European Union Risk Management Plan
DARZALEX (daratumumab)

Data lock point for current RMP	31 July 2024	Version number	12.1

QPPV Sign-off Date: 10 March 2025
RMP Version Number: 12.1
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QPPV Name(s):	Dr. Laurence OSTER-GOZET, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission

Version Number	12.1
Rationale for submitting an updated RMP:	Adding a new daratumumab indication for subcutaneous administration as monotherapy for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma, based on data from Trial 54767414SMM3001, supplemented by data from the supportive Trial 54767414SMM2001.
Summary of significant changes in this RMP:	The following indication for subcutaneous administration of daratumumab is added: 'DARZALEX as monotherapy is indicated for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma', based on data from Trials 54767414SMM3001 and 54767414SMM2001. Clinical trial exposure tables are updated and risk frequency tables are added to include the data from Trials 54767414SMM3001 and 54767414SMM2001.

Other RMP Versions Under Evaluation

RMP Version Number	Submitted on	Procedure Number
NA		

Details of the Currently Approved RMP

Version number of last agreed RMP:	11.1
Approved within procedure	EMEA/H/C/004077/II/0076
Date of approval (Competent Authority opinion date)	27 February 2025 (CHMP Positive Opinion)

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	daratumumab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, CD38 (Clusters of Differentiation 38) inhibitors (L01FC01)
Marketing Authorization Holder	Janssen-Cilag International, NV
Medicinal products to which the RMP refers	1
Invented name(s) in the European Economic Area (EEA)	DARZALEX
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Cluster of differentiation (CD)38-directed cytolytic antibody Daratumumab is an immunoglobulin G1 (IgG1) kappa human monoclonal antibody against CD38 antigen. Daratumumab is produced in a mammalian cell line (Chinese hamster ovary) using recombinant DNA technology. The subcutaneous (SC) formulation of daratumumab contains recombinant human hyaluronidase enzyme PH20 (rHuPH20), which is an endoglycosidase used to increase the dispersion and absorption of daratumumab when administered subcutaneously.
Reference to the Product Information	Product Information in the eCTD sequence: Module 1.3.1
Indication(s) in the EEA	Current: DARZALEX (intravenous [IV] and subcutaneous [SC] administration) is indicated for multiple myeloma: • in combination with lenalidomide and dexamethasone or with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. • in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. • in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

	• as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who demonstrated disease progression on the last therapy. DARZALEX (SC administration) is indicated for multiple myeloma: • in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma. • in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy. DARZALEX administered via SC injection is indicated in combination with cyclophosphamide, bortezomib, and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

	Proposed: DARZALEX (intravenous [IV] and subcutaneous [SC] administration) is indicated for multiple myeloma: • in combination with lenalidomide and dexamethasone or with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. • in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. • in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. • as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who demonstrated disease progression on the last therapy. DARZALEX (SC administration) is indicated for multiple myeloma: • in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma. • in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy. DARZALEX as monotherapy administered via SC injection is indicated for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma. DARZALEX administered via SC injection is indicated in combination with cyclophosphamide, bortezomib, and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

Dosage in the EEA	Current: *Multiple Myeloma* Intravenous formulation The recommended dose is daratumumab 16 mg/kg body weight administered as an IV infusion according to the dosing schedules outlined in the tables within the Summary of Product Characteristics (SmPC) Section 4.2 for daratumumab as monotherapy or in combination with lenalidomide and dexamethasone or bortezomib, thalidomide, and dexamethasone (4-week cycle regimens); bortezomib, melphalan, and prednisone (6-week cycle regimen); or bortezomib and dexamethasone (3-week cycle regimen). Subcutaneous formulation The recommended dose is daratumumab 1,800 mg administered SC according to the dosing schedules outlined in the tables within the SmPC Section 4.2 for daratumumab as monotherapy or in combination with pomalidomide and dexamethasone; lenalidomide and dexamethasone; bortezomib, thalidomide, and dexamethasone (for treatment of newly diagnosed patients eligible for ASCT); or bortezomib, lenalidomide, and dexamethasone (for treatment of newly diagnosed patients eligible for ASCT) (4-week cycle regimens); bortezomib, melphalan, and prednisone (6-week cycle regimen); or bortezomib and dexamethasone; or bortezomib, lenalidomide, and dexamethasone (for treatment of newly diagnosed patients who are ineligible for ASCT) (3-week cycle regimen). *Systemic Light Chain Amyloidosis (AL Amyloidosis)* Subcutaneous formulation The recommended dose is daratumumab 1,800 mg SC according to the dosing schedule outlined in the table within the SmPC Section 4.2 for daratumumab for AL amyloidosis in combination with bortezomib, cyclophosphamide, and dexamethasone (4-week cycle regimen).

	Proposed: *Multiple Myeloma* Intravenous formulation The recommended dose is daratumumab 16 mg/kg body weight administered as an IV infusion according to the dosing schedules outlined in the tables within the Summary of Product Characteristics (SmPC) Section 4.2 for daratumumab as monotherapy or in combination with lenalidomide and dexamethasone or bortezomib, thalidomide, and dexamethasone (4-week cycle regimens); bortezomib, melphalan, and prednisone (6-week cycle regimen); or bortezomib and dexamethasone (3-week cycle regimen). Subcutaneous formulation The recommended dose is daratumumab 1,800 mg administered SC according to the dosing schedules outlined in the tables within the SmPC Section 4.2 for daratumumab as monotherapy or in combination with pomalidomide and dexamethasone; lenalidomide and dexamethasone; bortezomib, thalidomide, and dexamethasone (for treatment of newly diagnosed patients eligible for ASCT); or bortezomib, lenalidomide, and dexamethasone (for treatment of newly diagnosed patients eligible for ASCT) (4-week cycle regimens); bortezomib, melphalan, and prednisone (6-week cycle regimen); or bortezomib and dexamethasone; or bortezomib, lenalidomide, and dexamethasone (for treatment of newly diagnosed patients who are ineligible for ASCT) (3-week cycle regimen). *Smouldering Multiple Myeloma (SMM)* Subcutaneous formulation The recommended dose is daratumumab 1,800 mg SC according to the dosing schedule outlined in the table within the SmPC Section 4.2 for daratumumab for SMM as monotherapy (4-week cycle regimen). *Systemic Light Chain Amyloidosis (AL Amyloidosis)* Subcutaneous formulation The recommended dose is daratumumab 1,800 mg SC according to the dosing schedule outlined in the table within the SmPC Section 4.2 for daratumumab for AL amyloidosis in combination with bortezomib, cyclophosphamide, and dexamethasone (4-week cycle regimen).

Pharmaceutical form(s) and strengths	Current: Intravenous formulation Concentrate for solution for infusion. The solution is colorless to yellow. • 5 mL vial: Each single-use vial contains 100 mg of daratumumab (20 mg daratumumab per mL). • 20 mL vial: Each single-use vial contains 400 mg of daratumumab (20 mg daratumumab per mL). Subcutaneous formulation Solution for injection. The solution is colorless to yellow, clear to opalescent. • 15 mL vial: Each single-use vial contains 1,800 mg daratumumab (120 mg daratumumab per mL).		
	Proposed: Not applicable.		
Is/will the product be subject to additional monitoring in the EU?		☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

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

Indication: Multiple myeloma and smouldering multiple myeloma at high risk of developing multiple myeloma

Multiple myeloma is an incurable malignant plasma cell disorder that represents approximately 1% to 1.8% of all new cancer cases and approximately 10% of hematological malignancies (Sung 2021; SEER 2022). Smouldering multiple myeloma (SMM) is an asymptomatic precursor to multiple myeloma. It is associated with an overall risk of progression to malignancy of 10% per year within the first 5 years (Rajkumar 2015). Over time, SMM has been characterized to determine high-risk subsets in the phase of multiple myeloma evolution (Rajkumar 2015). Several models characterizing patients as high-risk SMM have been proposed (Mateos 2016; Rajkumar 2013) and continue to evolve over time (Mateos 2020; Cowan 2023). Compared with the overall SMM population, risk models show that high-risk SMM patients have an increased risk of progression to symptomatic multiple myeloma of approximately 50% within the first 2 years (Mateos 2016; Rajkumar 2013).

Incidence:

Multiple myeloma is a rare disease. In 2020, an estimated 176,404 patients were diagnosed with multiple myeloma globally, with a crude incidence rate of 2.3 cases per 100,000 persons and a world population age-standardized incidence rate of 1.8 cases per 100,000 persons (Ferlay 2020).

In the European Union (EU)-27 countries, the 2022 crude incidence rate was 7.9 cases per 100,000 persons, and the European population age-standardized incidence rate was 7.3 cases per 100,000 persons. The estimated number of new cases for the EU overall was 35,333 cases in 2022. In general, Western Europe had the highest incidence rates of multiple myeloma. Crude incidence rates ranged from 3.0 per 100,000 persons in Bulgaria to 11.3 per 100,000 persons in Denmark (European Cancer Information System [ECIS] 2023).

SMM is an asymptomatic condition, which is usually detected incidentally when individuals seek healthcare because of other unrelated symptomatic conditions, and only a minority of SMM cases progress to multiple myeloma per year; the incidence of SMM might therefore be underestimated (Cowan 2018). In a study that utilized data from the Swedish Myeloma Registry, 14.4% of patients with newly diagnosed multiple myeloma had previously been identified with SMM. The age-standardized incidence of SMM was 0.44 cases per 100,000 persons and that of high-risk SMM was 0.14 cases per 100,000 persons (Kristinsson 2013).

Prevalence:

In Europe, the 5-year prevalence of multiple myeloma was 138,083 persons (GLOBOCAN 2020a). In comparison, the estimated worldwide 5-year prevalence was approximately 450,579 patients (GLOBOCAN 2020b). Based on Haematological Malignancy Research Network (HMRN) data from 2010 to 2020, the 10-year prevalence of myeloma in the United Kingdom (UK) was estimated

as 33.9 per 100,000 persons or approximately 22,260 persons (HMRN 2022). The 10-year prevalence of multiple myeloma in the 4 most populous countries in the EU (Germany, France, Italy, and Spain) is available through the CancerMPact® program of Kantar Health, updated through September 2023 (Table SI.1; CancerMPact® 2023).

Table SI.1: Ten-year or Total Prevalence per 10,000 Persons Estimated From Select European Country Registries

Country	Year	Prevalence Period	Prevalence Count	Prevalence per 10,000 Persons	Source
France	2023	10-year	32,428	4.9	CancerMPact® 2023
Germany	2023	10-year	37,393	4.5	CancerMPact® 2023
Italy	2023	10-year	30,762	5.1	CancerMPact® 2023
Spain	2023	10-year	17,651	3.7	CancerMPact® 2023

The 10-year prevalence in Nordic countries are available from the NORDCAN project (NORDCAN 2023). The data extracted from the NORDCAN database is updated as of October 2023 and presented below (Table SI.2).

Table SI.2: Ten-year and Total Prevalence of Multiple Myeloma in Nordic Countries from 2016 to the End of 2021 from NORDCAN Project

Country	10-year prevalence per 100,000 persons 2016	10-year prevalence per 100,000 persons 2021	Percent change in 10-year prevalence per 100,000 persons (2016 to 2021)	Total prevalence per 100,000 persons 2021
Denmark	2,162	3,093	43.1	3,577
Finland	1,754	1,731	1.3	2,181
Iceland	114	181	58.7	210
Norway	1,887	2,593	37.4	3,077
Sweden	3,363	4,149	19.8	4,962
Nordic countries	9,301	11,786	26.7	14,049

Source: NORDCAN 2023.

The lack of population-based disease registries as well as changes in the diagnostic criteria over the last decade have made epidemiological data on the prevalence of SMM difficult to acquire (Blum 2018).

Demographics of the Authorized Population in the Multiple Myeloma Indication – Age, Sex, Racial, and/or Ethnic Origin and Risk Factors for the Disease

Age: The median age at multiple myeloma diagnosis is approximately 69 years (SEER 2023). Myeloma incidence is strongly related to age, with older adults experiencing the highest incidence rates. At diagnosis, 36% of patients are younger than 65 years, 31% are aged 65 to 74 years, and 33% are 75 years of age or older (SEER 2021). The median age at diagnosis of SMM is approximately 70 years (Sørrig 2016).

Sex: Globally in 2020, the age-standardized incidence rate of multiple myeloma was estimated to be 2.2 per 100,000 in men and 1.5 per 100,000 in women (Sung 2021). In the EU 27 countries in 2022, the incidence rates were 8.8 per 100,000 in men versus 6.1 per 100,000 in women

(ECIS 2023). In Sweden, the incidence of multiple myeloma is approximately 1.5 times higher in men than women (Blimark 2018).

Racial and ethnic origin: Multiple myeloma occurs at a rate twice as high in black individuals as in white individuals. In the United States, the incidence is lower in Asian and Hispanic individuals when compared to white individuals (SEER*Explorer 2022). In the US, the average incidence rate from 2016 to 2020 was 14.4 per 100,000 for blacks and 6.4 per 100,000 persons for whites (SEER*Explorer 2022). Evidence from US studies suggests that the racial disparity may be influenced by differences in risk factors for monoclonal gammopathy of undetermined significance (MGUS) and transformation of MGUS to multiple myeloma between black and white patients (Marinac 2020).

Risk factors for the disease:

Risk factors for developing multiple myeloma include (American Cancer Society 2020; Normandin 2018):

- Age (the risk of multiple myeloma increases with increasing age);
- Sex (men are slightly more likely to develop multiple myeloma than women);
- Race (multiple myeloma is more than twice as common among blacks compared with whites);
- Radiation (exposure to radiation may increase the risk of multiple myeloma);
- Family history (an individual who has a sibling or parent with multiple myeloma is 4 times more likely to develop the disease than expected, but this represents only a minority of myeloma cases);
- Workplace exposures (some trials have suggested that workers in certain petroleum-related industries may be at a higher risk);
- Obesity (being overweight or obese increases a person's risk of developing myeloma);
- Other plasma cell diseases (people with MGUS or solitary plasmacytoma have a higher risk of developing multiple myeloma).

The Main Existing Treatment Options:

Treatments approved for multiple myeloma vary by country and patient population (newly diagnosed multiple myeloma versus relapsed/refractory multiple myeloma). The treatment options approved in the EU include the following:

- Stem cell transplant (usually autologous but allogeneic is a later-line option);
- Traditional chemotherapeutic agents (melphalan, melphalan flufenamide, doxorubicin pegylated liposomal, cyclophosphamide);
- Histone deacetylase inhibitors (panobinostat);
- Monoclonal antibodies (daratumumab, isatuximab, elotuzumab);

- Immunomodulatory imide drugs (thalidomide, lenalidomide, pomalidomide);
- Proteasome inhibitors (bortezomib, ixazomib, carfilzomib);
- Nuclear export inhibitor (selinexor);
- Antibody-drug conjugate (belantamab mafodotin);
- CAR-T products (idecabtagene vicleucel, ciltacabtagene autoleucel);
- Bispecific antibody (teclistamab, elranatamab, talquetamab);
- Corticosteroids (dexamethasone, methylprednisone, prednisone).

In US and European guidelines, treatment approaches depend on patient fitness and risk of toxicities (Dimopoulos 2021; NCCN 2024). The initial evaluation of patients includes an assessment of eligibility for high-dose therapy and ASCT based on age, performance status, and comorbidities. Transplant eligible patients will typically receive induction therapy followed by high-dose chemotherapy and ASCT; consolidation and/or maintenance therapy is utilized after ASCT depending upon the country. In clinical practice, many patients who are transplant eligible choose to defer/delay transplant to the first salvage therapy after relapse from frontline therapy. Delaying transplant is becoming more common, in part due to the availability of more effective treatments for multiple myeloma, both in the frontline and relapsed/refractory settings. For patients not considered eligible for high-dose chemotherapy and ASCT, or for whom transplant was not planned as initial therapy, the current standard of care is long-term treatment with triplet or quadruplet combinations (Mo 2023). European Society for Medical Oncology-recommended initial therapy for transplant ineligible patients is a lenalidomide- or bortezomib-containing regimen with or without daratumumab (Dimopoulos 2021). Despite advances in treatment options, multiple myeloma remains incurable in the vast majority of cases and is characterized by patterns of remissions and relapses until death. With each successive relapse and new line of treatment, the chance of response, duration of response, and median overall survival (OS) typically decreases (Gandhi 2019).

There is no approved treatment for patients with SMM. The standard of care for SMM has been observation (Rajkumar 2015) and clinical management involves monitoring patients for progression to symptomatic disease (Landgren 2013). Current European Hematology Association (EHA), European Society for Medical Oncology (ESMO), and NCCN guidelines recommend entry into clinical studies or observation for patients with high risk SMM (Dimopoulos 2021; NCCN 2024). Clinical studies suggest that treatment of patients with SMM at high risk of progression may provide clinical benefit by delaying the onset of active multiple myeloma (Mateos 2013, 2021, 2022; Lonial 2019).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

In the 27 EU countries, multiple myeloma is the 17th most common cause of death with an age-standardized mortality rate of 4.6 per 100,000 (ECIS 2023). The 5-year relative survival for patients with multiple myeloma ranged from 45.6% to 60.3% in Nordic countries (NORDCAN

2023). Five-year survival decreases as age increases. For example, the 5-year relative survival in Sweden was 66% for patients 65 years and younger and 39% for patients >65 years (Blimark 2018). A recent update from the Swedish Myeloma Registry, which covers 100% of national cases, reported an observed median OS of 4.68 years and relative median OS of 5.84 years after diagnosis with active or SMM from 2012 to 2019 (Blimark 2020, 2022).

Active multiple myeloma is preceded by precursor states of MGUS and SMM, which represent a continuum of progression of the tumor burden in the absence of symptoms or signs of end organ damage. The current standard practice for patients diagnosed with SMM is observation (Moreau 2015). Investigators have determined that almost all cases of multiple myeloma evolve from the MGUS precursor stage. The risk of progression to multiple myeloma is estimated to be approximately 1% per year (Kazandjian 2016). Monoclonal gammopathy of undetermined significance is one of the most common pre-malignancies with a 3% prevalence in the white population 50 years of age or older and is approximately double in the African American population. Similar to MGUS, not all SMM cases evolve to symptomatic multiple myeloma with end-organ damage. However, all cases of multiple myeloma evolve from SMM (Kazandjian 2016).

The aggressiveness of multiple myeloma depends upon several variables that impact disease biology. Genetic abnormalities seen in the myeloma cells are 1 of the strongest predictors of tumor aggressiveness. As such, all newly diagnosed multiple myeloma patients are classified as having high, intermediate, or standard risk disease based upon tumor genetics. Approximately 25% of people with multiple myeloma have high-risk disease based on cytogenetic testing. Patients who lack high or intermediate risk genetic abnormalities are considered to have standard risk multiple myeloma. With modern therapy, patients with standard risk multiple myeloma have an estimated median survival of 8 to 10 years (Rajkumar 2018).

For all patients with multiple myeloma, frontline treatment typically involves induction therapy with a combination of an injectable proteasome inhibitor (such as bortezomib), an oral immunomodulatory agent (such as lenalidomide), and dexamethasone, and is associated with a median PFS of 41 months, compared with historical reports of 8.5 months without therapy. This induction therapy combined with autologous hematopoietic stem cell transplantation followed by maintenance lenalidomide is standard of care for transplant eligible patients (Cowan 2022). Daratumumab, lenalidomide, and dexamethasone (D-Rd) and bortezomib, lenalidomide, and dexamethasone (VRd) are preferred regimens for transplant ineligible patients with newly diagnosed multiple myeloma. Treatment with VRd and D-Rd is recommended for transplant ineligible patients with newly diagnosed multiple myeloma by both US and European treatment guidelines (Dimopoulos 2021; NCCN 2024).

Important Comorbidities:

Infection, neutropenia, thrombocytopenia, anemia, renal disease, osteolytic bone disease, hypercalcemia, heart failure, second primary malignancy, and hyperviscosity are the most common comorbidities among patients with multiple myeloma.

Indication: Light chain amyloidosis (AL amyloidosis)

Incidence:

Systemic light chain amyloidosis (AL amyloidosis) is a rare disease. There is a noticeable global trend indicating an increase in the incidence of AL amyloidosis. In Spain, the incidence of AL amyloidosis in 2018 was reported as 1.19 per 100,000 person-years (Ríos-Tamayo 2023). According to a recent population-based study encompassing 31 countries/territories, including European nations, Canada, Japan, Russia, South Korea, Taiwan, and the US, the crude annual incidence for all countries collectively was calculated at 10.44 per million population (PMP), with variations ranging from 6.72 PMP in Brazil to 14.3 PMP in Japan. European countries, including Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Republic of Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom, reported incidence cases ranging from 10.8 to 13.49 PMP (Kumar 2022).

In a population-level study in the Limousin region of France, laboratory, pathology, and diagnosis data from a centralized database were used to identify 46 patients with AL amyloidosis from 2012-2015, giving a crude annual incidence rate of 12.5 AL amyloidosis cases per million persons (95% CI: 5.6; 19.4) (Duhamel 2017). The most contemporary European incidence estimates of AL amyloidosis come from the UK National Amyloidosis Centre (Ravichandran 2020). From 2016 to 2019, approximately 1,600 cases of AL amyloidosis were documented (about 400 cases annually). The National Amyloidosis Centre sees approximately 48% of the country's AL amyloidosis cases based on death certificate data (Pinney 2013). When considering the 52% of AL amyloidosis cases not observed at the National Amyloidosis Centre, there were approximately 833 patients diagnosed with AL amyloidosis in the UK annually, which when divided by the 66.65 million persons in the UK in 2019 (EUROSTAT 2020), gives a crude annual incidence rate of 12.5 cases per million persons as was found in the French study.

The incidence of AL amyloidosis has increased over time, largely due to improved identification of AL (Ravichandran 2020). The number of cases increased by 670% from the period 1987–1999 to the period 2010–2019. Compared to the 12.5 cases per person-years observed in 2016, incidence rates of AL amyloidosis were only estimated to be 2.4 cases per million person-years (95% CI: 1.0; 3.7) from 3 Eastern France regions in 2003-2005 (Magy-Bertrand 2008).

Prevalence:

In a population-level study using laboratory, pathology, and diagnosis data from persons living in the Limousin region of France from 2012-2015, the 5-year limited duration prevalence of AL amyloidosis was estimated as 0.58 cases per 10,000 persons (95% CI: 0.43; 0.73) (Duhamel 2017). Assuming that prevalence of AL amyloidosis is equivalent across EU countries and was stable since 2016, we can apply the prevalence proportion from the Limousin region of France to the 2019 population in the EU-27 countries of 446.8 million (EUROSTAT 2020), giving an estimated 25,914 patients with systemic AL amyloidosis in the EU.

This estimate from the French Limousin region aligns with earlier prevalence calculations using incidence and mortality data from the 42% of UK residents seen at the UK National Amyloidosis Center; findings indicate approximately 1,051 persons (or 0.204 per 10,000 persons) were living with systemic amyloidosis in 2008 (Pinney 2013). In the latest prevalence estimates derived from a global study, it was determined that approximately 73,567 cases were prevalent across all countries over the past 20 years. The 20-year prevalence for all countries was calculated at 51.27 PMP, with variations spanning from 32.22 PMP to 71.08 PMP. The reported 20-year prevalence for European countries varied between 42.99 and 64.59 PMP (Kumar 2022).

Demographics of the Authorized Population in the AL Amyloidosis Indication – Age, Sex, Racial, and/or Ethnic Origin and Risk Factors for the Disease

Age: AL amyloidosis is primarily diagnosed in older adults. The incidence rate of AL amyloidosis specific to age rises with each successive decade beyond 40 years, with a median age at diagnosis of 64 years (Baker 2022). In large European cohort studies, the mean age at AL amyloidosis diagnosis in Sweden between 1995 and 2013 was 66 years (Weiss 2016) while the median age at diagnosis in the Limousin region of France from 2012 to 2016 was 73 years (Duhamel 2017). No cases of AL amyloidosis age ≤ 18 years have been identified globally. In Europe, the youngest reported case was diagnosed at age 30 in the UK (Pinney 2013).

Sex: In most studies of patients with AL amyloidosis, it is observed that men are disproportionately affected. For example, in a study by Weiss et al, 59% of the 1,430 AL amyloidosis patients identified in Sweden between 1995 and 2013 were men (Weiss 2016). Similarly, in the Limousin region of France, 70% of AL amyloidosis patients were male (Duhamel 2017). In a recent study, the disproportionate impact on men with AL amyloidosis continues to be notable with a male:female ratio of 5:3 (Kumar 2022).

Racial, and/or ethnic origin: AL amyloidosis occurs in all races and geographic locations, but data are limited regarding the incidence of AL amyloidosis across different ethnic groups (Vaxman 2019; Kumar 2022).

Risk factors for the disease: The primary risk factor associated with AL amyloidosis is increased age (McCausland 2018). AL amyloidosis is also more common in men than in women. MGUS is present in about 2% of the general population and confers a relative risk of 13.1 for the development of AL amyloidosis (Kyle 2018). Cardiovascular risk factors have surfaced as potential contributors to the risk of developing AL amyloidosis. It is noteworthy that heart failure stands out as the most prevalent cause of mortality in individuals with AL amyloidosis (Saunders 2021).

The Main Existing Treatment Options:

Daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone is currently the only regimen approved for treatment of AL amyloidosis. As both AL amyloidosis and multiple myeloma are clonal plasma cell disorders, the general treatment approach is to use multiple myeloma regimens to achieve rapid, deep, and durable hematologic response. Eradicating

the clonal plasma cell in AL amyloidosis eliminates the production of the immunoglobulin light chain that is both amyloidogenic and proteotoxic to the heart. Achieving deep hematologic remissions allows for organ improvement to occur over time. It has been clearly demonstrated that the depth of hematologic response is associated with organ improvement and OS (Palladini 2012).

Treatments for systemic AL amyloidosis include ASCT, the combination of steroids and alkylating agents, IMiDs, and various PI-based therapies (Kumar 2023). Treatment choices are individualized based on age, comorbidities, organ involvement, local availability, and patient preference. These same therapeutic principles apply for treatment selection in the newly diagnosed and relapsed setting.

The only approved regimen to treat patients with AL amyloidosis and the preferred regimen in treatment recommendations is daratumumab, bortezomib, cyclophosphamide, and dexamethasone (D-VCd) (Kumar 2023). Use of this regimen is supported by data from the ANDROMEDA trial that found that D-VCd was associated with a higher hematologic complete response (53.3% versus 18.1%) (odds ratio, 5.1; 95% CI, 3.2 to 8.2; P<0.001) and survival free from major organ deterioration or hematologic progression than the control group (hazard ratio, 0.58; 95% CI, 0.36 to 0.93; P=0.02) (Kastritis 2021). In Europe from 2014 through 2018, the most frequently used first-line regimens for AL amyloidosis were based on bortezomib, with only 6.2% of patients receiving autologous stem cell transplant (Palladini 2023).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

AL amyloidosis arises when clonal plasma cells secrete immunoglobulin light chains that misfold and form insoluble amyloid fibrils (Gertz 2020). Deposition of amyloid fibrils in organs interferes with normal tissue architecture and, in the case of the heart, leads to direct toxicity to cardiomyocytes (Merlini 2018). The heart and kidney are the most affected organs, with 50 to 83% and 61 to 68% of patients affected, respectively (McCausland 2018; Muchtar 2017; Quock 2018; Schulman 2020). The nervous system, gastrointestinal system, liver, and soft tissue are also affected (McCausland 2018; Schulman 2020). Approximately 72% of patients have ≥ 2 organs involved at diagnosis (McCausland 2018). Prior to diagnosis, patients present with a large constellation of signs and symptoms that are non-specific or depend on the affected organs, including malaise and fatigue, edema, proteinuria, cardiomyopathy, peripheral neuropathy, periorbital purpura, and macroglossia (Gertz 2020; McCausland 2018). Biomarkers such as monoclonal gammopathy and serum free light chains are detectable before diagnosis; one study found that 42% of patients had serum free light chains detectable 11 or more years before diagnosis (Weiss 2014).

Systemic AL amyloidosis is associated with a poor prognosis. The median OS for patients with AL amyloidosis ranges from 3.1 years in a German institution study of 1,224 patients observed from July 2002 to March 2017 (Dittrich 2019; Ríos-Tamayo 2023) to 3.5 years among patients diagnosed in the Swedish National Registries from 2010 to 2013 (Weiss 2016).

Survival length is largely dependent on cardiac involvement, with other prognostic markers including involvement of multiple organs and elevated serum free light chain levels at diagnosis (Muchtar 2017; Wechalekar 2013). Patients with Mayo 2012 stage I or II disease have a median survival from 6 to 10 years (Dittrich 2019; Kumar 2022). However, among patients with AL amyloidosis who have advanced amyloidosis (Mayo 2004 cardiac stage III; Mayo 2012 stage III and IV) in European studies, survival is only 7 months (Wechalekar 2013; Dittrich 2019). The median 7 months survival in patients with advanced AL amyloidosis was observed despite treatment with VCd, which elicited a longer OS in patients with less advanced disease (Palladini 2015).

Important Comorbidities:

AL amyloidosis is a plasma cell dyscrasia that is preceded by monoclonal gammopathy of unknown significance. Other plasma cell dyscrasias can occur before or alongside AL amyloidosis, with approximately 17% with co-occurring multiple myeloma (Ríos-Tamayo 2023; Weiss 2016). OS is lower for patients with AL amyloidosis who have multiple myeloma diagnosed before or concurrently. Twenty-three percent of patients with a new AL amyloidosis had a diagnosis of malignancy other than multiple myeloma in their year of diagnosis.

Patients with AL amyloidosis have numerous other conditions at diagnosis, largely which are signs/symptoms of the disease. These include arrhythmia (51%), cardiomegaly (27%), cardiomyopathy (21%), chronic kidney disease (45%), and peripheral nerve disease (46%) (Hester 2019).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Daratumumab binds to human and chimpanzee CD38, but not to CD38 of species typically used for nonclinical toxicology testing, ie, mouse, rat, rabbit, pig, cynomolgus, or rhesus monkey. The pivotal studies for daratumumab were limited to human and chimpanzee tissue cross-reactivity studies and a 6-week repeat dose toxicity study in chimpanzees with an approximate 3-month recovery period.

Acute toxicity, local tolerance, and safety pharmacology endpoints were incorporated into the repeat dose toxicity study in chimpanzees. In accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S6(R1) and S9 guidelines, no genotoxicity, carcinogenicity, or specific reproductive toxicology testing have been conducted, as daratumumab is an antibody indicated for use in advanced cancer.

Key Safety Findings (from nonclinical studies)	**Relevance to Human Usage**
Toxicity:	
Single and repeat dose toxicity	
A 6-week repeat-dose toxicity study in chimpanzees was performed administering daratumumab by IV infusion, once weekly. The primary toxicities identified were infusion related reactions (IRRs) (apparent cytokine release that resulted in the death of one animal), during the first, but not subsequent, daratumumab infusions and thrombocytopenia. The effect on platelets was reversible. Toxicokinetic data indicated that recovery of platelets was closely linked to the clearance of daratumumab from the circulation. The binding affinity of daratumumab is ≥ 15-fold higher for chimpanzee platelets than for human platelets.	Infusion related reactions is well characterized and adequately reflected within current SmPC. The recognition and management of IRRs has been integrated into clinical practice. Thrombocytopenia is well characterized and adequately reflected within current SmPC. The recognition and management of thrombocytopenia has been integrated into clinical practice.
Reproductive toxicity	
No reproductive toxicity studies were conducted with daratumumab. Reproductive toxicity studies are generally not applicable to therapies for advanced cancer indications (ICH S9).	Reproductive toxicity was not assessed in nonclinical studies.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Developmental toxicity	
No developmental toxicity studies were conducted with daratumumab.	Developmental toxicity was not assessed in nonclinical studies. Immunoglobulin G (IgG) antibodies are known to cross the human placenta during pregnancy and have been detected in the serum of infants born to patients treated with therapeutic antibodies. Women of child-bearing potential should use effective contraception during, and up to 3 months after, daratumumab treatment.
Genotoxicity	
No genotoxicity studies were conducted with daratumumab. Routine genotoxicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material (ICH S6).	Daratumumab is not expected to be genotoxic due to the nature of IgG1.
Carcinogenicity	
No carcinogenicity studies were conducted with daratumumab. Routine carcinogenicity studies are generally not applicable to therapies for advanced cancer indications (ICH S9).	Daratumumab is not expected to be carcinogenic.
<u>Safety pharmacology:</u>	
Cardiovascular (including potential for QT interval prolongation)	
No cardiovascular effects were identified in the 6-week chimpanzee study.	Immunoglobulin G1 (IgG1) antibodies are too large to directly access the human Ether-à-go-go-Related Gene (hERG) potassium channel and cause QT prolongation. Daratumumab is not expected to affect cardiovascular function. There was no increase in cardiovascular toxicities in randomized clinical trials.
Nervous system	
No nervous system effects were identified in the 6-week chimpanzee study.	Daratumumab is not expected to affect the nervous system function. Central nervous system toxicity has not been seen in clinical trials.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Mechanisms for drug interactions	
No nonclinical drug interaction studies were performed with daratumumab.	Daratumumab is an IgG1 antibody, as such it is metabolized by endogenous processes used in the turnover of native immunoglobulins and is not expected to interact with the metabolism of other drugs (ICH S6).
Other	
Nephrotoxicity	
No nephrotoxicity was identified in the clinical pathology assessments in the 6-week chimpanzee study.	Daratumumab is not expected to be nephrotoxic. Renal insufficiency is common in multiple myeloma, no additive nephrotoxicity has been seen in clinical trials.
Hepatotoxicity	
No hepatotoxicity was identified in the clinical pathology assessments in the 6-week chimpanzee study.	Daratumumab is not expected to be hepatotoxic. Hepatotoxicity has not been seen in clinical trials.
Other toxicity-related information or data	
No other toxicity studies were conducted with daratumumab.	

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The full protocol number for all trials conducted by Janssen Research & Development, LLC in this EU-RMP begins with the prefix of "54767414" (the applicant's internal reference number for daratumumab). For brevity, these trials are referred to throughout the EU-RMP without the numeric prefix (eg, Trial 54767414MMY3007 is referred to as MMY3007, Trial 54767414GEN501 is referred to as GEN501).

The clinical development program for daratumumab includes clinical trials to develop an intravenous formulation (daratumumab 20 mg/mL concentrate for solution for infusion) and clinical trials to develop a subcutaneous (SC) formulation (daratumumab 1,800 mg solution for injection).

The SC formulation of daratumumab, DARZALEX 1,800 mg solution for injection, is a drug product containing 1,800 mg daratumumab (120 mg/mL) co-formulated with 30,000 U recombinant human hyaluronidase enzyme PH20 (rHuPH20; 2000 U/mL) in a single vial (hereafter referred to as "daratumumab SC"). Data supporting daratumumab SC in subjects with multiple myeloma were derived from 3 monotherapy clinical trials (1 Phase 3 trial [MMY3012] supported by 2 Phase 1/1b trials [MMY1004 and MMY1008]) and 1 Phase 2 combination therapy trial (MMY2040):

- MMY3012: A Phase 3 randomized, multicenter trial of subcutaneous administration of daratumumab (daratumumab SC) versus intravenous administration of daratumumab (daratumumab IV) in subjects with relapsed or refractory multiple myeloma.
- MMY2040: A multicenter Phase 2 trial to evaluate subcutaneous daratumumab in combination with standard multiple myeloma treatment regimens. The following cohorts are included: daratumumab in combination with VELCADE® (bortezomib)-melphalan-prednisone (D-VMP); daratumumab, lenalidomide, and dexamethasone (D-Rd); and daratumumab in combination with bortezomib, lenalidomide, and dexamethasone (D-VRd).
- MMY1004: An open-label, multicenter, dose escalation Phase 1b trial to assess the safety and pharmacokinetics of subcutaneous delivery of daratumumab with the addition of recombinant human hyaluronidase (rHuPH20) for the treatment of subjects with relapsed or refractory multiple myeloma. Part 1 of this trial tested a mix and deliver formulation of daratumumab and rHuPH20 ("Dara-MD") in order to select an appropriate subcutaneous therapeutic dose. Part 2 tested the Marketing Authorization Holder's (MAH's) final commercial flat-dose preparation. Part 3 tested daratumumab SC delivery without pre- and post-dose corticosteroids.
- MMY1008: A Phase 1 trial of subcutaneous delivery of daratumumab in Japanese subjects with relapsed or refractory multiple myeloma.

The indication for subcutaneous administration of daratumumab as monotherapy for the treatment of adult patients with SMM at high risk of developing multiple myeloma is based on Trial SMM3001 (pivotal study), which utilized the daratumumab SC formulation, and Trial SMM2001 (supporting study), which utilized the daratumumab IV formulation:

- Trial SMM3001: A Phase 3 randomized, multicenter study of subcutaneous daratumumab versus active monitoring in subjects with high-risk SMM.
- Trial SMM2001: A Phase 2 randomized, multicenter study to evaluate 3 different daratumumab IV dose schedules (long intense, intermediate, and short intense) in subjects with intermediate or high-risk SMM.

The indication for the treatment of adult patients with systemic light chain (AL) amyloidosis is supported by Trial AMY3001, which utilized the daratumumab SC formulation:

- Trial AMY3001: A randomized Phase 3 trial to evaluate the efficacy and safety of daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone (D-VCd) compared with bortezomib, cyclophosphamide, and dexamethasone (VCd) alone in newly diagnosed systemic AL amyloidosis.

The expanded indication in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy is supported by Trial MMY3013, which utilized the daratumumab SC formulation (after amendment 1):

- Trial MMY3013: A Phase 3 study comparing pomalidomide and dexamethasone with or without daratumumab in subjects with relapsed or refractory multiple myeloma who have received at least one prior line of therapy with both lenalidomide and a proteasome inhibitor (the APOLLO study).

The extended indication in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of adult patients with previously untreated multiple myeloma is supported by Trials MMY3014 and MMY3019, which utilized the daratumumab SC formulation:

- Trial MMY3014: A Phase 3 study comparing daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) in subjects with previously untreated multiple myeloma who are eligible for high-dose therapy (the PERSEUS study). The treatment phase of the trial includes an induction/ASCT/consolidation part comparing daratumumab in combination with VRd versus VRd alone for induction and consolidation and a part comparing maintenance with daratumumab and lenalidomide versus lenalidomide alone.

- Trial MMY3019: A Phase 3 study comparing daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd) with bortezomib, lenalidomide, and dexamethasone (VRd) in subjects with untreated multiple myeloma and for whom hematopoietic stem cell transplant was not planned as initial therapy (the CEPHEUS study).

The remaining trials (described below; ie, GEN501, GEN503, MMY1001, MMY1002, MMY2002, MMY2004, MMY3003, MMY3004, MMY3006, MMY3007, and MMY3008) investigated the intravenous formulation of daratumumab, DARZALEX 20 mg/mL concentrate for solution for infusion.

The indication in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for ASCT is supported by Trial MMY3006:

- Trial MMY3006: Trial of daratumumab (JNJ-54767414 [HuMax® CD38]) in combination with VELCADE® (bortezomib), thalidomide, and dexamethasone (VTD) in the first line treatment of transplant eligible subjects with newly diagnosed multiple myeloma. The trial is comprised of 2 parts: Part 1 (induction/ASCT/consolidation) comparing daratumumab in combination with VTD versus VTD alone for induction and consolidation and Part 2 comparing maintenance with daratumumab versus observation only for subjects achieving at least a partial response after consolidation.

The indication in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT is supported by Trial MMY3008:

- Trial MMY3008: A Phase 3 trial comparing daratumumab, lenalidomide, and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in subjects with previously untreated multiple myeloma who are ineligible for high dose therapy.

The combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for ASCT is supported by Trial MMY3007:

- Trial MMY3007: A Phase 3, randomized, controlled, open-label trial of VELCADE® (bortezomib)-melphalan-prednisone (VMP) compared with daratumumab in combination with VMP (D-VMP), in subjects with previously untreated multiple myeloma who are ineligible for high-dose therapy.

Additionally, data from 12 subjects from the D-VMP cohort of Trial MMY1001 was used in support of Trial MMY3007.

The monotherapy for treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression

on the last therapy indication is supported by 3 single agent clinical trials: MMY2002, GEN501, and MMY1002:

- Trial MMY2002: An open-label, multicenter, Phase 2 trial investigating the efficacy and safety of daratumumab in subjects with multiple myeloma who have received at least 3 prior lines of therapy (including a PI and an IMiD) or are double refractory to a PI and an IMiD.
- Trial GEN501: An open-label, dose escalation followed by open-label, single-arm trial, the first-in-human proof of concept and dose-finding trial in the daratumumab program. The trial was a Phase 1/2 single agent trial in subjects with multiple myeloma whose disease was relapsed or refractory to at least 2 prior lines of therapies.
- Trial MMY1002: A Phase 1, dose escalation trial of daratumumab in Japanese patients with relapsed or refractory multiple myeloma. The trial evaluated the safety and tolerability of daratumumab in Japanese patients with multiple myeloma who were relapsed or refractory to at least 2 prior lines of therapy (PI or IMiD).

The combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy indication is supported by 4 combination clinical trials: MMY3004, MMY3003, GEN503, and MMY1001:

- Trial MMY3004: A Phase 3, randomized trial comparing daratumumab, bortezomib, and dexamethasone (D-Vd) versus bortezomib and dexamethasone (Vd) in subjects with relapsed or refractory multiple myeloma.
- Trial MMY3003: A Phase 3, randomized trial comparing D-Rd versus Rd in subjects with relapsed or refractory multiple myeloma.
- Trial GEN503: An open-label, international, multicenter, dose-escalating Phase 1/2 trial investigating the safety of D-Rd in patients with relapsed and refractory multiple myeloma after receiving a minimum of 2 and a maximum of 4 prior lines of therapy and be eligible for treatment with Rd.
- Trial MMY1001: An open-label, multicenter, Phase 1b trial to evaluate the safety, tolerability, and dose regimen of daratumumab in combination with various backbone treatment regimens (Vd, VMP, bortezomib-thalidomide-dexamethasone [VTd], and pomalidomide-dexamethasone [Pd]) for the treatment of patients with multiple myeloma in either the newly diagnosed patients who are unsuitable for stem cell transplant or those who had received prior therapies depending on the backbone treatment regimen.

The combination with bortezomib, lenalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma is supported by Trial MMY2004:

- Trial MMY2004: A Phase 2, randomized, open-label study comparing daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) in subjects with newly diagnosed multiple myeloma eligible for high-dose chemotherapy and autologous stem cell transplantation. The trial is comprised of an induction/stem cell mobilization + high-dose chemotherapy + ASCT/consolidation phase comparing daratumumab in combination with VRd versus VRd alone for induction and

consolidation and a maintenance phase comparing daratumumab and lenalidomide versus lenalidomide alone.

SIII.2. Clinical Trial Exposure

Exposure in Randomized Clinical Trials

The randomized clinical trials (with non-daratumumab control) population includes 11 trials:

- MMY2004;
- MMY3003;
- MMY3004;
- MMY3006 (Parts 1 and 2);
- MMY3007;
- MMY3008;
- MMY3013;
- MMY3014;
- MMY3019;
- SMM3001;
- AMY3001.

Only trials with a non-daratumumab control are included; therefore, subjects from MMY3012 (randomized trial of daratumumab SC versus daratumumab IV) and SMM2001 (randomized trial evaluating 3 different daratumumab IV dose schedules) are not included in the randomized clinical trials population.

Exposure to daratumumab in the randomized clinical trials population is summarized by indication (multiple myeloma, SMM, AL amyloidosis, and all indications) in Tables SIII.1 through SIII.4 for all subjects by duration, by age group and sex, by dose, and by special populations (renal impairment at baseline and hepatic impairment at baseline).

Table SIII.1: Exposure by Duration; All Randomized Trials of Safety Population

Duration of exposure	Persons	Person-Months
Multiple Myeloma		
Cumulative up to 3 months	195	248.5
Cumulative up to 6 months	602	2,077.3
Cumulative up to 9 months	700	2,801.9
Cumulative up to 12 months	795	3,778.5
Cumulative up to 18 months	960	6,228.1
Cumulative up to 24 months	1,197	11,340.3
Cumulative up to 30 months	1,584	21,912.5
Cumulative up to 36 months	1,875	31,593.6
Cumulative up to 42 months	2,045	38,177.4
Cumulative up to 48 months	2,167	43,691.3
Cumulative up to 54 months	2,246	47,694.0

Table SIII.1: Exposure by Duration; All Randomized Trials of Safety Population

	Persons	Person-Months
Cumulative up to 60 months	2,365	54,535.0
Cumulative up to 66 months	2,470	61,063.4
Cumulative up to 72 months	2,537	65,681.3
Cumulative up to 78 months	2,596	70,089.5
Cumulative up to 84 months	2,687	77,415.5
Cumulative up to 90 months	2,754	83,252.6
Cumulative up to 96 months	2,777	85,391.1
Cumulative up to 102 months	2,779	85,585.8
Total	2,779	85,585.8
Smouldering Multiple Myeloma		
Cumulative up to 3 months	6	5.5
Cumulative up to 6 months	10	25.1
Cumulative up to 9 months	13	50.1
Cumulative up to 12 months	24	168.0
Cumulative up to 18 months	50	544.0
Cumulative up to 24 months	55	650.4
Cumulative up to 30 months	63	861.6
Cumulative up to 36 months	190	5,337.4
Cumulative up to 42 months	193	5,445.6
Total	193	5,445.6
Amyloidosis		
Cumulative up to 3 months	28	36.6
Cumulative up to 6 months	43	106.1
Cumulative up to 9 months	50	155.3
Cumulative up to 12 months	58	237.1
Cumulative up to 18 months	64	331.3
Cumulative up to 24 months	184	2,968.4
Cumulative up to 30 months	193	3,192.4
Total	193	3,192.4
All Indications		
Cumulative up to 3 months	229	290.6
Cumulative up to 6 months	655	2,208.5
Cumulative up to 9 months	763	3,007.3
Cumulative up to 12 months	877	4,183.7
Cumulative up to 18 months	1,074	7,103.3
Cumulative up to 24 months	1,436	14,959.1
Cumulative up to 30 months	1,840	25,966.5
Cumulative up to 36 months	2,258	40,123.4
Cumulative up to 42 months	2,431	46,815.4
Cumulative up to 48 months	2,553	52,329.3
Cumulative up to 54 months	2,632	56,332.0
Cumulative up to 60 months	2,751	63,173.0
Cumulative up to 66 months	2,856	69,701.4
Cumulative up to 72 months	2,923	74,319.3
Cumulative up to 78 months	2,982	78,727.5
Cumulative up to 84 months	3,073	86,053.5
Cumulative up to 90 months	3,140	91,890.6
Cumulative up to 96 months	3,163	94,029.1
Cumulative up to 102 months	3,165	94,223.8
Total	3,165	94,223.8

Note: 1 month equals 365.25/12 days. Only trials with a non-daratumumab control are included (MMY2004, MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3013, MMY3014, MMY3019, SMM3001, and AMY3001).

[TSIEXP01_SMM.RTF] [PROD/JNJ-54767414/Z_RMP/DBR_MMY_DVRD_SMM_2024/RE_MMY_DVRD_SMM_2024/TSIEXP01_SMM.SAS] 07OCT2024, 09:56

Table SIII.2: Exposure by Age Group and Sex; All Randomized Trials of Safety Population

	Men		Women	
	Persons	Person-Months	Persons	Person-Months
Age Group				
Multiple Myeloma				
<30 years	1	3.2	2	58.1
30-54 years	306	7,616.9	196	5,320.2
55-64 years	507	11,781.8	405	10,324.4
65-74 years	514	18,856.1	474	18,279.4
75-84 years	179	6,100.1	177	6,581.5
>=85 years	10	495.1	8	169.1
Total	1,517	44,853.1	1,262	40,732.7
Smouldering Multiple Myeloma				
<30 years	0	-	0	-
30-54 years	20	562.2	28	836.7
55-64 years	25	744.5	32	948.2
65-74 years	39	1,127.1	28	764.8
75-84 years	9	182.2	9	196.0
>=85 years	2	70.1	1	13.8
Total	95	2,686.1	98	2,759.5
Amyloidosis				
<30 years	0	-	0	-
30-54 years	20	336.7	19	347.5
55-64 years	39	663.5	28	501.8
65-74 years	36	584.5	31	489.5
75-84 years	10	78.8	8	155.9
>=85 years	1	16.6	1	17.7
Total	106	1,680.0	87	1,512.4
All Indications				
<30 years	1	3.2	2	58.1
30-54 years	346	8,515.7	243	6,504.3
55-64 years	571	13,189.8	465	11,774.5
65-74 years	589	20,567.7	533	19,533.8
75-84 years	198	6,361.1	194	6,933.4
>=85 years	13	581.7	10	200.5
Total	1,718	49,219.2	1,447	45,004.6

Note: 1 month equals 365.25/12 days. Only trials with a non-daratumumab control are included (MMY2004, MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3013, MMY3014, MMY3019, SMM3001, and AMY3001).

[TSIEXP02_SMM.RTF] [PROD/JNJ-54767414/Z_RMP/DBR_MMY_DVRD_SMM_2024/RE_MMY_DVRD_SMM_2024/TSIEXP02_SMM.SAS] 10JUL2024, 14:20

Table SIII.3: Exposure by Dose; All Randomized Trials of Safety Population

	Persons	Person-Months
Dose of exposure		
Multiple Myeloma		
16 mg/kg IV	1,576	36,174.6
1,800 mg SC	690	22,928.6
16 mg/kg IV ->1,800 mg SC	302	22,038.9
Total	2,568	81,142.1
Smouldering Multiple Myeloma		
1,800 mg SC	193	5,445.6

Table SIII.3: Exposure by Dose; All Randomized Trials of Safety Population

	Persons	Person-Months
Amyloidosis		
1,800 mg SC	193	3,192.4
All Indications		
16 mg/kg IV	1,576	36,174.6
1,800 mg SC	1,076	31,566.6
16 mg/kg IV ->1,800 mg SC	302	22,038.9
Total	2,954	89,780.1

Note: 1 month equals 365.25/12 days. Only trials with a non-daratumumab control are included (MMY2004, MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3013, MMY3014, MMY3019, SMM3001, and AMY3001).
IV = intravenous administration; SC= subcutaneous administration co-formulated with human hyaluronidase PH20 (rHuPH20).
Note: 4 subjects in MMY3013 started the study receiving IV Daratumumab prior to the protocol amendment to change the study to SC Daratumumab. For studies MMY3003, MMY3004, MMY3007, MMY3008, and MMY3012 the protocols were amended to allow subjects to switch to SC Daratumumab at the investigator discretion due to the global COVID-19 pandemic.

Modified from: [TSIEXP03_SMM.RTF] [PROD/JNJ-54767414/Z_RMP/DBR_MMY_DVRD_SMM_2024/RE_MMY_DVRD_SMM_2024/TSIEXP03_SMM.SAS] 10JUL2024, 14:20

Table SIII.4: Exposure by Special Populations; All Randomized Trials of Safety Population

Population	Persons	Person-Months
Multiple Myeloma		
Renal impairment at baseline		
Normal (CrCl >= 90 mL/min)	1,029	27,902.1
Mild (CrCl 60 to < 90 mL/min)	1,021	33,127.4
Moderate (CrCl 30 to < 60 mL/min)	601	20,950.5
Severe (CrCl < 30 mL/min)	108	2,975.3
Missing	20	630.5
Total	2,779	85,585.8
Hepatic impairment at baseline[a]		
Normal	2,392	74,896.4
Mild	282	7,646.3
Moderate	12	345.4
Severe	1	18.4
Missing	92	2,679.4
Total	2,779	85,585.8
Smouldering Multiple Myeloma		
Renal impairment at baseline		
Normal (CrCl >= 90 mL/min)	53	1,525.9
Mild (CrCl 60 to < 90 mL/min)	119	3,297.1
Moderate (CrCl 30 to < 60 mL/min)	21	622.6
Severe (CrCl < 30 mL/min)	0	-
Missing	0	-
Total	193	5,445.6
Hepatic impairment at baseline[a]		
Normal	172	4,890.8
Mild	12	304.1
Moderate	0	-
Severe	0	-
Missing	9	250.6
Total	193	5,445.6
Amyloidosis		
Renal impairment at baseline		
Normal (CrCl >= 90 mL/min)	66	1,029.1

Table SIII.4: Exposure by Special Populations; All Randomized Trials of Safety Population		
	Persons	Person-Months
Mild (CrCl 60 to < 90 mL/min)	60	1,037.1
Moderate (CrCl 30 to < 60 mL/min)	56	982.0
Severe (CrCl < 30 mL/min)	11	144.2
Missing	0	-
Total	193	3,192.4
Hepatic impairment at baseline[a]		
Normal	154	2,664.4
Mild	36	497.3
Moderate	3	30.7
Severe	0	-
Missing	0	-
Total	193	3,192.4
All Indications		
Renal impairment at baseline		
Normal (CrCl >= 90 mL/min)	1,148	30,457.1
Mild (CrCl 60 to < 90 mL/min)	1,200	37,461.6
Moderate (CrCl 30 to < 60 mL/min)	678	22,555.1
Severe (CrCl < 30 mL/min)	119	3,119.5
Missing	20	630.5
Total	3,165	94,223.8
Hepatic impairment at baseline[a]		
Normal	2,718	82,451.6
Mild	330	8,447.7
Moderate	15	376.0
Severe	1	18.4
Missing	101	2,930.0
Total	3,165	94,223.8

[a] Normal hepatic function (per NCI organ dysfunction criteria): total bilirubin ≤ ULN and AST ≤ ULN; Mild: (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN); Moderate: 1.5 x ULN < total bilirubin ≤ 3 x ULN; Severe: total bilirubin > 3 x ULN.
Key: AST = aspartate aminotransferase; CrCl = creatinine clearance; NCI = National Cancer Institute; ULN = upper limit normal.
Note: 1 month equals 365.25/12 days. Only trials with a non-daratumumab control are included (MMY2004, MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3013, MMY3014, MMY3019, SMM3001, and AMY3001).

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Exposure in All Clinical Trials

The all clinical trials population includes 21 trials:

- GEN501;
- GEN503;
- MMY1001 (daratumumab-bortezomib-dexamethasone [D-Vd], daratumumab-bortezomib-thalidomide-dexamethasone [D-VTd], daratumumab-bortezomib-melphalan-prednisone [D-VMP], and daratumumab-pomalidomide-dexamethasone [D-Pd] cohorts);
- MMY1002;
- MMY2002;
- MMY2004;
- MMY3003;

- MMY3004;
- MMY3006 (Parts 1 and 2);
- MMY3007;
- MMY3008;
- MMY1004 (Parts 2 and 3);
- MMY1008;
- MMY2040 (D-VMP, D-Rd, and D-VRd cohorts);
- MMY3012;
- MMY3013;
- MMY3014;
- MMY3019;
- SMM2001;
- SMM3001;
- AMY3001.

Exposure to daratumumab in the all clinical trials population is summarized by indication (multiple myeloma, SMM, AL amyloidosis, and all indications) in Tables SIII.5 through SIII.8 for all subjects by duration, by age and sex, by dose, and by special populations (renal impairment at baseline and hepatic impairment at baseline). As shown in Table SIII.5, a total of 1,949 patients in the all clinical trials population have been treated with daratumumab for more than 2 years (4,536 total patients minus 2,587 patients with exposure up to 24 months).

Table SIII.5: Exposure by Duration; All Clinical Trials of Safety Population

Duration of exposure	Persons	Person-Months
Multiple Myeloma		
Cumulative up to 3 months	610	938.9
Cumulative up to 6 months	1,215	4,752.1
Cumulative up to 9 months	1,432	6,371.7
Cumulative up to 12 months	1,645	8,682.5
Cumulative up to 18 months	1,900	12,553.6
Cumulative up to 24 months	2,198	20,976.4
Cumulative up to 30 months	2,722	37,499.3
Cumulative up to 36 months	3,073	49,122.5
Cumulative up to 42 months	3,260	56,372.8
Cumulative up to 48 months	3,384	61,978.5
Cumulative up to 54 months	3,466	66,134.1
Cumulative up to 60 months	3,585	72,975.1
Cumulative up to 66 months	3,691	79,567.9
Cumulative up to 72 months	3,758	84,185.8
Cumulative up to 78 months	3,817	88,594.0
Cumulative up to 84 months	3,908	95,920.0
Cumulative up to 90 months	3,975	101,757.0
Cumulative up to 96 months	3,998	103,895.6
Cumulative up to 102 months	4,000	104,090.3

Table SIII.5: Exposure by Duration; All Clinical Trials of Safety Population

	Persons	Person-Months
Total	4,000	104,090.3
Smouldering Multiple Myeloma		
Cumulative up to 3 months	49	73.9
Cumulative up to 6 months	58	119.7
Cumulative up to 9 months	61	144.6
Cumulative up to 12 months	75	294.9
Cumulative up to 18 months	152	1,443.0
Cumulative up to 24 months	177	1,946.5
Cumulative up to 30 months	185	2,157.7
Cumulative up to 36 months	312	6,633.6
Cumulative up to 42 months	315	6,741.7
Total	315	6,741.7
Amyloidosis		
Cumulative up to 3 months	31	41.6
Cumulative up to 6 months	51	138.0
Cumulative up to 9 months	59	194.7
Cumulative up to 12 months	69	296.3
Cumulative up to 18 months	77	418.7
Cumulative up to 24 months	212	3,384.8
Cumulative up to 30 months	221	3,608.8
Total	221	3,608.8
All Indications		
Cumulative up to 3 months	690	1,054.5
Cumulative up to 6 months	1,324	5,009.8
Cumulative up to 9 months	1,552	6,711.0
Cumulative up to 12 months	1,789	9,273.7
Cumulative up to 18 months	2,129	14,415.3
Cumulative up to 24 months	2,587	26,307.7
Cumulative up to 30 months	3,128	43,265.8
Cumulative up to 36 months	3,606	59,364.8
Cumulative up to 42 months	3,796	66,723.3
Cumulative up to 48 months	3,920	72,329.1
Cumulative up to 54 months	4,002	76,484.6
Cumulative up to 60 months	4,121	83,325.6
Cumulative up to 66 months	4,227	89,918.4
Cumulative up to 72 months	4,294	94,536.3
Cumulative up to 78 months	4,353	98,944.5
Cumulative up to 84 months	4,444	106,270.5
Cumulative up to 90 months	4,511	112,107.6
Cumulative up to 96 months	4,534	114,246.1
Cumulative up to 102 months	4,536	114,440.8
Total	4,536	114,440.8

Note: 1 month equals 365.25/12 days. The following trials are included: GEN501, GEN503, MMY1001 (D-Vd, D-VTd, D-VMP, and D-Pd cohorts), MMY1002, MMY1004 Parts 2 and 3, MMY1008, MMY2002, MMY2004, MMY2040 (D-VMP, D-Rd, and D-VRd cohorts), MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3012, MMY3013, MMY3014, MMY3019, SMM2001, SMM3001, and AMY3001.
Key: D-Pd = daratumumab-pomalidomide dexamethasone; D-Rd = daratumumab-lenalidomide-dexamethasone; D-Vd = daratumumab-bortezomib-dexamethasone; D-VMP = daratumumab-bortezomib melphalan-prednisone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; D-VTd = daratumumab-bortezomib-thalidomide-dexamethasone.

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Table SIII.6: Exposure by Age Group and Sex; All Clinical Trials of Safety Population

	Men		Women	
	Persons	Person-Months	Persons	Person-Months
Age Group				
Multiple Myeloma				
<30 years	1	3.2	2	82.3
30-54 years	415	9,798.7	265	6,748.6
55-64 years	724	15,626.9	565	13,062.4
65-74 years	771	21,759.8	674	21,089.7
75-84 years	280	7,364.4	272	7,791.1
>=85 years	18	555.0	13	208.2
Total	2,209	55,108.0	1,791	48,982.3
Smouldering Multiple Myeloma				
<30 years	0	-	0	-
30-54 years	34	679.7	42	965.9
55-64 years	40	910.4	59	1,244.4
65-74 years	59	1,316.8	51	1,076.0
75-84 years	14	222.7	13	242.2
>=85 years	2	70.1	1	13.8
Total	149	3,199.5	166	3,542.2
Amyloidosis				
<30 years	0	-	0	-
30-54 years	20	336.7	23	397.7
55-64 years	45	745.0	29	523.0
65-74 years	44	707.2	35	575.3
75-84 years	12	81.3	10	203.2
>=85 years	1	16.6	1	17.7
Total	122	1,886.8	98	1,716.9
All Indications				
<30 years	1	3.2	2	82.3
30-54 years	469	10,815.0	330	8,112.2
55-64 years	809	17,282.2	653	14,829.8
65-74 years	874	23,783.8	760	22,741.0
75-84 years	306	7,668.4	295	8,236.5
>=85 years	21	641.6	15	239.6
Total	2,480	60,194.3	2,055	54,241.4

Note: 1 month equals 365.25/12 days. The following trials are included: GEN501, GEN503, MMY1001 (D-Vd, D-VTd, D-VMP, and D-Pd cohorts), MMY1002, MMY1004 Parts 2 and 3, MMY1008, MMY2002, MMY2004, MMY2040 (D-VMP, D-Rd, and D-VRd cohorts), MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3012, MMY3013, MMY3014, MMY3019, SMM2001, SMM3001, and AMY3001.
Key: D-Pd = daratumumab-pomalidomide dexamethasone; D-Rd = daratumumab-lenalidomide-dexamethasone; D-Vd = daratumumab-bortezomib-dexamethasone; D-VMP = daratumumab-bortezomib melphalan-prednisone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; D-VTd = daratumumab-bortezomib-thalidomide-dexamethasone.

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Table SIII.7: Exposure by Dose; All Clinical Trials of Safety Population

	Persons	Person-Months
Dose of exposure		
Multiple Myeloma		
8 mg/kg IV	56	296.8
16 mg/kg IV	2,161	43,022.5
1,800 mg SC	1,222	29,224.9
16 mg/kg IV ->1,800 mg SC	315	22,412.5

Table SIII.7: Exposure by Dose; All Clinical Trials of Safety Population

	Persons	Person-Months
Other IV[a]	35	246.2
Total	3,789	95,202.8
Smouldering Multiple Myeloma		
16 mg/kg IV	122	1,296.2
1,800 mg SC	193	5,445.6
Total	315	6,741.7
Amyloidosis		
1,800 mg SC	221	3,608.8
All Indications		
8 mg/kg IV	56	296.8
16 mg/kg IV	2,283	44,318.6
1,800 mg SC	1,636	38,279.2
16 mg/kg IV ->1,800 mg SC	315	22,412.5
Other IV[a]	35	246.2
Total	4,325	105,553.3

[a] Other IV doses include 0.005 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 4 mg/kg, and 24 mg/kg.
Note: 1 month equals 365.25/12 days. The following trials are included: GEN501, GEN503, MMY1001 (D-Vd, D-VTd, D-VMP, and D-Pd cohorts), MMY1002, MMY1004 Parts 2 and 3, MMY1008, MMY2002, MMY2004, MMY2040 (D-VMP, D-Rd, and D-VRd cohorts), MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3012, MMY3013, MMY3014, MMY3019, SMM2001, SMM3001, and AMY3001. In Trial MMY2002, 3 subjects crossed over from 8 mg/kg to 16 mg/kg and they are only included in the 8 mg/kg category.
Key: D-Pd = daratumumab-pomalidomide dexamethasone; D-Rd = daratumumab-lenalidomide-dexamethasone; D-Vd = daratumumab-bortezomib-dexamethasone; D-VMP = daratumumab-bortezomib melphalan-prednisone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; D-VTd = daratumumab-bortezomib-thalidomide-dexamethasone; IV = intravenous administration; SC= subcutaneous administration co-formulated with human hyaluronidase PH20 (rHuPH20).

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Table SIII.8: Exposure by Special Populations; All Clinical Trials of Safety Population

Population	Persons	Person-Months
Multiple Myeloma		
Renal impairment at baseline		
Normal (CrCl >= 90 mL/min)	1,391	34,870.4
Mild (CrCl 60 to < 90 mL/min)	1,493	40,329.5
Moderate (CrCl 30 to < 60 mL/min)	927	24,406.1
Severe (CrCl < 30 mL/min)	167	3,789.0
Missing	22	695.2
Total	4,000	104,090.3
Hepatic impairment at baseline[a]		
Normal	3,428	91,052.9
Mild	440	9,410.4
Moderate	19	392.7
Severe	1	18.4
Missing	112	3,215.8
Total	4,000	104,090.3
Smouldering Multiple Myeloma		
Renal impairment at baseline		
Normal (CrCl >= 90 mL/min)	115	2,142.9
Mild (CrCl 60 to < 90 mL/min)	168	3,899.2
Moderate (CrCl 30 to < 60 mL/min)	32	699.6
Severe (CrCl < 30 mL/min)	0	-

Table SIII.8: Exposure by Special Populations; All Clinical Trials of Safety Population

	Persons	Person-Months
Missing	0	-
Total	315	6,741.7
Hepatic impairment at baseline[a]		
Normal	283	6,080.1
Mild	23	411.0
Moderate	0	-
Severe	0	-
Missing	9	250.6
Total	315	6,741.7
Amyloidosis		
Renal impairment at baseline		
Normal (CrCl >= 90 mL/min)	77	1,159.8
Mild (CrCl 60 to < 90 mL/min)	70	1,218.9
Moderate (CrCl 30 to < 60 mL/min)	62	1,080.7
Severe (CrCl < 30 mL/min)	11	144.2
Missing	1	5.2
Total	221	3,608.8
Hepatic impairment at baseline[a]		
Normal	176	3,009.0
Mild	42	569.1
Moderate	3	30.7
Severe	0	-
Missing	0	-
Total	221	3,608.8
All Indications		
Renal impairment at baseline		
Normal (CrCl >= 90 mL/min)	1,583	38,173.1
Mild (CrCl 60 to < 90 mL/min)	1,731	45,447.6
Moderate (CrCl 30 to < 60 mL/min)	1,021	26,186.4
Severe (CrCl < 30 mL/min)	178	3,933.3
Missing	23	700.4
Total	4,536	114,440.8
Hepatic impairment at baseline[a]		
Normal	3,887	100,142.1
Mild	505	10,390.5
Moderate	22	423.4
Severe	1	18.4
Missing	121	3,466.4
Total	4,536	114,440.8

[a] Normal hepatic function (per NCI organ dysfunction criteria): Total bilirubin ≤ ULN and AST ≤ ULN; Mild: (Total bilirubin ≤ ULN and AST > ULN) or (ULN < Total bilirubin ≤ 1.5 x ULN); Moderate: 1.5 x ULN < Total bilirubin ≤ 3 x ULN; Severe: Total bilirubin > 3 x ULN.
Note: 1 month equals 365.25/12 days. The following trials are included: GEN501, GEN503, MMY1001 (D-Vd, D-VTd, D-VMP, and D-Pd cohorts), MMY1002, MMY1004 Parts 2 and 3, MMY1008, MMY2002, MMY2004, MMY2040 (D-VMP, D-Rd, and D-VRd cohorts), MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3012, MMY3013, MMY3014, MMY3019, SMM2001, SMM3001, and AMY3001. In Trial MMY2002, 3 subjects crossed over from 8 mg/kg to 16 mg/kg and they are only included in the 8 mg/kg category.
Key: AST = aspartate aminotransferase; CrCl = creatinine clearance; D-Pd = daratumumab-pomalidomide dexamethasone; D-Rd = daratumumab-lenalidomide-dexamethasone; D-Vd = daratumumab-bortezomib-dexamethasone; D-VMP = daratumumab-bortezomib melphalan-prednisone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; D-VTd = daratumumab-bortezomib-thalidomide-dexamethasone; NCI = National Cancer Institute; ULN = upper limit normal.

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

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

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	Known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume in 1 second percentage of predicted <50% of predicted normal), persistent asthma, or a history of asthma within 2 to 5 years
Reason for being an exclusion criterion	It is common clinical practice not to include subjects with severe and potentially life-threatening pulmonary conditions in trials on anticancer therapy. Additionally, COPD and asthma may increase the risk to develop bronchospasms associated with IRRs.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	There are no specific data available for use of daratumumab in patients with COPD with a forced expiratory volume in 1 second <50%; nor severe or moderate persistent asthma. The treating physician would be expected to weigh the benefit and risks for each individual patient.
Criterion 2	Known seropositive for human immunodeficiency virus (HIV) or hepatitis B (defined by a positive test for hepatitis B surface antigen or antibodies to hepatitis B surface and/or core antigens [anti-HBs and anti-HBc, respectively]) or hepatitis C (anti-hepatitis C virus [HCV] antibody positive or HCV-RNA quantitation positive).
Reason for being an exclusion criterion	It is common clinical practice to exclude subjects with active infections because they potentially confound the interpretation of safety.
Considered to be included as missing information: Yes/No	No.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Rationale (if not included as missing information)	There are no specific data available for use of daratumumab in patients with HIV or HCV infection. The treating physician would be expected to weigh the benefit and risks for each individual patient. Hepatitis B virus (HBV) reactivation is considered an important identified risk based on clinical trial observations and postmarketing data. The SmPC and package leaflet (PL) provide instruction and guidelines for risk mitigation measures.
Criterion 3	Subject is a woman who is pregnant or breast feeding or planning to become pregnant while enrolled in this trial or within 3 months after the last dose of study drug.
Reason for being an exclusion criterion	Due to ethical reasons: to minimize the potential risk to fetus.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	Although no data are available on the use of daratumumab in pregnancy and lactating women, and no nonclinical studies were conducted to evaluate the potential effects of daratumumab on reproduction or development, no additional pharmacovigilance activities are in place or planned to further characterize this population. As multiple myeloma and AL amyloidosis are usually diagnosed in a post-reproductive age, it is anticipated that the potential for use in pregnant and lactating women and reproductive toxicity is low. As stated in the SmPC, daratumumab is not recommended during pregnancy and in women of childbearing potential not using contraception. A decision should be made whether to discontinue breast feeding or to discontinue daratumumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Criterion 4	Subject has peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) Version 4 or Version 5.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Reason for being an exclusion criterion	Standard practice in oncology clinical trials. Inclusion of patients with neuropathy can confound the efficacy and safety assessments of the trial. Patients with Grade 2 or higher neuropathy/neuropathic pain were excluded in trials with regimens containing a PI (eg, Trial MMY3006) due to toxicity of PIs.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	There are limited data available for use of daratumumab in patients with these conditions. Patients with neuropathy/neuropathic pain were not excluded in Trials MMY3008, MMY1004, MMY1008, and MMY3012. The treating physician would be expected to weigh the benefit and risks for each individual patient.
Criterion 5	History of significant cerebrovascular disease.
Reason for being an exclusion criterion	It is common clinical practice not to include subjects with significant and potentially life-threatening conditions in trials on anticancer therapy.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	There are limited data available for use of daratumumab in patients with significant cerebrovascular diseases. Patients with history of cerebrovascular disease were not excluded in Trials MMY3006, MMY3008, MMY1004, MMY1008, MMY2040, MMY3012, MMY3014, MMY3019, SMM2001, and SMM3001. The treating physician would be expected to weigh the benefit and risks for each individual patient.
Criterion 6	Hepatic impairment: Alanine aminotransferase or aspartate aminotransferase level > 2.5 times (x) the upper limit of normal (ULN). Total bilirubin level > 2 × or > 1.5 × ULN, (except for Gilbert Syndrome: direct bilirubin > 2 × or > 1.5 × ULN).
Reason for being an exclusion criterion	The clinical safety of daratumumab administration in subjects with hepatic impairment were not fully elucidated. The combination with other anti-myeloma agents require adequate hepatic function.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	The SmPC Section 4.2 states that changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolized through hepatic pathways.
Criterion 7	Creatinine clearance (CrCl) ≤ 20 mL/min/1.73 m^2
Reason for being an exclusion criterion	The clinical safety of daratumumab administration in subjects with CrCl ≤ 20 mL/min/1.73 m^2 was not studied.
Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	The SmPC Section 4.2 states that no formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic analyses, no dosage adjustment is necessary for patients with renal impairment.
Criterion 8a (multiple myeloma and SMM patients)	Clinically significant cardiac disease including: • active angina pectoris; • myocardial infarction; • congestive heart failure as defined by New York Heart Association Class III-IV; • uncontrolled cardiac arrhythmia (NCI-CTCAE Version 4 Grade ≥ 2) or clinically significant electrocardiogram abnormalities; • decreased left ventricular ejection fraction of < 40%; • baseline QT interval corrected for heart rate (QTc) by Fridericia's Correction Formula (QTcF) >470 msec for patients or a complete left bundle branch block (defined as a QRS interval ≥120 msec in left bundle branch block form).
Reason for being an exclusion criterion	Common clinical practice to treat these severe and potentially life-threatening cardiac conditions first before starting long term anticancer therapy. Patients whose severe/advanced cardiac disorders cannot be managed or improved are excluded as they are not able to tolerate the backbone or comparator regimen.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Considered to be included as missing information: Yes/No	No.
Rationale (if not included as missing information)	There are no specific data available for use of daratumumab in multiple myeloma patients with significant cardiac disease. The treating physician would be expected to weigh the benefit and risks for each individual patient. The QTc substudy in Trial SMM2001 showed that daratumumab does not cause clinically meaningful QTc prolongation. Therefore, the following exclusion criterion will be removed from future daratumumab trials: baseline QTcF > 470 msec for patients or a complete left bundle branch block (defined as a QRS interval ≥ 120 msec in left bundle branch block form).
Criterion 8b (AL amyloidosis patients)	Clinically significant cardiac disease including: • N-terminal pro b-type natriuretic peptide (NT-ProBNP) > 8,500 mg/L • New York Heart Association Class IIIB-IV heart failure • heart failure due to ischemic heart disease or uncorrected valvular disease and not primarily due to AL amyloid cardiomyopathy; • hospitalization for unstable angina or myocardial infarction, or percutaneous cardiac intervention or coronary artery bypass grafting (within 6 months); • congestive heart failure with cardiovascular-related hospitalization within 4 weeks; • history of sustained ventricular tachycardia or aborted ventricular fibrillation or history of atrioventricular nodal or sinoatrial nodal dysfunction for which a pacemaker/ implantable cardioverter defibrillator (ICD) is indicated but not placed); • baseline QTcF > 500 msec; • supine systolic blood pressure < 90 mmHg or symptomatic orthostatic hypotension.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Reason for being an exclusion criterion	Common clinical practice to treat these severe and potentially life-threatening cardiac conditions first before starting long-term anticancer therapy. Patients whose severe/advanced cardiac disorders cannot be managed or improved are excluded as they are not able to tolerate the backbone or comparator regimen.
Considered to be included as missing information: Yes/No	Yes (Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement)
Rationale (if not included as missing information)	Not applicable

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 rare adverse reactions.

In the all clinical trial population of 4,536 daratumumab-treated patients, 1,949 patients were treated for > 24 months (Table SIII.5), with maximum durations of treatment and follow-up of approximately 100 months. The extent of exposure to daratumumab in the clinical program was sufficient to adequately characterize the safety profile of daratumumab in patients with multiple myeloma. Due to the extent of exposure in the clinical trials population treated by daratumumab, adverse reactions due to prolonged or cumulative exposure and adverse reactions with a long latency should have been detected in this population.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Population with relevant different ethnic origin	Not applicable.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	Not applicable

Type of Special Population	Exposure
Patients with relevant comorbidities: • Patients with renal impairment	No formal studies of daratumumab in patients with renal impairment have been conducted. The clinical safety of daratumumab administration in subjects with CrCl ≤ 20 mL/min/1.73 m^2 was not studied. No clinically-important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function. Based on population pharmacokinetic analyses, no dosage adjustment is necessary for patients with renal impairment. In the daratumumab-treated patients who had renal impairment at baseline (all indications), there were 1,731 patients with mild renal impairment (CrCl 60 to < 90 mL/min), 1,021 patients with moderate renal impairment (CrCl 30 to < 60 mL/min), and 178 patients with severe renal impairment (CrCl < 30 mL/min).
• Patients with moderate or severe hepatic impairment	No formal studies of daratumumab in patients with hepatic impairment have been conducted. The clinical safety of daratumumab administration in subjects with hepatic impairment were not fully elucidated. No dosage adjustments are necessary for patients with hepatic impairment. In the daratumumab-treated patients who had hepatic impairment at baseline (all indications), there were 505 patients with mild hepatic impairment (total bilirubin ≤ ULN and aspartate aminotransferase > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN), 22 patients with moderate hepatic impairment (1.5 x ULN < total bilirubin, ≤ 3 x ULN), and 1 patient with severe hepatic impairment (total bilirubin > 3 x ULN).

Type of Special Population	Exposure
• Patients with cardiovascular impairment	For multiple myeloma, SMM, and AL amyloidosis indications, patients with clinically significant cardiac disease were excluded from clinical trials (unstable angina, acute myocardial infarction within 6 months of the Screening Visit before the first infusion, congestive heart failure, a known decreased cardiac ejection fraction of < 40%). For AL amyloidosis specifically, patients often present with cardiac involvement (i.e., AL amyloidosis-related cardiomyopathy) at baseline due to the underlying disease (Merlini 2018). There are no specific data available for use of daratumumab in AL amyloidosis patients who have the most clinically significant cardiac disease such as NYHA Class IIIB and IV cardiac disease, as these patients were excluded from Study AMY3001, and there are limited data in patients with Cardiac Stage IIIB (based on European Modification of Mayo 2004 Cardiac Stage). Patients with pre-existing cardiac involvement were included in Study AMY3001 as the study enrolled patients who had Cardiac Stage I-IIIA (based on the Mayo 2004 classification) and NYHA Class I-IIIA disease, however, additional information with regards to safety in patients with AL amyloidosis who have pre-existing serious cardiac involvement is required. **Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement is considered missing information**
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Pediatric population	The safety assessment in pediatric patients is based on the limited safety data from a Phase 2 study (ALL2005) to evaluate safety and efficacy of daratumumab in pediatric and young adult patients (aged 1 year and older) with relapsed or refractory Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma. No new safety signal was observed in this study. Product-specific waivers have been granted for daratumumab in mature B-cell neoplasms including multiple myeloma and for the treatment of systemic light chain amyloidosis.

Type of Special Population	Exposure
Elderly	No dose adjustments are considered necessary. Based on population pharmacokinetic analysis in patients receiving daratumumab monotherapy or various combination therapies, age (range: 31 to 93 years) had no clinically important effect on the pharmacokinetics of daratumumab. In the elderly population (all indications), 637 patients treated with daratumumab in clinical trials were ≥ 75 years of age; 1,634 daratumumab-treated patients were between ≥ 65 and 74 years of age, 601 daratumumab-treated patients were between ≥ 75 and 84 years of age, and 36 daratumumab-treated patients were ≥ 85 years.

CrCl = creatinine clearance; NYHA = New York Heart Association; ULN = upper limit of normal.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Important identified risks	None
Important potential risks	None
Missing information	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement

PART II: SAFETY SPECIFICATION

Module SV: Post-authorization Experience

SV.1. Post-authorization Exposure

SV.1.1. Method used to Calculate Exposure

Daratumumab 20 mg/mL Concentrate for Solution for Infusion

Patient exposure for the intravenous formulation was estimated by calculation from distribution data of daratumumab (20 mg/mL concentrate for solution for infusion). Estimates of exposure are based upon finished product. Region-specific bodyweight has been used to calculate exposure. The recommended dosing is 16 mg/kg. Assuming that the majority is in combination therapy, the suggested dose to use is 22 doses/year. The dosing schedules have been provided as EU: 70.8 kg = 1,132.8 mg per administered dose or 24,921.6 mg per year; North America: 80.7 kg = 1,291.2 mg per administered dose or 28,406.4 mg per year, and Rest of World: 62 kg = 992 mg per administered dose or 21,824.0 mg per year. Total yearly dose is 23 for a 4-week cycle, 22 for a 6-week cycle, and 21 for a 3-week cycle. The average is 22 doses/per year assuming a compliance rate of 100%.

Daratumumab 1,800 mg Solution for Injection

For the subcutaneous formulation, the recommended fixed dosing is 1,800 mg. Assuming that the majority is in combination therapy, it is suggested to use 22 doses/year. Total yearly dose will be 23 for a 4-week cycle, 22 for a 6-week cycle, and 21 for a 3-week cycle. The average is 22 doses/per year assuming a compliance rate of 100%.

SV.1.2. Exposure

The cumulative exposure for daratumumab intravenous formulation (20 mg/mL concentrate for solution for infusion) and daratumumab subcutaneous formulation (1,800 mg solution for injection) from launch to 31 Jul 2024 is summarized in Table SV.1.

Table SV.1: Cumulative Nonstudy Post-authorization Exposure by Region and Formulation (Launch to 31 Jul 2024)

Intravenous formulation		
Region	**Total milligrams**	**Person-years**
European Union	1,502,473,000	60,287
North America	2,089,875,440	73,571
Rest of world	1,502,752,300	68,858
Total (Intravenous)[a]	**5,095,100,740**	**202,716**

Table SV.1: Cumulative Nonstudy Post-authorization Exposure by Region and Formulation (Launch to 31 Jul 2024)

Subcutaneous formulation		
Region	**Total milligrams**	**Person-years**
European Union	3,810,623,400	96,229
North America	4,059,136,800	102,503
Rest of world	1,774,646,982	44,814
Total (Subcutaneous)[b]	**9,644,407,182**	**243,546**
Worldwide Total[c]	**14,739,507,922**	**446,262**

[a] The distribution was first observed in November 2015.

[b] The distribution was first observed in May 2020.

[c] The United Kingdom is no longer a part of the European Union and has been grouped under rest of world from January 2021 onwards.

Based on 5,095,100,740 mg distributed from launch to 31 Jul 2024, the estimated worldwide exposure to intravenous daratumumab is 202,716 person-years.

Based on 9,644,407,182 mg distributed worldwide from launch to 31 Jul 2024, the estimated exposure to subcutaneous daratumumab is 243,546 person-years.

Based on 14,739,507,922 mg distributed worldwide from launch to 31 Jul 2024, the estimated exposure to subcutaneous and intravenous daratumumab is 446,262 person-years.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Daratumumab is an antineoplastic agent which is administered by a healthcare professional (HCP) and has no abuse potential. Therefore, there is no concern for potential illegal use.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

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

Not applicable.

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

Not applicable.

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

Not applicable.

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

Not applicable.

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

The important identified risks, important potential risks, and missing information with daratumumab are based on the nonclinical, clinical trial experience, and postmarketing experience.

The important identified risks are:

- Interference for blood typing (minor antigen) (positive indirect Coombs' test);
- Hepatitis B virus reactivation.

There are no important potential risks.

The missing information is:

- Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement.

Version 26.0 of Medical Dictionary for Regulatory Activities (MedDRA) was used to classify the clinical trial adverse event information that is summarized in this section.

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

Important identified risk – Interference for blood typing (minor antigen) (positive indirect Coombs' test)

Potential Mechanisms:

Human red blood cells (RBCs) express low levels of CD38 compared with multiple myeloma cells. The number of CD38 molecules detected by daratumumab is in the range of 301 to 634 per RBCs versus 5,000 to 100,000 per plasma cell of multiple myeloma.

Daratumumab may interfere with routine blood bank compatibility tests by binding to endogenous CD38 found at low levels on erythrocytes. The binding of daratumumab from the patient's serum results in agglutination of erythrocytes during cross-matching, resulting in a false-positive indirect Coombs' test, which may interfere with cross-matching of blood. This interference is limited to the minor antigens and does not interfere with ABO or Rh typing.

Evidence Source(s) and Strength of Evidence:

Daratumumab binds to RBCs and interferes with compatibility testing, including antibody screening and cross-matching, which may persist for up to 6 months after the last administration of daratumumab. Events of relevance to interference for blood typing have occurred during clinical trials. The determination of a patient's blood group (type O, A, B, or AB) and Rh blood type are not impacted.

Characterization of the Risk:

Important identified risk – Interference for blood typing (minor antigen) (positive indirect Coombs' test): Frequency, Seriousness, Outcomes and Severity; Indication: Multiple Myeloma; All Clinical Trials of Safety Population

	Randomized Trials with Controls[a]			Trials without non-Dara Control[b]	All Clinical Trials
	Daratumumab[g]	Comparator[g]	Safety Run-In	Daratumumab	Daratumumab
Multiple Myeloma					
Number of subjects treated	2,779	2,797	16	1,205	4,000
Frequency[c]	0	0	0	4 (0.3%)	4 (0.1%)
Odds Ratio (95% CI)[f]	NE				
Seriousness	0	0	0	4 (0.3%)	4 (0.1%)
Outcomes					
Resulted in death	0	0	0	0	0
Not recovered/Not Resolved	0	0	0	3 (0.2%)	3 (0.1%)
Recovered with sequelae[d]	0	0	0	0	0
Recovered/Resolved	0	0	0	1 (0.1%)	1 (<0.1%)
Unknown[e]	0	0	0	0	0
Severity (toxicity grade)					
Worst Grade=1	0	0	0	1 (0.1%)	1 (<0.1%)

Important identified risk – Interference for blood typing (minor antigen) (positive indirect Coombs' test): Frequency, Seriousness, Outcomes and Severity; Indication: Multiple Myeloma; All Clinical Trials of Safety Population

	Randomized Trials with Controls[a]			Trials without non-Dara Control[b]	All Clinical Trials
	Daratumumab[g]	Comparator[g]	Safety Run-In	Daratumumab	Daratumumab
Worst Grade=2	0	0	0	0	0
Worst Grade=3	0	0	0	0	0
Worst Grade=4	0	0	0	0	0
Worst Grade=5	0	0	0	0	0
Missing	0	0	0	3 (0.2%)	3 (0.1%)

[a] Includes trials MMY2004, MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3013, MMY3014, and MMY3019.
[b] Includes trials MMY1001 (D-Vd, D-VTd, D-VMP, and D-Pd cohorts), MMY1002, MMY2002, GEN501, GEN503, MMY3012, MMY1004 Parts 2 and 3, MMY1008, and MMY2040 (D-VMP, D-Rd, and D-VRd cohorts).
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the following MedDRA PTs: Coombs indirect test positive, Laboratory test interference, Crossmatch incompatible, Blood type incompatibility, Haemolytic transfusion reaction; the subject is counted only once regardless of the number of events or the number of occurrences.
[d] Includes outcome of 'chronic/stable'.
[e] Includes outcome of 'recovering/resolving'.
[f] Odds Ratio is for event comparison of Daratumumab versus Comparator stratified by trial.
[g] Due to the rerandomization in MMY3006, subjects may be counted in both columns.
Note: Adverse Events were coded using MedDRA Version 26.0.
Note: The denominators are total number of subjects in each group.
Note: Additionally treatment emergent adverse events in MMY3006 reported to be related to study drug by the investigator are summarized in the Daratumumab column.
Key: D-Vd = daratumumab-bortezomib-dexamethasone; D-VTd = daratumumab-bortezomib-thalidomide-dexamethasone; D-VMP = daratumumab-bortezomib-melphalan-prednisone; D-Pd = daratumumab-pomalidomide-dexamethasone; D-Rd = daratumumab-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; NE-=not evaluable.

[TSFAE01B_DVRD.RTF] [PROD/JNJ-54767414/Z_RMP/DBR_MMY_DVRD_SMM_2024/RE_MMY_DVRD_SMM_2024/TSFAE01B_DVRD.SAS] 10JUL2024, 14:14

As shown in the table below, there were no adverse events of interference for blood typing for the SMM indication (Trials SMM2001 and SMM3001).

Important identified risk – Interference for blood typing (minor antigen) (positive indirect Coombs' test): Frequency, Seriousness, Outcomes and Severity; Indication: Smouldering Multiple Myeloma; All Clinical Trials of Safety Population

	Randomized Trial with Controls[a]		Trial without non-Dara Control[b]	All Clinical Trials
	Daratumumab	Comparator	Daratumumab	Daratumumab
Smouldering Multiple Myeloma				
Number of subjects treated	193	196	122	315
Frequency[c]	0	0	0	0
Odds Ratio (95% CI)[f]	NE			
Seriousness	0	0	0	0
Outcomes				
Resulted in death	0	0	0	0
Not recovered/Not Resolved	0	0	0	0
Recovered with sequelae[d]	0	0	0	0
Recovered/Resolved	0	0	0	0

Important identified risk – Interference for blood typing (minor antigen) (positive indirect Coombs' test): Frequency, Seriousness, Outcomes and Severity; Indication: Smouldering Multiple Myeloma; All Clinical Trials of Safety Population

	Randomized Trial with Controls[a]		Trial without non-Dara Control[b]	All Clinical Trials
	Daratumumab	Comparator	Daratumumab	Daratumumab
Unknown[e]	0	0	0	0
Severity (toxicity grade)				
Worst Grade=1	0	0	0	0
Worst Grade=2	0	0	0	0
Worst Grade=3	0	0	0	0
Worst Grade=4	0	0	0	0
Worst Grade=5	0	0	0	0
Missing	0	0	0	0

[a] Includes trial SMM3001.
[b] Includes trial SMM2001.
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the following MedDRA PTs: Coombs indirect test positive, Laboratory test interference, Crossmatch incompatible, Blood type incompatibility, Haemolytic transfusion reaction; the subject is counted only once regardless of the number of events or the number of occurrences.
[d] Includes outcome of 'chronic/stable'.
[e] Includes outcome of 'recovering/resolving'.
[f] Odds Ratio is for event comparison of Daratumumab versus Comparator.
Note: Adverse Events were coded using MedDRA Version 26.0.
Note: The denominators are total number of subjects in each group.

[TSFAE01_SMM.RTF] [PROD/JNJ-54767414/Z_RMP/DBR_MMY_DVRD_SMM_2024/RE_MMY_DVRD_SMM_2024/TSFAE01_SMM.SAS] 13AUG2024, 15:31

As shown in the table below, there were no adverse events of interference for blood typing for the AL amyloidosis indication (Trial AMY3001).

Important identified risk – Interference for blood typing (minor antigen) (positive indirect Coombs' test); Indication: AL Amyloidosis

	AMY3001			
	Daratumumab	**Comparator**	**Not randomized Run-in subjects**	**Total Daratumumab**
AL Amyloidosis				
Number of subjects treated	193	188	28	221
Frequency [a]	0	0	0	0
Odds Ratio (95% CI) [b]	NE			
Seriousness	0	0	0	0
Outcomes				
Resulted in death	0	0	0	0
Not recovered/Not resolved	0	0	0	0
Recovered with sequelae [c]	0	0	0	0
Recovered/Resolved	0	0	0	0
Unknown [d]	0	0	0	0

Important identified risk – Interference for blood typing (minor antigen) (positive indirect Coombs' test); Indication: AL Amyloidosis

	AMY3001			
	Daratumumab	Comparator	Not randomized Run-in subjects	Total Daratumumab
Severity (toxicity Grade)				
Worst grade=1	0	0	0	0
Worst grade=2	0	0	0	0
Worst grade=3	0	0	0	0
Worst grade=4	0	0	0	0
Worst grade=5	0	0	0	0
Missing	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that coded to the following MedDRA PTs: Coombs indirect test positive, Crossmatch incompatible, Laboratory test interference, Blood type incompatibility, Haemolytic transfusion reaction; a subject is counted only once regardless of the number of events or the number of occurrences.

[b] Odds Ratio is for event comparison of daratumumab versus comparator.

[c] Includes outcome of 'chronic/stable'.

[d] Includes outcome of 'recovering/resolving'.

Note: Adverse events were coded using MedDRA version 26.0.

Note: The denominators are total number of subjects in each group.

Key: CI = confidence interval; NE = not evaluable; PT = preferred term.

[TSFAE01A_AMY.RTF] [PROD/JNJ-54767414/Z_RMP/DBR_MMY_DVRD_SMM_2024/RE_MMY_DVRD_SMM_2024/TSFAE01A_AMY.SAS] 08AUG2024, 09:32

Daratumumab has high possibility to interfere with blood bank comparability. However, it did not impact the determination of ABO and Rh blood type. Only minor RBC antigens were impacted. Daratumumab mediated positive indirect Coombs' test may persist for up to 6 months after the last administration of daratumumab. Lack of RBC phenotyping prior to daratumumab treatment could result in delaying transfusion due to the need to address false positive indirect Coombs' tests. In the case of urgent transfusion, using non-cross-matched ABO/RhD-compatible RBC could result in a small risk of transfusion related hemolysis. No RBC transfusion-related events associated with interference for blood typing were reported during any of the clinical trials. Overall, it is not believed that this risk will have an impact on patient's quality of life.

Review of postmarketing data for this important identified risk of interference for blood typing was consistent with findings in the clinical trials database.

Risk Factors and Risk Groups:

Patients with multiple myeloma, SMM, and AL amyloidosis could potentially require blood testing for blood type and cross-match for severe anemia, which is a common complication of these diseases and their treatment.

Preventability:

Educational materials are distributed to HCPs who prescribe or dispense daratumumab and to blood banks and Patient Alert Cards are distributed to patients to increase awareness about the risk of interference for blood typing and how to minimize it.

Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping or genotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.

Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs (see SmPC Section 4.5).

In case of urgent need for transfusion, uncross-matched, ABO/Rh compatible RBC units should be administered as per local blood bank practice. In the event of a planned transfusion, notify blood transfusion centers of this interference with blood antigen typing.

Impact on the Risk-benefit Balance of the Product:

Given that no clinically significant hemolysis associated with RBC transfusions have been observed in clinical trials or postmarketing experience, the impact on the risk-benefit balance is deemed to be limited.

Public Health Impact:

Interference with blood typing (minor antigens) was included in the SmPC Section 4.4. Daratumumab is administered IV or SC to the limited disease population by trained medical staff. All usage is well controlled by health professional. No impact to public health is anticipated.

Annex 1 MedDRA Term:

Preferred Term (PT): Crossmatch incompatible.

Important identified risk – Hepatitis B virus reactivation

Potential Mechanisms:

The daratumumab patient population is immunosuppressed and at increased risk of infections due to underlying malignancy, in some cases also due to bone marrow transplantation, and the concurrent use of immunosuppressive agents (dexamethasone, chemotherapy). Neutropenia and depletion of natural killer cells associated with daratumumab may also contribute to the risk of infection.

Evidence Source(s) and Strength of Evidence:

Randomized controlled trials investigating daratumumab for the treatment of multiple myeloma, either as monotherapy or in combination with standard therapy, have reported an increased incidence of certain infections in association with daratumumab. Hepatitis B virus (HBV) reactivation has been observed in daratumumab clinical trials and in the postmarketing setting.

Characterization of the Risk:

Important identified risk – Hepatitis B virus reactivation: Frequency, Seriousness, Outcomes and Severity; Indication: Multiple Myeloma; All Clinical Trials of Safety Population

	Randomized Trials with Controls[a]			Trials without non-Dara Control[b]	All Clinical Trials
	Daratumumab[g]	Comparator[g]	Safety Run-In	Daratumumab	Daratumumab
Multiple Myeloma					
Number of subjects treated	2,779	2,797	16	1,205	4,000
Frequency[c]	9 (0.3%)	5 (0.2%)	0	5 (0.4%)	14 (0.4%)
Odds Ratio (95% CI)[f]	1.80 (0.60,5.39)				
Seriousness	0	1 (<0.1%)	0	2 (0.2%)	2 (0.1%)
Outcomes					
Resulted in death	0	0	0	1 (0.1%)	1 (<0.1%)
Not recovered/Not Resolved	1 (<0.1%)	1 (<0.1%)	0	2 (0.2%)	3 (0.1%)
Recovered with sequelae[d]	0	0	0	0	0
Recovered/Resolved	8 (0.3%)	4 (0.1%)	0	2 (0.2%)	10 (0.3%)
Unknown[e]	0	0	0	0	0

Important identified risk – Hepatitis B virus reactivation: Frequency, Seriousness, Outcomes and Severity; Indication: Multiple Myeloma; All Clinical Trials of Safety Population

	Randomized Trials with Controls[a]			Trials without non-Dara Control[b]	All Clinical Trials
	Daratumumab[g]	Comparator[g]	Safety Run-In	Daratumumab	Daratumumab
Severity (toxicity grade)					
Worst Grade=1	2 (0.1%)	2 (0.1%)	0	1 (0.1%)	3 (0.1%)
Worst Grade=2	6 (0.2%)	2 (0.1%)	0	2 (0.2%)	8 (0.2%)
Worst Grade=3	1 (<0.1%)	1 (<0.1%)	0	1 (0.1%)	2 (0.1%)
Worst Grade=4	0	0	0	0	0
Worst Grade=5	0	0	0	1 (0.1%)	1 (<0.1%)
Missing	0	0	0	0	0

[a] Includes trials MMY2004, MMY3003, MMY3004, MMY3006 Parts 1 and 2, MMY3007, MMY3008, MMY3013, MMY3014, and MMY3019.
[b] Includes trials MMY1001 (D-Vd, D-VTd, D-VMP, and D-Pd cohorts), MMY1002, MMY2002, GEN501, GEN503, MMY3012, MMY1004 Parts 2 and 3, MMY1008, and MMY2040 (D-VMP, D-Rd, and D-VRd cohorts).
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the following MedDRA PTs: Hepatitis viral, Acute hepatitis B, Hepatitis B, Hepatitis B reactivation, Chronic hepatitis B, Hepatitis B DNA assay positive, Hepatitis B DNA increased; the subject is counted only once regardless of the number of events or the number of occurrences.
[d] Includes outcome of 'chronic/stable'.
[e] Includes outcome of 'recovering/resolving'.
[f] Odds Ratio is for event comparison of Daratumumab versus Comparator stratified by trial.
[g] Due to the rerandomization in MMY3006, subjects may be counted in both columns.
Note: Adverse Events were coded using MedDRA Version 26.0.
Note: The denominators are total number of subjects in each group.
Note: Additionally treatment emergent adverse events in MMY3006 reported to be related to study drug by the investigator are summarized in the Daratumumab column.
Key: D-Vd = daratumumab-bortezomib-dexamethasone; D-VTd = daratumumab-bortezomib-thalidomide-dexamethasone; D-VMP = daratumumab-bortezomib-melphalan-prednisone; D-Pd = daratumumab-pomalidomide-dexamethasone; D-Rd = daratumumab-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; NE-=not evaluable.

[TSFAE02B_DVRD.RTF] [PROD/JNJ-54767414/Z_RMP/DBR_MMY_DVRD_SMM_2024/RE_MMY_DVRD_SMM_2024/TSFAE02B_DVRD.SAS] 10JUL2024, 14:15

As shown in the table below, there were no adverse events of HBV reactivation for the SMM indication (Trials SMM2001 and SMM3001).

Important identified risk – Hepatitis B virus reactivation: Frequency, Seriousness, Outcomes and Severity; Indication: Smouldering Multiple Myeloma; All Clinical Trials of Safety Population

	Randomized Trial with Controls[a]		Trial without non-Dara Control[b]	All Clinical Trials
	Daratumumab	Comparator	Daratumumab	Daratumumab
Smouldering Multiple Myeloma				
Number of subjects treated	193	196	122	315
Frequency[c]	0	0	0	0
Odds Ratio (95% CI)[f]	NE			
Seriousness	0	0	0	0
Outcomes				
Resulted in death	0	0	0	0
Not recovered/Not Resolved	0	0	0	0
Recovered with sequelae[d]	0	0	0	0
Recovered/Resolved	0	0	0	0
Unknown[e]	0	0	0	0

Important identified risk – Hepatitis B virus reactivation: Frequency, Seriousness, Outcomes and Severity; Indication: Smouldering Multiple Myeloma; All Clinical Trials of Safety Population

	Randomized Trial with Controls[a]		Trial without non-Dara Control[b]	All Clinical Trials
	Daratumumab	Comparator	Daratumumab	Daratumumab
Severity (toxicity grade)				
Worst Grade=1	0	0	0	0
Worst Grade=2	0	0	0	0
Worst Grade=3	0	0	0	0
Worst Grade=4	0	0	0	0
Worst Grade=5	0	0	0	0
Missing	0	0	0	0

[a] Includes trial SMM3001.
[b] Includes trial SMM2001.
[c] Includes all subjects who had one or more occurrences of an adverse event that coded to the following MedDRA PTs: Hepatitis viral, Acute hepatitis B, Hepatitis B, Hepatitis B reactivation, Chronic hepatitis B, Hepatitis B DNA assay positive, Hepatitis B DNA increased; the subject is counted only once regardless of the number of events or the number of occurrences
[d] Includes outcome of 'chronic/stable'.
[e] Includes outcome of 'recovering/resolving'.
[f] Odds Ratio is for event comparison of Daratumumab versus Comparator.
Note: Adverse Events were coded using MedDRA Version 26.0.
Note: The denominators are total number of subjects in each group.

[TSFAE02_SMM.RTF] [PROD/JNJ-54767414/Z_RMP/DBR_MMY_DVRD_SMM_2024/RE_MMY_DVRD_SMM_2024/TSFAE02_SMM.SAS] 13AUG2024, 15:31

As shown in the table below, there were no adverse events of HBV reactivation for the AL amyloidosis indication (Trial AMY3001).

Important identified risk – Hepatitis B virus reactivation; Indication: AL Amyloidosis

	AMY3001			
	Daratumumab	**Comparator**	**Not randomized Run-in subjects**	**Total Daratumumab**
AL Amyloidosis				
Number of subjects treated	193	188	28	221
Frequency [a]	0	0	0	0
Odds Ratio (95% CI) [b]	NE			
Seriousness	0	0	0	0
Outcomes				
Resulted in death	0	0	0	0
Not recovered/Not resolved	0	0	0	0
Recovered with sequelae [c]	0	0	0	0
Recovered/Resolved	0	0	0	0
Unknown [d]	0	0	0	0

Important identified risk – Hepatitis B virus reactivation; Indication: AL Amyloidosis

	AMY3001			
	Daratumumab	Comparator	Not randomized Run-in subjects	Total Daratumumab
Severity (toxicity Grade)				
Worst grade=1	0	0	0	0
Worst grade=2	0	0	0	0
Worst grade=3	0	0	0	0
Worst grade=4	0	0	0	0
Worst grade=5	0	0	0	0
Missing	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that coded to the following MedDRA PTs: Hepatitis viral, Acute hepatitis B, Hepatitis B, Hepatitis B reactivation, Chronic hepatitis B, Hepatitis B DNA assay positive, Hepatitis B DNA increased; the subject is counted only once regardless of the number of events or the number of occurrences. [b] Odds Ratio is for event comparison of daratumumab versus comparator.

[c] Includes outcome of 'chronic/stable'.

[d] Includes outcome of 'recovering/resolving'.

Note: Adverse events were coded using MedDRA version 26.0.

Note: The denominators are total number of subjects in each group.

Key: CI = confidence interval; NE = not evaluable; PT = preferred term.

[TSFAE02A_AMY.RTF] [PROD/JNJ-54767414/Z_RMP/DBR_MMY_DVRD_SMM_2024/RE_MMY_DVRD_SMM_2024/TSFAE02A_AMY.SAS] 07AUG2024, 13:20

The clinical trial reporting frequency of HBV reactivation-related adverse events was uncommon.

In the single serious clinical trial case with a fatal outcome, acute hepatitis B was subsequently determined to be a reactivation of the chronic HBV infection. Given the time to onset, biological plausibility, and lack of other factors confounding the case assessment, HBV reactivation was assessed as related to daratumumab.

Of the 14 clinical trial cases of HBV reactivation in patients receiving daratumumab (all in patients with multiple myeloma), 2 were serious and 12 were nonserious. In addition to these 14 reported AEs of HBV reactivation, there are another 2 cases of HBV reactivation, one was reported in a cohort not included in the integrated data set (MMY1004 Part 1 that received a mix and deliver formulation of daratumumab and rHuPH20) and the other was not reported as an AE. There were no adverse events of HBV reactivation in SMM patients (Trials SMM2001 and SMM3001) and in AL amyloidosis patients (Trial AMY3001).

The impact of this risk on the individual patient can vary from minimal to potentially significant. Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during, and for at least 6 months following the end of daratumumab treatment. The risk needs to be carefully weighed against the benefit conferred by the use of this medication.

Reports of HBV reactivation have been received from postmarketing experience with daratumumab. Review of postmarketing data for this important identified risk is consistent with findings from clinical trials. No new safety information pertaining to this risk has emerged from post-marketing experience.

Risk Factors and Risk Groups:

Patients with evidence of positive HBV serology or with chronic HBV infection are at risk for developing HBV reactivation.

Preventability:

Hepatitis B virus (HBV) screening should be performed in all patients prior to the initiation of treatment with daratumumab. Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during, and for at least 6 months following the end of daratumumab treatment, and managed according to current clinical guidelines. In addition, consulting a hepatitis disease expert should be considered as clinically indicated.

In patients who develop reactivation of HBV while on daratumumab, treatment with daratumumab should be suspended and appropriate treatment should be instituted. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV (see SmPC Section 4.4).

Impact on the Risk-benefit Balance of the Product:

Given that there is limited incidence of HBV reactivation in clinical trials or postmarketing experience, the impact on the risk-benefit balance is deemed to be limited.

Public Health Impact:

Hepatitis B virus (HBV) reactivation is included in the SmPC Section 4.4. Daratumumab is administered IV or SC to the limited disease population by trained medical staff. All usage is well controlled by health professional. No impact to public health is anticipated.

Annex 1 MedDRA Term:

PT: Hepatitis B reactivation.

SVII.3.2. Presentation of the Missing Information

Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement
Evidence source: Patients with AL amyloidosis often present with cardiac involvement (i.e., AL amyloidosis-related cardiomyopathy) at baseline due to the underlying disease (Merlini 2018). There are no specific data available for use of daratumumab in AL amyloidosis patients who have the most clinically significant cardiac disease such as NYHA Class IIIB and IV cardiac disease, as these patients were excluded from Study AMY3001, and there are limited data in patients with Cardiac Stage IIIB disease (based on European Modification of Mayo 2004 Cardiac Stage). Patients with pre-existing cardiac involvement were included in Study AMY3001 as the study enrolled patients who had Cardiac Stage I-IIIA (based on the Mayo 2004 classification) and NYHA Class I-IIIA disease, however, additional information with regards to safety in patients with AL amyloidosis who have pre-existing serious cardiac involvement is required.
Population in need of further characterization: AL amyloidosis patients with pre-existing serious cardiac involvement. The treating physician would be expected to weigh the benefit and risks for each individual patient.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
	Hepatitis B virus reactivation
Important potential risks	None
Missing information	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement

PART III: PHARMACOVIGILANCE PLAN (Including Post-authorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific follow-up questionnaires for safety concerns	
Safety Concern	**Purpose/Description**
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Targeted follow-up questionnaire to collect additional information concerning adverse events associated with interference and transfusion reactions.

Other forms of routine pharmacovigilance activities		
Activity	**Objective/Description**	**Milestones**
Not applicable.		

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Study name and title	A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis.
Rationale and study objectives:	Safety concern addressed: Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement This is a study in AL amyloidosis patients to assess all serious cardiovascular adverse events on study treatment, all deaths on study treatment, and the risk factors for cardiac toxicity in patients treated with daratumumab subcutaneous. Study objective: The primary objective of the study is to further characterize cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome.
Study design	Multicenter prospective study. The data collected for AL amyloidosis is to include, but may not be limited to: demographic data; baseline disease characteristics including cardiac parameters as appropriate to determine cardiac risk status; treatment regimen and dosing; hematologic response as per standard of care; serious adverse events with a focus on major cardiac events including non-fatal myocardial infarction, cardiac failure, arrhythmia, as well as fatal cardiac events and events of sudden death. Management and outcome of major cardiac events, including hospitalizations, are to be analyzed. Data collection is to be considered complete for a participating patient if data are available for 2 years following initiation of daratumumab therapy (or until initiation of subsequent treatment, withdrawal of consent, death, or loss to follow-up).

Additional Pharmacovigilance Activities		
	Study duration: The overall duration of the study, including recruitment and follow-up, is anticipated to be approximately 5 years.	
Study population	Patients with light chain amyloidosis who initiate subcutaneous daratumumab based therapy within 90 days prior to study enrollment. At least 100 patients are to be recruited across multiple sites in the US and other countries.	
Milestones	Draft Protocol:	Aug 2021
	Trial completion:	3rd Quarter 2025
	Interim report submission:	2nd Quarter 2024
	Final report submission:	1st Quarter 2026

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis. Ongoing	Primary objective is to further characterize cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome.	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Draft Protocol: Interim report: Final report:	Aug 2021 2nd Quarter 2024 1st Quarter 2026

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Post-Authorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
54767414AMY3001 A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared with CyBorD in Newly Diagnosed Systemic AL Amyloidosis Ongoing	To further evaluate the efficacy of subcutaneous daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis	The initial efficacy assessment for Study AMY3001 was based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions.	Submission of the final overall survival (OS) analysis	Q3 2025
Efficacy studies which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
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 Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Routine risk communication: • SmPC Section 4.4; • SmPC Section 4.5 and PL Section 2. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that patients should be typed and screened, and phenotyping or genotyping may be considered prior to starting daratumumab treatment as described in SmPC Section 4.4; • Advise HCPs that in the event of a planned transfusion, blood transfusion centers should be notified of this interference with indirect antiglobulin tests as described in SmPC Section 4.4; • Recommendation that if an emergency transfusion is required, non-cross-matched ABO/RhD compatible RBCs can be given per local blood bank practices as described in SmPC Section 4.4; • Recommendation to mitigate daratumumab interference by treating reagent RBCs with DTT to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs as described in SmPC Section 4.5; • Instruction to patients who need a blood transfusion to inform the person doing the blood test to match blood type that they are receiving treatment with daratumumab as described in PL Section 2. Other routine risk minimization measures beyond the Product Information: • None.
Hepatitis B virus reactivation	Routine risk communication: • SmPC Section 4.4; • SmPC Section 4.8; • PL Sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk:

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
	• Recommendation that HBV screening should be performed before initiation of treatment with daratumumab as described in SmPC Section 4.4 and PL Section 2; • Recommendation to monitor for clinical and laboratory signs of HBV reactivation during, and for at least 6 months following the end of daratumumab treatment for patients with evidence of positive HBV serology as described in SmPC Section 4.4 and PL Section 2; • Recommendation to manage patients according to current clinical guidelines, and to consider consulting a hepatitis disease expert as clinically indicated as described in SmPC Section 4.4; • Recommendation to suspend treatment with daratumumab and to institute appropriate treatment in patients who develop reactivation of HBV while on daratumumab. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV as described in SmPC Section 4.4; • Warning to patients with history or current HBV infection as described in PL Section 2. Other routine risk minimization measures beyond the Product Information: • None.
Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Routine risk communication: • SmPC Section 5.1. Routine risk minimization activities recommending specific clinical measures to address the risk: • None. Other routine risk minimization measures beyond the Product Information: • None.

Key: AL amyloidosis = light chain amyloidosis; HBV = hepatitis B virus; DTT = dithiothreitol; HCP = healthcare professional; PL = package leaflet; RBC = red blood cell; SmPC = Summary of Product Characteristics.

V.2. Additional Risk Minimization Measures

Additional Risk Minimization Activity 1

Additional Risk Minimization Activity 1: Educational Materials for Health Care Professionals and Patient Alert Cards	
Objectives:	Educational materials distributed to HCPs and blood banks and Patient Alert Cards distributed to patients, aiming at increasing awareness about the important identified risk of Interference for blood typing (minor antigen) (positive indirect Coombs' test) and providing guidance on how to manage it.
Rationale for the additional risk minimization activity:	Educational materials intended to increase awareness of the daratumumab profile and the risks associated with daratumumab induced 'false positive' results in the indirect Coombs' test including: • Guide for Health Care Professionals and Blood Bank Personnel, to advise of the risk of interference with blood typing and how to minimize it; • Patient Alert Card.
Target audience and planned distribution path:	Healthcare professionals (HCPs) who prescribe or dispense daratumumab Blood banks Patient Alert Cards that include prescriber contact details and reference to the need to consult the package leaflet (PL)
Plans to evaluate the effectiveness of the interventions and criteria for success:	Reports of interference of blood typing are evaluated during postmarketing surveillance. Criteria for success includes: • Decreased or stable frequency of adverse event reports as a result of interference of blood typing; • Decreased or stable reporting trend analysis of postmarketing safety data of interference of blood typing.

Additional Risk Minimization Activity 2: Direct Healthcare Professional Communication (DHPC) The DHPC was distributed in the European Union in June 2019.	
Objectives:	To address the important identified risk of Hepatitis B virus reactivation.
Rationale for the additional risk minimization activity:	To increase awareness of HCPs to the possible risk of HBV reactivation and to provide guidance for risk mitigation.

Additional Risk Minimization Activity 2: Direct Healthcare Professional Communication (DHPC) The DHPC was distributed in the European Union in June 2019.	
Target audience and planned distribution path:	HCPs who prescribe daratumumab.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Reporting trend analyses from postmarketing safety data are to be monitored in the PSUR. Assessments are to be done at the end of each PSUR reporting interval. Stable reporting trend analysis from postmarketing safety data is the criteria for success.

V.2.1. Removal of Additional Risk Minimization Activities

Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Routine risk minimization measures: • SmPC Section 4.4, which advises that patients should be typed and screened, and phenotyping or genotyping be considered prior to starting daratumumab treatment; • SmPC Sections 4.4, which advises HCPs to notify blood transfusion centers of this interference with indirect antiglobulin tests in the event of a planned transfusion; • SmPC Section 4.4, which recommend that if an emergency transfusion is required, non-cross-matched ABO/RhD compatible RBCs can be given per local blood bank practices; • SmPC Section 4.5, which recommend mitigating daratumumab interference by treating reagent RBCs with DTT to disrupt daratumumab binding or other locally validated methods, and that Kell negative units should be supplied after ruling out or identifying alloantibodies using DTT treated RBCs; • PL Section 2, which instructs patients to inform the person doing the blood test to match blood type that they are receiving treatment with daratumumab. Additional risk minimization measures: • Distribution of educational materials and Patient Alert Cards to HCPs and blood banks as described in the PL, in Annex II, D.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A guided targeted follow-up questionnaire to collect additional information concerning adverse events associated with interference and transfusion reactions. Additional pharmacovigilance activities: • None.

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hepatitis B virus reactivation	Routine risk minimization measures: • SmPC Section 4.8 and PL Section 4; • SmPC Section 4.4 and PL Section 2, which advise HBV screening before initiation of treatment with daratumumab and to monitor for clinical and laboratory signs of HBV reactivation during and for at least 6 months following the end of daratumumab treatment for patients with evidence of positive HBV serology; • SmPC Section 4.4, which advises to manage patients according to current clinical guidelines, and to consider consulting a hepatitis disease expert as clinically indicated; • SmPC Section 4.4, which advises to suspend treatment with daratumumab and to institute appropriate treatment in patients who develop reactivation of HBV while on daratumumab. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV; • PL Section 2, which includes a warning to patients with history or current HBV infection; Additional risk minimization measures: • Distribution of a DHPC to HCPs who prescribe daratumumab was issued in the EU member states in June 2019.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Routine risk minimization measures: • SmPC Section 5.1. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis. Final report by 1st Quarter 2026.

Key: AL amyloidosis = light chain amyloidosis; DHPC = Direct Healthcare Professional Communication; DTT = dithiothreitol; HBC = hepatitis B virus; HCP = healthcare professional; PL = package leaflet; RBC = red blood cell; SmPC = Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for DARZALEX

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

DARZALEX's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how DARZALEX should be used.

This summary of the RMP for DARZALEX should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 DARZALEX's RMP.

I. The Medicine and What it is Used For

DARZALEX 20 mg/mL concentrate for solution for infusion is authorized as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma. DARZALEX 20 mg/mL concentrate for solution for infusion is also indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma. DARZALEX 20 mg/mL concentrate for solution for infusion is also indicated in combination with bortezomib, melphalan, and prednisone, or lenalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) and in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for ASCT. Refer to the SmPC for the full indication. It contains daratumumab as the active substance and it is given by intravenous infusion.

DARZALEX 1,800 mg solution for injection is authorized as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma. DARZALEX 1,800 mg solution for injection is also indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma. DARZALEX 1,800 mg solution for injection is also indicated in combination with bortezomib, melphalan, and prednisone, or lenalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT), in combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for ASCT, and in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after

the last therapy in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor. DARZALEX 1,800 mg solution for injection is also indicated in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma. Refer to the SmPC for the full indication. It contains daratumumab as the active substance and it is given by subcutaneous injection.

DARZALEX 1,800 mg solution for injection is also authorized as monotherapy for the treatment of adult patients with smouldering multiple myeloma at high risk of developing multiple myeloma and in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

Further information about the evaluation of DARZALEX's benefits can be found in DARZALEX's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the product's EPAR summary landing page on the EMA webpage.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of DARZALEX, together with measures to minimize such risks and the proposed studies for learning more about DARZALEX'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 patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of DARZALEX, these measures are supplemented with an additional risk minimization measure mentioned under relevant important risks, below.

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. If important information that may affect the safe use of DARZALEX is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of DARZALEX 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 DARZALEX. 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	Interference for blood typing (minor antigen) (positive indirect Coombs' test) Hepatitis B virus reactivation
Important potential risks	None
Missing information	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement

II.B. Summary of Important Risks

Important identified risk: Interference for blood typing (minor antigen) (positive indirect Coombs' test)	
Evidence for linking the risk to the medicine	Daratumumab binds to red blood cells (RBCs) and interferes with compatibility testing, including antibody screening and cross-matching, which may persist for up to 6 months after the last administration of daratumumab. Events of relevance to interference for blood typing have occurred during clinical trials. The determination of a patient's blood group (type O, A, B, or AB) and Rh blood type are not impacted.
Risk factors and risk groups	Patients with multiple myeloma could potentially require blood testing for blood type and cross-match for severe anemia, which is a common complication of myeloma and its treatment.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, which advises that patients should be typed and screened, and phenotyping or genotyping be considered prior to starting daratumumab treatment; • SmPC Section 4.4, which advises healthcare professionals (HCPs) to notify blood transfusion centers of this interference with indirect antiglobulin tests in the event of a planned transfusion; • SmPC Section 4.4, which recommends that if an emergency transfusion is required, non-cross-matched ABO/RhD

Important identified risk: Interference for blood typing (minor antigen) (positive indirect Coombs' test)	
	compatible RBCs can be given per local blood bank practices; • SmPC Section 4.5, which recommends mitigating daratumumab interference by treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods, and that Kell negative units should be supplied after ruling out or identifying alloantibodies using DTT treated RBCs; • PL Section 2, which instructs patients to inform the person doing the blood test to match blood type that they are receiving treatment with daratumumab. Additional risk minimization measures: • Distribution of educational materials and Patient Alert Cards to HCPs and blood banks as described in PL Annex II, D.

Important identified risk: Hepatitis B virus reactivation	
Evidence for linking the risk to the medicine	Randomized controlled trials investigating daratumumab for the treatment of multiple myeloma, either as monotherapy or in combination with standard therapy, have reported an increased incidence of certain infections in association with daratumumab. Hepatitis B virus (HBV) reactivation has been observed in daratumumab clinical trials and in the postmarketing setting.
Risk factors and risk groups	Patients with evidence of positive HBV serology or with chronic HBV infection are at risk for developing HBV reactivation.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 and PL Section 4; • SmPC Section 4.4 and PL Section 2, which advise HBV screening before initiation of treatment with daratumumab and to monitor for clinical and laboratory signs of HBV reactivation during and for at least 6 months following the end of daratumumab treatment for patients with evidence of positive HBV serology; • SmPC Section 4.4, which advises to manage patients according to current clinical guidelines, and to consider consulting a hepatitis disease expert as clinically indicated;

Important identified risk: Hepatitis B virus reactivation	
	• SmPC Section 4.4, which advises to suspend treatment with daratumumab and to institute appropriate treatment in patients who develop reactivation of HBV while on daratumumab. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV; • PL Section 2, which includes a warning to patients with history or current HBV infection. Additional risk minimization measures: • Distribution of a Direct Healthcare Professional Communication to HCPs who prescribe daratumumab in the EU member states in June 2019.

Missing information: Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 5.1. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis. Final report by 1st Quarter 2026.

II.C. Post-authorization Development Plan

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

The following study is a condition of the marketing authorization for AL amyloidosis:

54767414AMY3001 - A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared with CyBorD in Newly Diagnosed Systemic AL Amyloidosis

Purpose of the study: The initial efficacy assessment for Study AMY3001 was based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions. The final overall survival (OS) analysis will be submitted by Q3 2025 to further evaluate the efficacy of subcutaneous daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

II.C.2. Other Studies in Post-authorization Development Plan

A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis.

Purpose of the study: This is a study in AL amyloidosis patients to assess all serious cardiovascular adverse events on study treatment, all deaths on study treatment, and the risk factors for cardiac toxicity in patients treated with daratumumab subcutaneous. The primary objective of the study is to further characterize cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome. This study addresses use in patients with AL amyloidosis who have pre-existing serious cardiac involvement.

PART VII: ANNEXES

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Annex 4: Specific Adverse Drug Reaction Follow-up Forms

The following questionnaires are utilized in conjunction with standard case follow-up procedures to obtain complete case information:

Follow-up Form - Interference for blood typing (minor antigen) and hemolytic transfusion reactions

Daratumumab (Darzalex®) Targeted Follow-Up Questionnaire (TFUQ) for Interference for Blood Typing (Minor Antigens) and Haemolytic Transfusion Reactions

To the Health Care Provider: Complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number: Date of Report: [dd-MMM-yyyy]

1. **Co-Suspect Medications** *(Pay particular attention to drugs that are known to cause drug induced haemolytic anaemia.)*

☐ Cephalosporins	☐ Nitrofurantoin
☐ Dapsone	☐ NSAIDs
☐ Levodopa	☐ Penicillin
☐ Methyldopa	☐ Phenazopyridine
☐ Quinidine	☐ Other (Specify):

2. **Medical History and Concurrent Conditions**

Drug Screen: ☐ In Urine ☐ In Blood ☐ Negative ☐ Positive

(If positive, for which substances?):

Other Medical History:

☐ Autoimmune haemolytic anaemia ☐ Recent history of incompatible blood match
☐ Previous transfusion reaction

3. **Adverse Event Description**

Time from initiation of **Daratumumab (Darzalex®)** to event:
If patient experienced signs and symptoms specify below (*Check all that apply and provide details.*):

☐ Fever	☐ Flushing	☐ Hypotension	☐ Anaemia
☐ Chills	☐ Red urine	☐ Severe shortness of breath	☐ Shock
☐ DIC	☐ Renal Failure	☐ Jaundice	

4. **Relevant Results of Diagnostic Tests Including Laboratory Tests, Imaging, Biopsies, etc.** *(Note positive/negative, and date performed.)*

☐ Lab data including Haemoglobin, Total Bilirubin, Indirect Bilirubin, Clotting studies, Renal function tests, Brain Natriuretic Peptide:
☐ Indirect Antiglobulin test:
☐ Direct Antiglobulin test:
☐ Results of retyping of donor and recipient red blood cells:
☐ Urine analysis:

MCN:

5. Treatment and Outcome

Associated, or any preceding relevant, treatment emergent adverse events:

Annex 6: Details of Proposed Additional Risk Minimization Measures

Additional Risk Minimization Measure 1

Important Risk Minimization Information for Healthcare Professionals, Blood Bank Professionals and Patients Regarding Interference of Blood Typing

Educational Brochure and Patient Alert Card

Additional risk minimization measures for specially defined products risks are considered appropriate to increase daratumumab's safe and effective use for patients diagnosed with multiple myeloma and for patients diagnosed with AL amyloidosis. This information brochure and patient alert card on the use of daratumumab was created to minimize the risk of interference of blood typing (minor antigen) and therefore prevent blood transfusion delays in routine clinical practice or emergency situations.

1. Invented name, active substance(s) and therapeutic class

Daratumumab is a first-in-class, human IgG1 monoclonal antibody (mAb) that binds to CD38 expressing malignant cells with high affinity, inducing tumor cell death through diverse mechanisms of immune-mediated actions (complement dependent cytotoxicity [CDC], antibody dependent cell-mediated cytotoxicity [ADCC], antibody-dependent cell phagocytosis [ADCP]) as well as induction of apoptosis and modulation of CD38 enzyme activities.

2. Rationale for the additional risk minimization measure

Prescribers and patients are referred to the local label for detailed information on the safety and known risks of daratumumab. Nevertheless, additional risk minimization measures for the interference of blood typing (minor antigens) are considered appropriate to increase awareness of daratumumab safety profile.

To meet this objective, the MAH (Janssen-Cilag international NV) developed a brochure and a patient alert card as educational tools for all potential prescribers (ie, HCPs), blood bank professionals, and patients. These educational tools will inform about the risks associated with the interference of daratumumab and blood compatibility (minor antigen) testing and provide guidance for risk management activities.

<u>Specified/detailed rationale and objective for additional risk minimization measures for daratumumab</u>

CD38 is expressed at low levels on RBCs. Daratumumab in the patient's serum binds to reagent or donor RBCs in an indirect antigen testing (IAT), resulting in pan-agglutination, and masking the presence of antibodies to minor antigens. If steps are not taken to mitigate daratumumab interference, delays in the release of blood products for transfusion may occur.

Therefore, the educational materials are intended to inform HCPs, blood banks and patients regarding appropriate monitoring, assessment and management of interference of blood typing.

3. Educational Program Tools

The educational material is focused on the following additional risk minimization measures:

- Education on the interference of daratumumab with minor antigen blood typing, ie, the indirect Coombs' test or IAT.
- Mitigation strategies to allow safe and efficient blood typing and blood transfusion
  - Treatment of RBCs with DTT;
  - Genotyping.
- Intended audience to be addressed
  - The additional risk minimization measures relevant for daratumumab therapy are intended toward HCPs who prescribe and administer, blood banks involved with blood typing and patients receiving daratumumab.
- Communication dates and channels
  - The educational material defined for risk minimization activities in scope of Annex 6 will be implemented by the Local Operating Companies and made available to HCPs and blood banks by printed matter and/or digital methods. HCPs will be provided with an initial packet of Patient Alert Card that is to be handed out to patients. Additional packets can be re-ordered by the HCP via standard medical response system at any time.

4. Content of educational materials - messages

HCP

- Inform that daratumumab interferences with blood bank compatibility testing
- Inform HCPs to communicate to blood banks that their patient is on daratumumab
- Inform HCPs that daratumumab will not impact ABO/Rh blood typing and only impacts cross match in the laboratory assay. The blood banks are aware of this risk and will provide the blood to meet the patient requirement of blood transfusion.
- Inform interference can last for up to 6 months after last infusion of daratumumab
- Highlight consequences (transfusion delays, incompatible donor match)
- Inform your patient about the blood typing issue

Blood Banks

- Inform that daratumumab interferences with blood bank compatibility testing
- A solution to help blood banks is available (eg, providing ABO/RhD compatible, genotypically matched units and DTT assay)
- Inform that in urgent cases, uncrossmatched, ABO/RhD compatible RBC units should be administered

Patients

- Inform patients that daratumumab will not impact ABO/Rh blood typing and only impacts cross match of laboratory testing which is needed before blood transfusion
- Inform patients that the blood bank is aware of how to provide the appropriate matched blood for their transfusion. They need to present the card to the HCPs and they will communicate this with blood banks.

These educational materials included as additional risk minimization activities within the RMP should be implemented by Local Operating Companies. If necessary, where mandated by local competent authorities, additional materials may be requested.

Additional Risk Minimization Measure 2

Direct Healthcare Professional Communication (DHPC) (was distributed in the European Union in June 2019)

Key Messages of the Additional Risk Minimization Measures

The proposed Direct Healthcare Professional Communication (DHPC) addresses the important identified risk 'hepatitis B virus reactivation.'

The specific objective is to increase awareness of healthcare professionals (HCPs) to the possible risk of hepatitis B virus (HBV) reactivation and guidance for risk mitigation.

Content of the DHPC – Messages for the HCP

- Inform that HBV reactivation, including some fatal cases, has been reported in patients treated with daratumumab;
- Inform that all patients should be screened for HBV before initiation of daratumumab treatment and that patients already under daratumumab treatment and for which HBV serology is unknown should be tested for HBV serology;
- Inform that patients with positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during treatment, and for at least 6 months following the end of daratumumab treatment, and to consult experts in the treatment of hepatitis B, as necessary;
- Inform that daratumumab treatment should be stopped in patients with HBV reactivation, and to consult experts in the treatment of HBV infection;
- Inform that resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV;
- Provide background information related to the reported HBV reactivation cases.