (if applicable)							
Amgen Product Lot Number _____ ☐ Lot Number Not Known							

List any other medications used within 3 months prior to or during the pregnancy

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER) *continued*

Section 4 – Pregnancy Complication and Adverse Event Information

If the **mother** experienced any pregnancy complications (e.g. preeclampsia, gestational diabetes, placenta previa, etc.) please complete the following:

Pregnancy Complication or Adverse Event	**Date the Complication or Event Started** (dd/mm/yy)	**Date the Complication or Event Resolved** (dd/mm/yr)	**Outcome** (for example: resolved, not resolved, unknown, other, etc.)

Section 5 – Mother Relevant Medical History

Please provide pertinent medical history:

☐ hypertension ☐ seizure ☐ diabetes ☐ difficulty conceiving ☐ asthma ☐ thyroid dysfunction ☐ other_____

Please describe any additional factors that may have an impact on the outcome of this pregnancy, including relevant medical or family history, mother's occupation, illnesses during pregnancy etc. Please specify other disorders including familial birth defects/genetic/chromosomal disorders, etc.:

Section 6 – Mother Previous Obstetrical (Pregnancy) History

Please provide the number of pregnancies after treatment with an Amgen product was initiated. Include the pregnancy outcome for each of these pregnancies and any additional relevant details:

Number of pregnancies and outcome details:

☐ Normal healthy baby: _____

☐ Stillbirth: _____

☐ Baby with birth defect: _____

☐ Outcome unknown: _____

_____

☐ Miscarriage: _____

☐ Abortion (induced for medical reason): _____

_____

_____

☐ Abortion (induced for non-medical [voluntary] reason):

_____

☐ Other (specify outcome) or any significant additional information:

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER) *continued*

Section 7 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (check the appropriate box below):

☐ Live birth
☐ Number of infants_____(1: single, 2: twins, etc.)
(If multiple births: Please provide all information for each infant in the additional information text box below:)

If live birth: Gender: ☐ Male ☐ Female

Length: _____ cm/inches Birth weight: _____ gram/lb

Head circumference: _____cm/inches

Did the baby have any complications/medical problems/ congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information on the medical problem:

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
☐ Due to health issue (mother or baby)
☐ For voluntary reason
☐ Other (please specify):_____

_____

Please confirm if there were there any tests done or results given for the baby/fetus? ☐ Yes ☐ No
If yes, please provide the details below.

Additional Information on pregnancy outcome and/or test/results:

Section 8 – Reporter Signature (can be digital or manual)

Signature of person completing questionnaire: _____ Date: _____
Please print name: _____
Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs.
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:
Name _____ Phone ( ) _____ Fax ( ) _____
Email _____Address _____ City _____
State/Province _____ Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:
Name _____ Phone ( ) _____ Fax ( ) _____
Email _____Address _____ City _____
State/Province _____ Zip/Postal Code _____

Health Care Provider for the child:
Name _____ Phone ( ) _____ Fax ( ) _____
Email _____Address _____ City _____
State/Province _____ Zip/Postal Code _____ Country _____

INITIAL PREGNANCY (FATHER) AUTHORIZATION AND QUESTIONNAIRE

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting that your [patient_initials] female partner became pregnant while [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire and signed consent form with requested information to the address, email or fax below.

Kindly note the following attachments:

- **AUTHORIZATION FOR RELEASE OF BIOLOGICAL FATHER AND INFANT HEALTH INFORMATION**
- **INITIAL PREGNANCY QUESTIONNAIRE (FATHER)**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

Authorization for Release of Personal and Infant Health Information

[*This is an example of text that can be used to obtain authorization for release of information from a male whose partner became pregnant or was already pregnant when he initiated an Amgen investigational or marketed product.]*

Make alterations as directed within each square bracket [ ] that are appropriate to the region/country of jurisdiction. This text should be altered only if required by local laws and regulations and following legal review. Discard all directions in the final form, including this one, before sending externally.]

Male Authorization Form to Obtain Biological Father and Infant Health Information

[*Authorization Author: Specify appropriate Amgen entity, e.g., Amgen Inc., Amgen Ltd., Amgen Canada*] has been informed that your partner has become pregnant, or was already pregnant during your treatment with *[add Amgen investigational or marketed product name.]*

Amgen Inc. and its respective global subsidiaries and affiliates (collectively referred to as "Amgen") collects father and infant (if applicable) health information when a man fathers a child or initiates treatment with an Amgen investigational or marketed drug product during his partner's pregnancy. The information collected will contribute to the body of knowledge that could ultimately help men and their health care providers (HCP) make more informed decisions about taking an Amgen medication during their partner's pregnancy or fathering a child while taking an Amgen medication.

We would like to collect this information whether or not you and your partner decide, in consultation with your or your partner's HCP(s), to continue with this pregnancy. With your partner's authorization, Amgen would also request to obtain her pregnancy related health information. Although Amgen collects information about your health, your partner's pregnancy related health, and the birth outcome, Amgen will not be responsible for any expenses relating to this pregnancy or its outcome. We do not provide any payment or compensation to you for providing information and there are no medications or treatments prescribed.

Because we are collecting personal health information, you are required to <<sign an authorization [*for regions where signed authorization is required or]* <<provide authorization>> *[for regions where verbal authorization may be acceptable such as the U.S.*] for release of health related information regarding your health and that of your child(ren). The medical information requested may include:

- your current health and the health of any children your previously fathered
- health information regarding your child(ren)'s born from this pregnancy (e.g., any newborn complications) up to 12 months following birth, if applicable.

[Authorization Author: Use this language if follow-up will only be conducted with the HCP]

If you agree to allow the collection of your and your child(ren)'s health information, Amgen will contact your HCP, and/or a study doctor (if your partner's pregnancy occurred during a clinical study), to request your health information. If applicable, additional information will be requested approximately 6 to 8 weeks after the estimated delivery date and when the child(ren) is/are 6 and 12

months of age. Your HCP may also contact other HCPs responsible for your or your child(ren)'s medical care to obtain additional information about your health and the health of your child(ren).

OR

[*Authorization Author*: Use this language if (acceptable per local laws and customs) follow-up may be conducted with the HCP and/or the patient (such as the US)]
If you agree to allow the collection of your and your child(ren)'s health information, Amgen will contact you and/or your HCP, or a study doctor (if your partner's pregnancy occurred during a study), to request your health information and the health of your child(ren). Amgen may also contact other HCPs responsible for your or your child(ren)'s medical care to obtain additional information about your health and the health of your child(ren). Contact information (name, phone number, etc.) about you and your child(ren) are not collected unless you have contacted Amgen or given authorization for Amgen to contact you directly. In that case, Amgen will continue to store your contact information. However, your personal identifiable information will not be released to any outside agencies unless required by law.

[*Authorization Author*: Include this language for all patients/subjects]
Because Amgen's medications may be taken by patients throughout the world, Amgen and its service providers have offices in many global locations. Other countries may not provide the same level of protection for your and your child(ren)'s personal information as is available in ***[patient's home** country name*]. Regardless of the country in which the data is collected and processed, Amgen maintains administrative, technical and physical safeguards to protect information about you and your child(ren).

Regulatory agencies and business partners who distribute [*add Amgen investigational or marketed product name*] both within and outside *[**patient's home** country name] [Authorization Author: Only include the Institutional Review Board and Ethics Committee information if father of the child was enrolled in a study]* and the *[specify appropriate name for the party responsible for ethics review and approval e.g., Institutional Review Board (IRB), Ethics Committee]* may review your and your child(ren)'s health information that Amgen collects. If you have provided your and/or your child(ren)'s name and any other identifying data, this information will not be revealed, unless required by applicable law or regulation.

The information collected may also be used in future scientific research into [*specify therapeutic area*] and related scientific or educational publications. Neither you nor your child(ren) will be identified in any such publications.

Your authorization to provide this information is completely voluntary and gives Amgen and its trusted service provider's permission to obtain, store, and analyse information about you and your child(ren). You are free to withdraw your authorization at any time. [*The following sentence may be used, depending on applicable laws and regulations for your country/region*]. You may also access information held about you and your child(ren), and you have the right to correct inaccuracies in the information held about you and your child(ren). If you withdraw your authorization, all information capable of identifying you or your child(ren) will be deleted from Amgen's database. Amgen may continue to use such anonymized information collected prior to the date of withdrawal. [*The following may be used, depending on applicable laws and regulations for your country/region*] In such

circumstances, since the data can no longer be linked to you, we will be unable to respond to access requests.

If you have any questions at any time, or you wish to withdraw your authorization, or you wish to exercise any rights you have with respect to information collected by Amgen (including on behalf of your child(ren), please write to Amgen (contact details given below).

Thank you for your willingness to provide Amgen with this important information.

By signing this authorization form, I confirm that I understand the terms above and agree to allow **the collection of my and my child(ren)'s personal medical information.**

Father's Full Name *(Printed)* Signature Date

Authorization on Behalf of Child

By signing this authorization form, I confirm that I agree that my child(ren) (born from this pregnancy) will take part in this activity and is/are subject to the same terms described above.

Child's Full Name (as applicable post birth) *Printed*

[Add additional lines for additional children resulting from this pregnancy]

Father's Full Name (Printer Signature Date

[Authorization Author: Include for Clinical Trials Only]

Healthcare Provider (Investigator) Full Name *(Printed)* (If applicable) Signature Date

Study Number _____ Site Number _____

Subject Number: _____

[*Authorization Author: Please add contact details for forwarding the signed authorization and if applicable for questions*]

INITIAL PREGNANCY QUESTIONNAIRE (FATHER)

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Father ☐ Health Care Professional ☐ Other _____

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the father sign the *Authorization for Release of Medical Information*? ☐ Yes ☐ No

Section 2 – Father Medication Information

Amgen Product Used	**Dose**	**Route** (e.g. oral, subq)	**Frequency** (e.g. daily, weekly)	**Date Drug Started** (dd/mm/yy)	**Date Drug Stopped** (dd/mm/yy)	**Indication for Treatment**
Resumed (if applicable)						

Amgen Product Lot Number _____ ☐ Lot Number Not Known

Father's initials: _____

Age: _____

Father's pertinent medical history (cardiac conditions, rheumatoid arthritis, cancer, hypertension, etc.): _____

Section 3 – Current Pregnancy Outcome (for Live Birth)

☐ Number of infants_____(1: single, 2: twins, etc.)

Multiple births: Please provide all information for each multiple birth infant in the additional information text box below*:

Gender: ☐ Male ☐ Female Birth weight: _____gram/lb

Length: _____cm/inches Head circumference: _____cm/inches

Did the baby have any complications/medical problems/ congenital anomalies (birth defects)? ☐ Yes ☐ No

If yes, please provide specific information on the medical problem:

*Additional information on pregnancy outcome:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name:_____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs.

May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider who is prescribing the Amgen product:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____

Health Care Provider for the Child:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting your [patient_initials] pregnancy while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire with requested information to the address, email or fax below.

Kindly note the following attachments:

- **6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other _____

Any change in the reporter contact information? ☐ Yes ☐ No If yes, please provide updated contact information:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

Section 2 – Mother Prenatal Medication History

Please provide any additional medication information for medicines used during your pregnancy not previously reported. For example, if you resumed or discontinued the Amgen Product or any other medications during the pregnancy (include vitamins, folic acid, herbal medications, and vaccines).

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 3 – Mother Pregnancy Complications and/or Adverse Event Information Not Previously Reported

Pregnancy Complication or Adverse Event (e.g. preeclampsia, gestation diabetes)	Date the Complication or Event Started (dd/mm/yy)	Date the Complication or Event Resolved (dd/mm/yr)	Outcome (for example: resolved, not resolved, unknown, other, etc.)

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER) *continued*

Section 4 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (please check the appropriate box below)

☐ Live birth
  ☐ Number of infants_____(1: single, 2: twins, etc.)
  (If multiple births: Please provide all information for each infant in the additional information text box below:)

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
  ☐ Due to health issue (mother or baby)
  ☐ For voluntary reason
  ☐ Other (please specify):_____

If live birth: Gender: ☐ Male ☐ Female

Length: _____cm/inches Birth weight: _____gram/lb Head circumference: _____cm/inches

Did the baby have any complications/medical problems/congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information below.

Additional Information on pregnancy outcome:

Section 5 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider for the child:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (FATHER)

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting that your [patient_initials] female partner became pregnant while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnarie with requested information to the address, email or fax below.

Kindly note the following attachments:

- **6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (FATHER)**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (FATHER)

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Father ☐ Health Care Professional ☐ Other_____

Any change in the reporter contact information? ☐ Yes ☐ No If yes, please provide updated contact information:

Name _____Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Section 2 – Father Medication History

If you have changed the dose, frequency of the Amgen product you are taking during your partner's pregnancy, please provide this information below.

Amgen Medications	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment
Resumed, if applicable						

Section 3 – Current Pregnancy Outcome (for Live Birth)

☐ Number of infants_____(1: single, 2: twins, etc.)
Multiple births: Please provide all information for each multiple birth infant in the additional information text box below*:

Gender: ☐ Male ☐ Female Birth weight: _____gram/lb

Length: _____cm/inches Head circumference: _____cm/inches

Did the baby have any complications/medical problems/ congenital anomalies (birth defects)? ☐ Yes ☐ No

If yes, please provide specific information on the medical problem:

*Additional multiple birth information:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____Date: _____

Please print name: _____

Title: _____

SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting your [patient_initials] pregnancy while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire with requested information to the address, email or fax below.

Kindly note the following attachments:

- **SIX AND TWELVE MONTH INFANT QUESTIONNAIRE**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

Mother Safety Database #

Infant Safety Database #

AMGEN

SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Father ☐ Health Care Professional (HCP) ☐ Other_____

Section 2 – Infant Healthcare Provider (HCP) Information

May Amgen contact the HCP for medical information regarding your child? ☐ Yes ☐ No

If yes, please provide contact information:

Name _____ Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Section 3 – Infant Medical Health Information

List any other medications/drugs (include vitamins and over-the-counter medications taken by the child)

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Has the infant had any abnormal screening tests? ☐ Yes ☐ No If yes, please explain:

Has the infant followed growth curves and developmental milestones as expected for chronological age?

☐ Yes ☐ No If no, please explain:

Has the infant had any illnesses or persistent health problems? ☐ Yes ☐ No If yes, please explain:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____Date: _____

Please print name: _____Title and specialty if HCP_____

LACTATION QUESTIONNAIRE

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting your [patient_initials] breastfeeding while on [product_name:first_suspect] ([generic_name:first_suspect])therapy. Please send the completed questionnaire with requested information to the address, email or fax below.

Kindly note the following attachments:

- **LACTATION QUESTIONNAIRE**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

AMGEN

LACTATION QUESTIONNAIRE

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Patient ☐ Health Care Professional (HCP) ☐ Other_____

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the patient sign the Authorization for Release of Medical Information? ☐ Yes ☐ No

Section 2 – Mother Demographic Information

Mother's initials: _____ **Age:** _____ **Date of birth** (if permitted by local laws): _____

Day Month Year

Section 3 – Mother Medication Information

Amgen Product Used While Breastfeeding	Dose	Route (e.g. oral, subcutan.)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment
Amgen Product Lot Number _____ ☐ Lot Number Not Known						

List any other medications/drugs (include vitamins, herbals, and vaccines) the Mother used while breastfeeding

Medications/Drugs	Dose	Route (e.g. oral, subcutan.)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 4 – Mother's Medical Information

Mother's pertinent medical information (e.g. arthritis, hypertension, thyroid dysfunction, etc.):

Is the mother continuing to take an Amgen product while continuing to breastfeed? ☐ Yes ☐ No

If no, please provide the date when the Amgen product was discontinued or the mother stopped breastfeeding:

_____

Day Month Year

LACTATION QUESTIONNAIRE *(continued)*

Section 5 – Infant Medical Information

Does the infant currently have any health issues? ☐ Yes ☐ No

If yes, please provide current health details and treatment provided:

Is the infant gaining weight and developing normally? ☐ Yes ☐ No If no, please specify:

Section 6 – Infant Medication Information

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 7 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____ Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your child's HCP
May Amgen contact your child's HCP? ☐ Yes ☐ No

Health Care Provider for the child:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable

Annex 6. Details of Proposed Additional Risk Minimization Activities

Not applicable.

Annex 7. Other Supporting Data (Including Referenced Material)

Table of Contents

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Annex 8. Summary of Changes to the Risk Management Plan Over Time

Initially, separate RMPs were developed for the nephrology and oncology indications (versions 1.0 to 3.0 of each). These RMPs have been consolidated and updated in version 4.

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
Nephrology RMP		
1.0	Date of RMP: 05 December 2008	**Safety Concerns** Important Identified Risks: • Hypertension • Venous thromboembolic events • Convulsions • Allergic reactions (hypersensitivity) • Antibody-mediated PRCA Important Potential Risks: • Ischemic heart disease, including myocardial infarction • Cardiac failure • Cerebrovascular hemorrhagic and ischemic conditions • Vascular access thrombosis Missing Information: • Pregnancy • Nursing mothers • Geriatric use • Pediatric use • Hyporesponders **Pharmacovigilance Plan** Pharmacovigilance Activities for Antibody-mediated PRCA: • Pregnancy surveillance program • A structured questionnaire for information on suspected cases • Antibody testing and systematic case follow-up • Comprehensive safety database searches • Multidisciplinary review and evaluation of cases Pharmacovigilance Studies: • Study 20070211: A prospective registry study observing the safety and patterns of use of darbepoetin alfa in EU pediatric chronic kidney disease patients receiving or not receiving dialysis **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Not applicable

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
Nephrology RMP (continued)		
2.0	Date of RMP: 28 July 2010	**Safety Concerns** Important Identified Risks: • Cerebrovascular hemorrhagic and ischemic conditions changed from a potential to an identified risk Important Potential Risks: • Nephrogenic systemic fibrosis added as a potential risk • Mortality in subjects with a history of malignancy added as a potential risk • Risks associated with different manufacturing processes (roller bottle vs high throughput) were removed **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Not applicable
3.0	Date of RMP: 14 December 2011 PSU – PSUR 085	**Safety Concerns** Important Identified Risks: • Vascular access thrombosis reclassified from a potential to an identified risk • 'Hypertension' renamed as 'Hypertension, including hypertensive crisis' Important Potential Risks: • Nephrogenic systemic fibrosis removed as a potential risk **Pharmacovigilance Plan** Lactation surveillance program Pharmacovigilance Activities for Antibody-mediated PRCA Added: • Adjudication of potential antibody-mediated PRCA cases Pharmacovigilance Studies Added: • Study 20050256: A multicenter, double-blind, randomized study evaluating de novo weekly and once every 2 week darbepoetin alfa dosing for the correction of anemia in pediatric subjects with chronic kidney disease receiving and not receiving dialysis **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Not applicable

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
Oncology RMP		
1.0	Date of RMP: April 2005	Areas of interest • Thrombotic events • Immunogenicity as defined by positive antibody binding to erythropoietin and PRCA • Survival and tumor progression
2.0	Date of RMP: 08 June 2009 EMEA/178006/2009	**Safety Concerns** Important Identified Risks: • Hypertension • Thromboembolic events (previously 'thrombotic events') • Convulsions • Allergic reactions (hypersensitivity) Important Potential Risks: • Antibody-mediated PRCA • Cerebrovascular disorders • Increased mortality and adverse tumor outcomes Missing Information: • Pregnancy • Nursing mothers • Pediatric use • Hyporesponders

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
Combined Nephrology/Oncology RMP		
4.0	Date of RMP: 08 October 2013 EMEA/H/C/000332/II/0118	**Safety Concerns** Important Identified Risks: • 'Venous thromboembolic events' (from nephrology RMP) and 'Thromboembolic events' (from oncology RMP) combined as 'Thromboembolic events (venous only for nephrology indication)' • 'Cerebrovascular hemorrhagic and ischemic conditions' (from nephrology RMP) renamed as 'Cerebrovascular disorders (nephrology indication only)' Important Potential Risks: • 'Mortality in subjects with a history of malignancy' (from nephrology RMP) and 'Increased mortality and adverse tumor outcomes' (from oncology RMP) combined as 'Mortality and/or tumor progression or recurrence in patients with cancer or a history of cancer' Missing Information: • Safety related to higher doses administered in patients with CRF (nephrology indication only) added as missing information • Geriatric use (from nephrology RMP) removed from missing information • 'Pregnancy' and 'Nursing mothers' combined as 'Pregnant or lactating women' **Pharmacovigilance Plan** Pharmacovigilance Studies Added: • Study 20070782: A randomized, double-blind, placebo-controlled study to evaluate the long-term safety and efficacy of darbepoetin alfa administered at 500 µg once-every-3-weeks in anemic subjects with advanced stage non-small cell lung cancer receiving multi-cycle chemotherapy • Study 20110226: START-CKD: Strategies using darbepoetin alfa to avoid transfusions in chronic kidney disease • Meta-analysis for re-analysis of clinical trial data concerning hemoglobin levels and ESA doses in CRF patients • Study 20110125: ESA APPRISE oncology program ESA utilization patterns (US-only requirement under risk evaluation and mitigation strategy [REMS])

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
Combined Nephrology/Oncology RMP (continued)		
4.0 (continued)		**Pharmacovigilance Plan (continued)** Pharmacovigilance Studies Removed as Complete: • Study 20070211: A prospective registry study observing the safety and patterns of use of darbepoetin alfa in EU pediatric chronic kidney disease patients receiving or not receiving dialysis **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Not applicable
5.0	Date of RMP: 29 August 2014 EMEA/H/C/332/II/130	**Safety Concerns** Missing Information: • 'Pregnant or lactating women' renamed as 'Risks during pregnancy and lactation' **Pharmacovigilance Plan** Pharmacovigilance Studies Removed as Complete: • Study 20050256: A multicenter, double-blind, randomized study evaluating de novo weekly and once every 2 week darbepoetin alfa dosing for the correction of anemia in pediatric subjects with chronic kidney disease receiving and not receiving dialysis **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Not applicable
6.0	Date of RMP: 12 December 2014 EMEA/H/C/332/II/130	**Safety Concerns** No change **Pharmacovigilance Plan** Pharmacovigilance Studies: • Milestone date amended for meta-analysis for re-analysis of clinical trial data concerning hemoglobin levels and ESA doses in CRF patients **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** • Risk minimization measures updated to include key concepts for corresponding sections of the SmPC and Patient Information Leaflet (PIL)

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
Combined Nephrology/Oncology RMP (continued)		
6.1	Date of RMP: 06 April 2015 EMEA/H/C/332/II/130	**Safety Concerns** No change **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** • Routine risk minimization measures updated to include relevant text from the SmPC and PIL
7.0	Date of RMP: 03 March 2017 EMEA/H/C/332/II/141	**Safety Concerns** Important Identified Risks: • Severe cutaneous adverse reaction added as an important identified risk **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Not applicable
7.1	Date of RMP: 13 July 2017 Date of approval: 21 July 2017 EMEA/H/C/332/II/141	**Safety Concerns** Important Identified Risks: No change **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Additional Risk Minimization Measure Added: • Direct Healthcare Professional Communication (DHPC) letter to inform HCPs about the risk of severe cutaneous adverse reaction
8.0 and 8.1	Date of RMPs: 17 March 2017 and 03 January 2018 EMEA/H/C/000332/II/0142	This variation was removed

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
Combined Nephrology/Oncology RMP (continued)		
9.0	Date of RMP: 12 June 2017 Not submitted	This RMP was not submitted to the EMA.
9.1	Date of RMP: 06 July 2018 EMEA/H/C/ 000332/II/0148	**Safety Concerns** Important Identified Risks Removed: • Hypertension, including hypertensive crisis • Thromboembolic events (venous only for nephrology indication) • Convulsions Important Identified Risks Renamed: • Important identified risk of allergic reactions (hypersensitivity) renamed as serious allergic reactions (hypersensitivity) Important Potential Risks Added: • Incorrect use of the pre-filled pen device associated with adverse reactions, including underdose and drug dose omission added as an important identified risk Important Potential Risks Removed: • Cardiac failure (nephrology indication only) Missing Information Removed: • Risks during pregnancy and lactation • Pediatric patients • Hyporesponders • Safety related to higher doses administered in patients with CRF (nephrology indication only) **Pharmacovigilance Plan** Pharmacovigilance Studies Removed as Complete: • Meta-analysis for re-analysis of clinical trial data concerning hemoglobin levels and ESA doses in CRF patients • Study 20110125: ESA APPRISE oncology program ESA utilization patterns (US-only requirement under risk evaluation and mitigation strategy [REMS]) **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Additional Risk Minimization Measure Added: • Demonstration device and training checklist for Aranesp SureClick® (pre-filled pen) self-administration

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
Combined Nephrology/Oncology RMP (continued)		
9.2	Date of RMP: 29 October 2018 EMEA/H/C/ 000332/II/0148	**Safety Concerns** Important Identified Risks Removed: • Serious allergic reactions (hypersensitivity) • Vascular access thrombosis (nephrology indication only) **Pharmacovigilance Plan** • Systematic case follow-up removed as an additional pharmacovigilance activity for antibody-mediated PRCA; systematic case follow-up is considered as routine pharmacovigilance **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** Additional Risk Minimization Measure Added: • Poster-size IFU for patients/caregivers with diminished eyesight for Aranesp SureClick® (pre-filled pen) self-administration **Annexes** • Annex 6, Details of Proposed Additional Risk Minimization Activities (if applicable): Description of additional risk minimization activities for Aranesp SureClick® (pre-filled pen) self-administration updated, including addition of poster-size IFU
9.3	Date of RMP: 30 November 2018 EMEA/H/C/000332/ II/0150	**Safety Concerns** No change **Pharmacovigilance Plan** • Study 20070782 removed as study complete **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** No change **Annexes** • Annex 2, Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program: Study 20070782 status updated from ongoing to complete; date of clinical study report for Study 20110226 added • Annex 3, Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan: Protocol for Study 20070782 removed as study complete

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Approval Date Procedure	Change
Combined Nephrology/Oncology RMP (continued)		
9.4	Date of RMP: 02 January 2019 Date of approval: 18 February 2019 EMEA/H/C/ 000332/II/0148	**Safety Concerns** Important Identified Risk Removed: • Severe cutaneous adverse reaction **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** No change **Annexes** No change
9.5	Date of RMP: 25 April 2019 EMEA/H/C/000332/ II/0150	**Safety Concerns** No change **Pharmacovigilance Plan** • Pregnancy and lactation follow-up questionnaires added. **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** No change **Annexes** • Annex 4: Pregnancy and lactation follow-up questionnaires appended.
9.6	Date of RMP: 21 August 2019 Date of approval: 14 November 2019 EMEA/H/C/000332/ II/0150	**Safety Concerns** Important Identified Risk Removed: • Cerebrovascular disorders (nephrology indication only) Important Potential Risks Removed: • Ischemic heart disease, including myocardial infarction (nephrology indication only) • Cerebrovascular disorders (oncology indication only) **Pharmacovigilance Plan** Pharmacovigilance Study Removed as Complete: • Study 20110226 Pharmacovigilance Study Added: • Study 20190404 **Postauthorization Efficacy Plan** Not applicable

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
Combined Nephrology/Oncology RMP (continued)		
9.6 (continued)		**Risk Minimization Measures** No change **Annexes** • Annex 2: Study 20110226 status updated from ongoing to complete; Study 20190404 added as planned pharmacovigilance study. • Annex 3: Protocol for Study 20110226 removed as study complete.
9.7	Date of RMP: 21 March 2022 Approval Date : 20 May 2022 Procedure : EMEA/H/C/000332/IB/0160	**Safety Concerns** No change **Pharmacovigilance Plan** • Protocol submission date and due date of final report for Study 20190404 updated. **Postauthorization Efficacy Plan** Not applicable **Risk Minimization Measures** No change **Annexes** • Annex 2: Protocol submission date and due date of final report for Study 20190404 updated. • Annex 3: Protocol for Study 20190404 appended.

Table 27. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
Combined Nephrology/Oncology RMP (continued)		
10.0	Date of RMP: 19 March 2025 Approval Date: To be determined Procedure: To be determined	**Safety Concerns** Important potential risk of 'Incorrect Use of the Pre-filled Pen Device Associated with Adverse Reactions, Including Underdose and Drug Dose Omission' was removed from the RMP **Pharmacovigilance Plan** Milestone date of final report for Study 20190404 updated. **Postauthorization Efficacy Plan** Not applicable. **Risk Minimization Measures** The aRMMs of demonstration device, training checklist, and poster-size IFU for patients/caregivers with diminished eyesight for Aranesp SureClick (pre-filled pen) self-administration were removed. **Annexes** • Annex 2: Study status and milestone date of final report for Study 20190404 updated. • Annex 3: Protocol Amendment 6 for Study 20190404 appended. • Annex 6: Details of the proposed additional risk minimization activities were removed.

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