European Union Risk Management Plan
Talquetamab

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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	2.1
Rationale for submitting an updated RMP (if applicable)	To change the milestone due date of the Additional Pharmacovigilance Activity (64407564MMY1001).
Summary of significant changes in this RMP:	The milestone due date of the 64407564MMY1001 Updated Safety Report was changed from Q3 2024 to Q2 2025.

Other RMP Versions Under Evaluation:

RMP Version Number	**Submitted on**	**Procedure Number**
Not Applicable		

Details of the Currently Approved RMP:

Version number of last agreed RMP:	1.5
Approved within procedure	EMEA/H/C/005864/0000
Date of approval (Competent authority opinion date)	21 August 2023 (EC Decision)

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Talquetamab
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorization Applicant	Janssen-Cilag International N.V.
Medicinal products to which the RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Not applicable
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: a humanized immunoglobulin g4-proline, alanine, alanine (IgG4-PAA) bispecific antibody
	Summary of mode of action: Talquetamab is a IgG4-PAA bispecific antibody directed against G protein-coupled receptor family C group 5 member D (GPRC5D) and the CD3 receptors on T cells. Talquetamab promotes enhanced T cell-mediated cytotoxicity through recruitment of CD3-expressing T cells to GPRC5D-expressing cells. This leads to the activation of T cells and induces subsequent lysis of GPRC5D-expressing cells mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells. Based on the expression of GPRC5D on plasma cells, with minimal to no expression detected on B cells and B cell precursors, talquetamab targets multiple myeloma cells particularly.
	Important information about its composition: Talquetamab is a humanized IgG4-PAA bispecific antibody produced in Chinese hamster ovary cells by recombinant DNA technology.
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics (SmPC); Package Leaflet (PL)
Indication(s) in the EEA	Current: Talquetamab is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.
	Proposed: Not applicable

<table>
<tr><td>Dosage in the EEA</td><td colspan="2">Current:

Talquetamab should be administered subcutaneously on a weekly or biweekly (every 2 weeks) dosing schedule, as shown below. Patients who receive talquetamab according to the 0.4 mg/kg weekly dosing schedule and have attained an adequate clinical response that is confirmed in at least 2 consecutive disease assessments can be considered for switch to the 0.8 mg/kg biweekly dosing schedule.
<table>
<tr><th>Dosing Schedule</th><th>Phase</th><th>Day</th><th>Talquetamab dose[a]</th></tr>
<tr><td rowspan="4">Weekly dosing schedule</td><td rowspan="3">Step-up phase</td><td>Day 1</td><td>0.01 mg/kg</td></tr>
<tr><td>Day 3[b]</td><td>0.06 mg/kg</td></tr>
<tr><td>Day 5[b]</td><td>0.4 mg/kg</td></tr>
<tr><td>Treatment phase</td><td>Once a week thereafter[c]</td><td>0.4 mg/kg</td></tr>
<tr><td rowspan="5">Biweekly (every 2 weeks) dosing schedule</td><td rowspan="4">Step-up phase</td><td>Day 1</td><td>0.01 mg/kg</td></tr>
<tr><td>Day 3[b]</td><td>0.06 mg/kg</td></tr>
<tr><td>Day 5[b]</td><td>0.4 mg/kg</td></tr>
<tr><td>Day 7[b]</td><td>0.8 mg/kg</td></tr>
<tr><td>Treatment phase</td><td>Once every 2 weeks thereafter[c]</td><td>0.8 mg/kg</td></tr>
</table>
[a] Based on actual body weight and administered subcutaneously.
[b] Dose may be administered between 2 to 4 days after the previous dose and may be given up to 7 days after the previous dose to allow for resolution of adverse reactions.
[c] Maintain a minimum of 6 days between weekly doses and a minimum of 12 days between biweekly (every 2 weeks) doses.</td></tr>
<tr><td></td><td colspan="2">Proposed: Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td colspan="2">Current: Talquetamab is available as a solution for injection and is provided in a 1.5 mL-vial containing 3 mg of talquetamab (2 mg/mL) or a 1 mL-vial containing 40 mg of talquetamab (40 mg/mL).</td></tr>
<tr><td></td><td colspan="2">Proposed: Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>☑ Yes</td><td>☐ No</td></tr>
</table>

PART II: SAFETY SPECIFICATION

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

Indication(s)

Multiple myeloma is a rare, 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 2021). The disease is considered incurable (Rajkumar 2020).

Incidence:

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 EU (27 countries), the 2020 crude incidence rate was 8.0 cases per 100,000 persons, and the European population age-adjusted incidence rate was 7.5 cases per 100,000 persons (ECIS 2021). The estimated number of new cases for the EU overall was 35,842. Similarly, the annual age-adjusted incidence rate was 7.1 per 100,000 in the UK with 4,650 cases (HMRN 2022). In general, Western Europe had the highest incidence rates of multiple myeloma, with a crude incidence rate of 9.2 per 100,000 persons (ECIS 2021). Crude incidence rates ranged from 2.5 per 100,000 persons in Bulgaria to 10.3 per 100,000 persons in France.

Prevalence:

Worldwide, the estimated 5-year prevalence in 2020 was approximately 450,579 patients (Ferlay 2020). In Europe, the 5-year prevalence count of multiple myeloma was 138,083 persons. Estimates for 10-year or total prevalence count and proportions of multiple myeloma are available from select European countries with longer data collection, as shown in Table SI.1. The prevalence data for France, Germany, Italy, and Spain are estimated for 2022 using 10 years of collected or projected data, as described by Kantar Health's Cancer MPact® program methods. The UK 10-year prevalence and Nordic countries' total prevalence comes from their respective cancer registry estimates in 2016.

Table SI.1 10-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	2022	10-year	24,076	3.7	CancerMPact® 2022
Germany	2022	10-year	32,755	3.9	CancerMPact® 2022
Italy	2022	10-year	24,426	4.0	CancerMPact® 2022
Spain	2022	10-year	12,000	2.6	CancerMPact® 2022
United Kingdom	2019	10-year	21,790	3.2	HMRN 2022
Denmark	2016	Total	2,407	4.2	Danckert 2019
Finland	2016	Total	1,755	3.2	Danckert 2019
Iceland	2016	Total	130	3.8	Danckert 2019
Norway	2016	Total	2,050	3.9	Danckert 2019
Sweden	2016	Total	3,680	3.6	Danckert 2019

The prevalence of multiple myeloma has increased in the past few decades due to better diagnostic techniques and improved patient survival, owing to widespread use of autologous hematopoietic stem cell transplantation and the development of novel therapeutic agents (Turesson 2018).

Demographics of the Population in the Proposed 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 to 71 years (SEER 2021; Palumbo 2011). 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).

Gender: The incidence of multiple myeloma is approximately 1.5 times higher in men than women (Blimark 2018). 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 2020, the incidence rates are 9.2 per 100,000 in men versus 6.9 per 100,000 in women (ECIS 2022).

Racial and ethnic origin: The incidence of multiple myeloma is 2 times higher in Black individuals than in White individuals but is lower in Asian and Hispanic individuals versus White persons (SEER*Explorer 2021). In the US, the average incidence rate from 2014 to 2018 was 13.8 per 100,000 for Blacks and 6.5 per 100,000 persons for Whites (SEER 2021). Evidence from US studies suggests that the racial disparity may be influenced by differences in risk factors for MGUS and transformation of MGUS to multiple myeloma between Black and White patients (Marinac 2020).

Other risk factors for multiple myeloma: Although there is a notably higher risk of multiple myeloma in older adults, men, and Black individuals, there is limited evidence on the underlying social, biological, or genetic factors increasing the risk of multiple myeloma in these populations. In a large case-control study, the odds of multiple myeloma were elevated in patients whose relatives had any hematologic malignancy versus none (odds ratio 1.89; 95% CI: 1.25, 2.86), suggesting that family history of hematologic malignancies is a potential predictor of disease (VanValkenburg 2016). Other potential risk factors for developing multiple myeloma include being overweight or obese, having workplace exposure to chemicals or pesticides, and increased alcohol intake (Perrotta 2013; Sergentanis 2015).

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)
- Chemotherapeutic agents (melphalan, vincristine, cyclophosphamide, etoposide, bendamustine, doxorubicin);
- Histone deacetylase inhibitors (panobinostat);

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

In US and European guidelines, treatment approaches depend on patient fitness and risk of toxicities (NCCN 2021; Dimopoulos 2021). 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. ESMO-recommended initial therapy for transplant ineligible patients is a lenalidomide- or bortezomib-containing regimen with or without daratumumab (Dimopoulos 2021). Bisphosphonate treatment is often started along with therapy to treat bone disease (Terpos 2013). If the areas of damaged bone continue to cause symptoms, radiation therapy may be used.

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 OS typically decreases (Gandhi 2019). A recent prospective observational study (LocoMMotion) evaluated the outcomes of 248 patients with relapsed or refractory multiple myeloma who were triple class exposed (Mateos 2022). The study enrolled patients from 10 countries; patients had to have received at least 3 prior lines of therapy or be considered double refractory to a PI and an IMiD. All patients were triple class exposed, 74% were triple class refractory, and 93% were refractory to the last line of therapy. The ORR was 30%. With a median duration of follow up of 11 months, the median duration of response was 7.4 months, the median PFS was 4.6 months, and the median OS was 12.4 months. Similar to the prospective study, an earlier retrospective medical record review of 275 patients from 14 academic institutions in the United States found that patients who were refractory to anti-CD38 monoclonal antibodies had a dismal prognosis. The median OS for the entire cohort was 8.6 months (95% CI: 7.5, 9.9) (Gandhi 2019). Patients who became refractory to anti-CD38 therapy and received ≥1 subsequent treatment had an ORR of 31%, with a median PFS and median OS of 3.4 months and 9.3 months, respectively. The median OS for patients who received no further treatment was 1.3 months.

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

Multiple myeloma is one of multiple disorders termed plasma cell dyscrasias (Kyle 2018). Plasma cell dyscrasias are a spectrum of progressively more severe monoclonal gammopathies, which range from pre-malignant conditions, such as MGUS and SMM, to paraneoplastic conditions, like AL amyloidosis and POEMS syndrome, to malignant conditions, like Waldenstrom's macroglobulinemia and multiple myeloma. Patients diagnosed with MGUS are 3.1 times more likely to develop multiple myeloma in 20 years than those without MGUS. Almost all cases of multiple myeloma evolve from the MGUS precursor stage (Landgren 2009; Kyle 2018). Over 50% of patients with newly diagnosed multiple myeloma had MGUS for at least 10 years before progression (Kyle 2018). The risk of progression to multiple myeloma is estimated to be approximately 1% per year (Landgren 2009).

Another plasma cell dyscrasia preceding active multiple myeloma is SMM, an asymptomatic stage of disease without end organ damage. SMM progresses to multiple myeloma at a rate of approximately 10% per year over the first 5 years following diagnosis, 3% per year over the next 5 years, and 1.5% per year thereafter (Kyle 2007; Ghobrial 2014).

In Europe, there were an estimated 23,275 deaths from multiple myeloma in 2020 (ECIS 2021). Multiple myeloma is the 17th most common cause of death in the 27 EU countries, with an age-standardized mortality rate of 4.8 per 100,000 (ECIS 2021). The 5-year relative survival for multiple myeloma patients ranged from 45.6% to 60.3% in Nordic countries (NORDCAN 2021). 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). The median OS was approximately 4.6 years in the Swedish Myeloma Registry in 2016.

Multiple factors are considered in risk stratification for multiple myeloma. The ISS and Durie-Salmon staging are both older tools that stratify patients according to patient characteristics and tumor burden (Greipp 2005; Durie 1975). Updated evidence suggests that cytogenetic abnormalities seen in myeloma cells are one of the strongest predictors of tumor aggressiveness. The R-ISS was introduced as a risk stratification tool for multiple myeloma in 2015 and considers patient cytogenetic risk factors along with serum lactate dehydrogenase levels, serum albumin, and serum beta-2-microglobulin (Palumbo 2015). In 11 pooled trials, the 5-year OS rate was 82% in the R-ISS I, 62% in the R-ISS II, and 40% in the R-ISS III groups at a median follow-up of 46 months.

High risk cytogenetic abnormalities in the R-ISS include t (4;14), t (14;16), or del(17p) (Palumbo 2015; Rajkumar 2020). The presence of del(17p), t(4;14), t(14;16), t(14;20), gain 1q, or p53 mutation is considered high-risk multiple myeloma. The presence of any 2 high risk factors is considered double-hit myeloma, and 3 or more high risk factors is triple-hit myeloma (Rajkumar 2022). Patients with standard risk multiple myeloma have an estimated median survival of 7 to 10 years, while patients with high-risk cytogenetics have a median survival closer to 5 years (Rajan 2015). As new treatments are introduced, the difference in survival is narrowing between patients with standard risk cytogenetics and certain high-risk cytogenetic abnormalities, like

del(17p), suggesting that individual cytogenetic abnormalities should be considered in risk stratification (Rajkumar 2020).

Multiple myeloma is defined as clonal bone marrow plasma cells ≥10%, or biopsy-proven bony or extramedullary plasmacytoma, and evidence of myeloma defining events. These include either end organ damage, including CRAB or biomarkers of malignancy (Rajkumar 2020). Tumor-induced bone destruction and the resulting bone disease is the main cause of morbidity during multiple myeloma.

Important Co-morbidities:

Compared with a matched general population, patients with multiple myeloma have significantly higher odds of the following comorbidities that are unrelated to the disease in the year before multiple myeloma diagnosis: congestive heart failure, connective tissue disease, dementia, inflammatory bowel disease, ulcers, mild liver disease, chronic pulmonary disease, diabetes mellitus with chronic complications, metastatic solid tumors, and lymphoma (Gregersen 2017; Sverrisdóttir 2021). Moderate to severe lung disease is an important predictor for survival that is unrelated to multiple myeloma and included in the revised multiple myeloma comorbidity index (Engelhardt 2017).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical safety program for talquetamab included an exploratory 4-week IV tolerability study in cynomolgus monkey, a single-dose SC local tolerability GLP study in New Zealand White rabbits, an in vitro binding profile in a human protein cell array, a tissue cross-reactivity GLP study in normal human tissues, human serum and blood compatibility assays, and cytokine release assays in normal human blood. Further nonclinical safety studies with talquetamab in the cynomolgus monkey were not considered useful for human risk assessment because talquetamab had no adverse findings in the tolerability study and lacked comparable cross-reactivity in common toxicology species relative to human. Therefore, hazard identification studies, ie, a 2-week IV tolerability study and a pivotal 1-month IV toxicity GLP study in cynomolgus monkey, were conducted with a tool molecule, JNJ-64024701, that has similar binding affinity and in vitro functional activity against cynomolgus monkey GPRC5D-expressing cells as that of talquetamab against human GPRC5D-expressing cells.

Talquetamab, an antibody developed for an advanced cancer indication, is not expected to interact with DNA; therefore, no genotoxicity testing or carcinogenicity assessment is required. No chronic or sub-chronic toxicology studies are planned with talquetamab or the tool molecule, JNJ-64024701, due to the lack of pharmacodynamic responses in cynomolgus monkeys, and production of ADA in ≥50% of animals dosed with talquetamab and >80% of animals dosed with the tool molecule with subsequent loss of exposure within 28 days of dosing. No in vivo developmental and reproductive toxicology studies are planned, and reproductive risk has been assessed through a weight-of-evidence approach.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
No single-dose toxicity studies were conducted. In cynomolgus monkeys, 4 weekly IV doses up to 30 mg/kg of talquetamab or the tool molecule (JNJ-64407564) were well tolerated, with no or weak pharmacodynamic activity and no adverse effects.	The lack of adverse findings in healthy monkeys administered talquetamab or the tool molecule may not fully represent the potential toxicities of talquetamab in patients.
Reproductive toxicity	
No reproductive toxicity studies were conducted.[a]	Conducting reproductive toxicity studies in cynomolgus monkeys would not be warranted and conducting these studies would not be feasible nor further inform our understanding of the pregnancy risk to patients in this treatment population.[a]

Key Safety Findings	Relevance to Human Usage
Developmental toxicity No developmental toxicity studies were conducted.	Conducting developmental reproductive toxicity studies in cynomolgus monkeys would not be warranted and conducting these studies would not be feasible nor further inform our understanding of the pregnancy risk to patients in this treatment population.[a]
Genotoxicity Routine genotoxicity studies are generally not applicable to biological pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material (ICH S6).	
Carcinogenicity No standard carcinogenicity studies were conducted with talquetamab. Standard carcinogenicity studies are generally not applicable to therapies for advanced cancer indications (ICH S9).	
Safety pharmacology:	
The tool molecule, JNJ-64024701, had no effects on cardiovascular endpoints in the 1-month repeat-dose toxicity study in cynomolgus monkeys administered weekly IV doses up to 30 mg/kg.	Due to limited pharmacodynamic activity and lack of toxicity observed with the tool molecule in healthy animals, the lack of cardiovascular findings may not translate to patients with multiple myeloma. Hypotension and tachycardia have been reported in cynomolgus monkeys following treatment with other CD3 redirectors, which are possibly related to cytokine release (Saber 2017).
Nervous system	
The tool molecule, JNJ-64024701, had no effects on central nervous system endpoints (clinical observations and body temperature) in the pivotal 1-month repeat-dose toxicity study in cynomolgus monkeys administered weekly IV doses up to 30 mg/kg.	Due to limited pharmacodynamic activity and lack of toxicity observed with the tool molecule in healthy animals, the lack of findings may not translate to patients with multiple myeloma.
Other toxicity-related information or data	
Cytokine Release: In vitro, talquetamab induced cytokine release in human blood of IL-1β, IL-2, IL-6, IL-8, IL-10, IL-13, IFN-γ, and TNF-α.	The biological relevance of the in vitro cytokine release to human risk is unclear; however, CRS is a known risk for CD3 redirectors.
Local Tolerance: In a cynomolgus monkey exploratory 4-week IV tolerability study and an SC local tolerance study in rabbits (non-cross-reactive species), there were no adverse effects noted at the injection sites.	The formulation tested was comparable to the clinical formulation.

Key Safety Findings	Relevance to Human Usage
Serum compatibility and hemolytic potential: In vitro, talquetamab did not cause hemolysis in human whole blood or precipitation in human serum.	Compatible with human blood and serum

GPRC5D = G Protein-coupled receptor family C group 5 member D; IFN = interferon; IL = interleukin; IV = intravenous; SC = subcutaneous; TNF = tumor necrosis factor

[a] Talquetamab does not meet the criteria for reproductive risk assessment in a nonclinical species. This is based on: 1) intended use in patients with advanced malignancies, and of generally older age; 2) restricted normal tissue expression, including low or no expression in human reproductive tissues; 3) consideration of the use of cynomolgus monkey as the only relevant nonclinical species; 4) minimal pharmacodynamic activity and absence of adverse effects in the toxicology studies, including reproductive organs and tissues; 5) development of anti-drug antibodies that reduced exposure of talquetamab following a single dose and the tool molecule (JNJ-64024701) following repeated dosing; 6) the restricted access of immunoglobulin to the embryo during embryogenesis; and 7) the known maternal effects of CD3 redirection pharmacology, such as cytokine release or TLS, which may pose a potential risk to a pregnant mother and her unborn child.

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 safety of talquetamab (JNJ-64407564) in the multiple myeloma population is supported by one clinical trial in this EU RMP, ie, Trial 64407564MMY1001 (also known as MonumenTAL-1; hereafter referred to as MMY1001). The clinical cutoff date for safety data from this trial is 17 January 2023.

Trial MMY1001 is an ongoing Phase 1/2, open-label, multicenter trial of talquetamab administered as monotherapy to adult participants with relapsed or refractory multiple myeloma. Phase 1 included dose escalation and dose expansion and evaluated the safety, pharmacokinetics, and pharmacodynamics of talquetamab, as well as selection and preliminary evaluation of the proposed RP2Ds. Based on data from Phase 1, two RP2Ds were identified to be further evaluated in Phase 2: 0.4 mg/kg weekly (preceded by step-up doses of 0.01 and 0.06 mg/kg) and 0.8 mg/kg Q2W (preceded by step-up doses of 0.01, 0.06, and 0.3 mg/kg), both administered SC. During Phase 2, the RP2Ds were evaluated in the following cohorts:

- Cohort A (0.4 mg/kg weekly SC) enrolled participants with multiple myeloma who had previously received ≥3 prior therapies that included at least one PI, one IMiD, and an anti-CD38 monoclonal antibody, and have not been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies.
- Cohort B (0.4 mg/kg weekly SC) enrolled participants with multiple myeloma who had previously received ≥3 prior therapies that included at least one PI, one IMiD, and an anti-CD38 monoclonal antibody, and had been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies.
- Cohort C (0.8 mg/kg Q2W SC) enrolled participants with multiple myeloma who had previously received ≥3 prior therapies that included at least one PI, one IMiD, and an anti-CD38 monoclonal antibody, and had not been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies.

The RMP includes data from participants who received talquetamab SC at the RP2Ds, either in Phase 1 or Phase 2, including participants with or without prior T cell redirection therapy. As of the clinical cutoff date of 17 January 2023, this includes 339 participants (186 participants who received the 0.4 mg/kg weekly dose and 153 participants who received the 0.8 mg/kg Q2W dose).

SIII.2. Clinical Trial Exposure

Exposure in Randomized Clinical Trials

- Not applicable.

Exposure in All Clinical Trials

The all clinical trials population includes 1 trial:

- Trial MMY1001

Exposure to talquetamab in the all clinical trials population is summarized in Tables SIII.1 through SIII.5 for all participants by duration, by age group and sex, by dose, and by variable stratifications relevant to the product (eg, ethnic origin, pregnant women, breast-feeding women, renal impairment at baseline, hepatic impairment at baseline).

Table SIII.1: Exposure by Duration (Multiple Myeloma); All Clinical Trials Population

	Persons	Person-Months
Duration of exposure (months) Multiple Myeloma		
0.4 mg/kg weekly		
0 - <3	46	65.6
3 - <6	41	181.8
6 - <9	25	180.4
9 - <12	15	154.6
12 - <18	23	338.6
18 - <24	31	614.9
24 - <30	4	107.9
>=30	1	32.9
Total	186	1676.6
0.8 mg/kg Q2W		
0 - <3	36	43.6
3 - <6	28	119.0
6 - <9	16	123.2
9 - <12	31	318.8
12 - <18	37	512.0
18 - <24	4	82.1
24 - <30	1	25.7
>=30	0	
Total	153	1224.4

Key: Q2W: once every 2 weeks.
Note: 1 month equals 365.25/12 days. Trial MMY1001 participants who received 0.4 mg/kg weekly or 0.8 mg/kg Q2W in Phase 1 and participants in Phase 2 Cohorts A, B, and C are included.

[TSIEXP01A.RTF] [PROD/JNJ-64407564/MMY1001_P3/DBR_SBLA/RE_RMP/TSIEXP01A.SAS] 30MAR2023, 10:02

Table SIII.2: Exposure by Age Group and Gender (Multiple Myeloma); All Clinical Trials Population

	Men		Women	
	Persons	Person-Months	Persons	Person-Months
Age Group				
Multiple Myeloma				
0.4 mg/kg weekly				
<30 years	0	0	0	0
30-54 years	15	105.5	13	132.7
55-64 years	41	364.3	23	185.9
65-74 years	34	335.0	36	310.5
75-84 years	14	142.1	9	100.5
>=85 years	0	0	1	0.2
Total	104	946.9	82	729.7
0.8 mg/kg Q2W				
<30 years	0	0	0	0
30-54 years	19	131.9	7	61.7
55-64 years	23	170.5	20	164.4
65-74 years	26	199.9	25	191.4
75-84 years	20	195.8	13	108.8
>=85 years	0	0	0	0
Total	88	698.1	65	526.3

Key: Q2W: once every 2 weeks
Note: 1 month equals 365.25/12 days. Trial MMY1001 participants who received 0.4 mg/kg weekly or 0.8 mg/kg Q2W in Phase 1 and participants in Phase 2 Cohorts A, B, and C are included.

[TSIEXP02A.RTF] [PROD/JNJ-64407564/MMY1001_P3/DBR_SBLA/RE_RMP/TSIEXP02A.SAS] 30MAR2023, 10:02

Table SIII.3: Exposure by Dose (Multiple Myeloma); All Clinical Trials Population

	Persons	Person-Months
Dose of exposure		
Multiple Myeloma		
0.4 mg/kg weekly	186	1676.6
0.8 mg/kg Q2W	153	1224.4

Key: Q2W: once every 2 weeks.
Note: 1 month equals 365.25/12 days. Trial MMY1001 participants who received 0.4 mg/kg weekly or 0.8 mg/kg Q2W in Phase 1 and participants in Phase 2 Cohorts A, B, and C are included.

[TSIEXP03A.RTF] [PROD/JNJ-64407564/MMY1001_P3/DBR_SBLA/RE_RMP/TSIEXP03A.SAS] 30MAR2023, 10:02

Table SIII.4: Exposure (0.4 mg/kg weekly) by Special Populations (Multiple Myeloma); All Clinical Trials Population

	Persons	Person-Months
Multiple Myeloma 0.4 mg/kg weekly		
Ethnicity		
Hispanic or Latino	13	105.7
Not-Hispanic or Latino	173	1570.9
Not Reported	0	0
Total	186	1676.6
Race		
White	170	1501.4
Black or African American	13	137.9
Asian	1	7.2
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Not Reported	2	30.2
Multiple[a]	0	0
Unknown	0	0
Total	186	1676.6
Renal impairment at baseline (e-GRF mL/min/1.73 m^2)[b]		
Normal (>= 90 mL/min)	42	366.0
Mild (60 to < 90 mL/min)	92	837.9
Moderate (30 to < 60 mL/min)	52	472.6
Severe (< 30 mL/min)	0	0
Missing	0	0
Total	186	1676.6
Hepatic impairment at baseline[c]		
Normal	155	1426.7
Mild	31	250.0
Moderate	0	0
Severe	0	0
Missing	0	0
Total	186	1676.6

Key: AST = Aspartate Aminotransferase; NCI = National Cancer Institute; ULN = Upper Limit Normal; GFR=Glomerular Filtration Rate; MDRD=Modified Diet in Renal Disease.
[a] Multiple=one or more category was selected,
[b] Renal function was measured using the MDRD formula to estimate GFR.
[c] 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. Trial MMY1001 participants who received 0.4 mg/kg weekly in Phase 1 and participants in Phase 2 Cohorts A and B are included.

[TSIEXP04A.RTF] [PROD/JNJ-64407564/MMY1001_P3/DBR_SBLA/RE_RMP/TSIEXP04A.SAS] 30MAR2023, 10:02

Table SIII.5: Exposure (0.8 mg/kg Q2W) by Special Populations (Multiple Myeloma); All Clinical Trials Population

	Persons	Person-Months
Multiple Myeloma 0.8 mg/kg Q2W		
Ethnicity		
Hispanic or Latino	18	120.6
Not-Hispanic or Latino	133	1076.7
Not Reported	2	27.1
Total	153	1224.4
Race		
White	130	1030.2
Black or African American	11	74.7
Asian	7	65.2
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	1	0.3
Not Reported	2	33.7
Multiple[a]	1	9.3
Unknown	1	10.9
Total	153	1224.4
Renal impairment at baseline (e-GRF mL/min/1.73 m^2)[b]		
Normal (>= 90 mL/min)	35	295.8
Mild (60 to < 90 mL/min)	70	614.5
Moderate (30 to < 60 mL/min)	48	314.1
Severe (< 30 mL/min)	0	0
Missing	0	0
Total	153	1224.4
Hepatic impairment at baseline[c]		
Normal	129	1048.7
Mild	21	170.9
Moderate	2	2.6
Severe	0	0
Missing	1	2.2
Total	153	1224.4

Key: Q2W: bi-weekly, AST = Aspartate Aminotransferase; NCI = National Cancer Institute; ULN = Upper Limit Normal; GFR=Glomerular Filtration Rate; MDRD=Modified Diet in Renal Disease.
[a] Multiple=one or more category was selected,
[b] Renal function was measured using the MDRD formula to estimate GFR.
[c] 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. Trial MMY1001 participants who received 0.8 mg/kg Q2W in Phase 1 and participants in Phase 2 Cohort C are included.

[TSIEXP04B.RTF] [PROD/JNJ-64407564/MMY1001_P3/DBR_SBLA/RE_RMP/TSIEXP04B.SAS] 30MAR2023, 10:02

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	**Pregnant or breast-feeding**
Reason for being an exclusion criterion	Pregnant women are normally excluded from clinical trials, particularly for indications in which pregnancy is uncommon. No reproductive toxicity studies have been conducted in the preclinical setting. Breast-feeding women are usually excluded from clinical trials. It is not known whether talquetamab is excreted in human milk.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Pregnancy and breast-feeding are uncommon in this heavily pretreated patient population, and thus use in these patients is not considered missing information. SmPC Section 4.6 states that talquetamab is not recommended for women who are pregnant or for women of childbearing potential not using contraception. SmPC Sections 4.4 and 4.6 also state that females of reproductive potential should use effective contraception during treatment and for 3 months after the last dose of talquetamab.
Criterion 2	**Known to be seropositive for HIV or AIDS**
Reason for being an exclusion criterion	It is common clinical practice to exclude patients with HIV or AIDS from clinical trials of anticancer therapy because it potentially places patients with these comorbidities at increased risk for severe adverse events and also may confound the interpretation of safety.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Serious infections is considered an important identified risk. Based on the mechanism of action, there is no indication that the safety profile would differ in patients with well controlled HIV. The treating physician would be expected to weigh the benefit and risks for each individual patient.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 3	**HBV infection or active HCV infection**
Reason for being an exclusion criterion	It is common clinical practice to exclude patients with active HBV or HCV infections from clinical trials on anticancer therapy because they potentially place patients with these comorbidities at increased risk for severe adverse events and also may confound the interpretation of safety.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Serious infections is considered an important identified risk for talquetamab. Based on the mechanism of action, there is no indication that the safety profile would differ in patients with non-active HBV/HCV infection. The SmPC includes guidance that patients should be monitored for signs and symptoms of infection prior to and during treatment with talquetamab and treated appropriately.
Criterion 4	**The following cardiac conditions:** • **New York Heart Association Class III or IV congestive heart failure** • **Myocardial infarction or CABG ≤6 months prior to enrollment** • **History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration** • **History of severe non-ischemic cardiomyopathy**
Reason for being an exclusion criterion	It is common clinical practice not to include patients with potentially life-threatening cardiac conditions in trials on anticancer therapy because it may potentially place patients with these comorbidities at increased risk for adverse events, and it may confound the interpretation of safety data.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	The tool molecule, JNJ-64024701, had no effects on cardiovascular endpoints in the 1-month cynomolgus monkey toxicological study. No safety signal has been observed for cardiovascular disease in the clinical trial with the exception of hypotension in the context of CRS. Cardiovascular toxicity is not expected following talquetamab therapy. The treating physician would be expected to weigh the benefit and risks for each individual patient.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 5	**Any serious underlying medical condition, such as:** • **Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection** • **Active autoimmune disease or a documented history of autoimmune disease, with the exception of vitiligo, resolved childhood atopic dermatitis, and prior Grave's disease that is currently euthyroid based on clinical symptoms and laboratory testing** • **Psychiatric conditions (eg, alcohol or drug abuse), severe dementia, or altered mental status** • **Stroke or seizure within 6 months of signing the informed consent form**
Reason for being an exclusion criterion	It is common clinical practice to exclude patients with uncontrolled infections from clinical trials on anticancer therapy because it potentially places patients with these comorbidities at increased risk for severe adverse events, and it may confound the interpretation of safety data. Also, infection may complicate the course and management of CRS. It is common clinical practice not to include patients with autoimmune diseases in oncology clinical trials because it may potentially place patients at increased risk for immune-related side effects and may confound the interpretation of safety data. In addition, patients with autoimmune disorders commonly require immune suppression which is not permitted in clinical trials as it could impact the efficacy of talquetamab. Neurologic toxicities have been reported with bispecific T cell redirection therapy. Therefore, inclusion of patients with altered mental status or previous stroke or seizure may confound analysis of neurologic toxicity and may increase risk to patients with these types of underlying conditions.
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)	The SmPC includes a recommendation to withhold talquetamab in the case of infection. There are no specific data on the use of talquetamab in patients with autoimmune disease, psychiatric conditions, or recent stroke or seizure. There is no expectation that the safety profile would substantially differ in these patient populations. The treating physician would be expected to weigh the benefit and risks for each individual patient. Immune-related events including autoimmune disease will continue to be monitored through routine pharmacovigilance activities in the postmarketing setting.
Criterion 6	**CNS involvement or clinical signs of meningeal involvement of multiple myeloma**
Reason for being an exclusion criterion	Neurologic toxicities have been reported with bispecific T cell redirection therapy. Therefore, inclusion of patients with known CNS involvement may increase their risk of neurologic toxicities.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Neurologic toxicity including ICANS is considered an important identified risk. The treating physician would be expected to weigh the benefit and risks for each individual patient.
Criterion 7	**Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the multiple myeloma, with exceptions of non-muscle invasive bladder cancer, skin cancer, noninvasive cervical cancer, localized prostate cancer, certain forms of breast cancer, or malignancies considered cured with minimal risk of recurrence**
Reason for being an exclusion criterion	It is common clinical practice to exclude patients with other active malignancies from clinical trials, in order to avoid overlapping toxicities from anticancer therapies.
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)	Overlapping malignancies are relatively rare. In case of 2 or more co-existing malignancies, it is common practice to focus treatment on the one that needs the most urgent attention and to hold treatment for other malignancies as those might interfere with treatment of the 'primary' malignancy. Physicians would be expected to weigh the benefit and risk and prioritize cancer therapies based on the individual patient. There is no scientific rationale to expect that the safety profile would differ in patients with active malignancies.
Criterion 8	**Patients with cytopenia at screening, ie, platelets <50×10^9/L or ANC <1.0×10^9/L**
Reason for being an exclusion criterion	Patients with decreased platelets may be at increased risk for bleeding. Patients with low hemoglobin may be at increased risk for organ complications such as myocardial infarction.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Thrombocytopenia and neutropenia are both considered to be known risks of talquetamab that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers.

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, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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	Not included in the clinical development program
Population with relevant different ethnic origin	Of 186 participants in the all clinical trials population who received 0.4 mg weekly SC, 170 participants (91.4%) were White, 13 participants (7.0%) were Black or African American, and 1 participant (0.5%) was Asian. For the remaining 2 participants (1.1%), race was not reported. Of 153 participants in the all clinical trials population who received 0.8 mg Q2W SC, 130 participants (85.0%) were White, 11 participants (7.2%) were Black or African American, 7 participants (4.6%) were Asian, and 1 (0.6%) was Native Hawaiian or other Pacific Islander. For the remaining 4 participants (2.6%), race was not reported, unknown, or more than one category was selected.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Patients with relevant comorbidities:	
Patients with hepatic impairment	Participants must have had ALT and AST ≤3 x the ULN at screening to be eligible for trial participation. Of 186 participants in the all clinical trials population who received 0.4 mg weekly SC, there were 31 participants (16.7%) with mild hepatic impairment at baseline (total bilirubin ≤ULN and AST >ULN, or ULN < total bilirubin ≤ 1.5 x ULN). No participants had moderate (1.5 x ULN < total bilirubin ≤ 3 x ULN) or severe (total bilirubin >3 x ULN) hepatic impairment at baseline. Of 153 participants in the all clinical trials population who received 0.8 mg Q2W SC, 21 participants (13.7%) had mild hepatic impairment at baseline and 2 participants (1.3%) had moderate impairment. No participant had severe hepatic impairment at baseline.

Patients with renal impairment	Participants must have had e-GFR of ≥40 mL/min/1.73 m^2 at screening to be eligible for trial participation. Of 186 participants in the all clinical trials population who received 0.4 mg weekly SC, 92 participants (49.5%) had mild renal impairment at baseline (e-GFR 60 to <90 mL/min/1.73 m^2) and 52 participants (28.0%) had moderate renal impairment (e-GFR 30 to <60 mL/min/1.73 m^2). No participants had severe renal impairment (eGFR <30 mL/min/1.73 m^2) at baseline. Of 153 participants in the all clinical trials population who received 0.8 mg Q2W SC, there were 70 participants (45.8%) with mild renal impairment at baseline and 48 participants (31.4%) with moderate renal impairment. No participant had severe renal impairment at baseline.
Patients with cardiovascular impairment	Patients with the following conditions were excluded from the clinical development program: New York Heart Association Class III or IV congestive heart failure; myocardial infarction or CABG ≤6 months prior to enrollment; history of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration; history of severe non-ischemic cardiomyopathy.
Immunocompromised patients	Not applicable
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable

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

Missing Information	Long-term safety Safety in patients with prior CAR-T cell therapy

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Talquetamab will be administered by a healthcare professional 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

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

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks not Included in the List of Safety Concerns in the RMP
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
Not applicable
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
Tumor lysis syndrome
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
Hypogammaglobulinemia
Neutropenia
Thrombocytopenia
Known risks that do not impact the risk-benefit profile:
Injection-site reactions
Skin-related adverse reactions
Nail toxicity
Oral toxicity
Other reasons for considering the risks not important:
Not applicable

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

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Important identified risks	
Cytokine release syndrome	Cytokine release syndrome is a known class effect associated with T cell redirection therapy. While CRS may be life-threatening or fatal, the majority of CRS events in the clinical trial were Grade 1 or 2. The risk of CRS was mitigated by the use of step-up dosing and pretreatment medicinal products. Detailed guidance for how to manage and mitigate this risk is provided in the SmPC and PL and reflects the guidance followed by investigators in the clinical trial. Follow-up data from Trial MMY1001 and results from Trial 64407564MMY3002 (hereafter referred to as MMY3002) will provide further information on the risk of CRS. A Patient Card is included as an additional risk minimization measure to further mitigate the risk of CRS, by increasing patient awareness of signs and symptoms requiring medical attention. Overall, the risk-benefit balance is positive for the product considering the severity of the proposed indication, the demonstrated efficacy for patients treated with talquetamab, and the primarily low-grade severity of CRS observed in the clinical trial.
Neurologic toxicity including ICANS	Neurologic toxicity, primarily ICANS, is a known class effect associated with T cell redirection therapy. While these events may be life threatening or fatal, the majority of events in the talquetamab clinical trial were Grade 1 or 2. Detailed guidance for how to manage and mitigate neurologic toxicity including ICANS is provided in the SmPC and PL. Follow-up data from Trial MMY1001 and results from Trial MMY3002 will provide further information on this risk. Additional risk minimization measures to further mitigate the risk of neurologic toxicity including ICANS include a Patient Card and HCP Educational Materials. Overall, the risk-benefit balance is positive for the product considering the severity of the proposed indication, the demonstrated efficacy for patients treated with talquetamab, and the primarily low-grade severity of neurologic toxicity including ICANS observed in the clinical trial.
Serious infections	Serious infections including pneumonia and sepsis have been reported in the talquetamab clinical trial. Multiple myeloma is a bone marrow disorder of immune system cells (plasma cells) with impaired immune function, thus the incidence of serious infection in this refractory and relapsing population is expected to be high. Follow-up data from Trial MMY1001 and results from Trial MMY3002 will provide further information on the risk of serious infections. The SmPC and PL provide information on how to manage the risk of serious infection. Overall, the risk benefit balance is positive for the

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
	product considering the severity of the proposed indication and the demonstrated efficacy for patients treated with talquetamab.
Important potential risks	
Not applicable	
Missing information	
Long-term safety	To date, there are no data on the long-term safety (ie, >2 years) of talquetamab. Additional follow-up data from Trial MMY1001 will provide further information on the long-term safety profile of the product.
Safety in patients with prior CAR-T cell therapy	To date, there are limited safety data from patients with prior CAR-T cell therapy. Additional follow-up data from Trial MMY1001 will provide further information.

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

Important identified risks

1. Cytokine release syndrome
2. Neurologic toxicity including ICANS
3. Serious infections

Important potential risks

Not applicable.

Missing Information:

1. Long-term safety
2. Safety in patients with prior CAR-T cell therapy

MedDRA version 25.0 was used to classify the clinical trials adverse event information that is summarized in this Section.

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

Important Identified Risk: Cytokine release syndrome

Potential Mechanisms:

Cytokine release syndrome is a consequence of the pharmacological effect associated with bispecific T cell redirection therapy. The specific mode of action of talquetamab is based on the binding and activation of T cells and the release of cytokines in the tumor environment; therefore, adverse events of CRS are anticipated.

Evidence Source(s) and Strength of Evidence:

Cytokine release syndrome is a known class effect associated with T cell redirection therapy. Cytokine release syndrome has been reported in participants treated in the talquetamab clinical trial and was identified as an adverse reaction. The risk for CRS and information regarding this adverse reaction are described in the SmPC for talquetamab.

Based on the strength of evidence from the clinical trial data and information from the literature, CRS is considered an important identified risk for talquetamab.

Characterization of the Risk:

Cytokine Release Syndrome: Frequency, Seriousness, Outcomes, and Severity (Multiple Myeloma); All Clinical Trials Population

	All Clinical Trials		
	Talquetamab SC 0.4 mg/kg Weekly	Talquetamab SC 0.8 mg/kg Q2W	All
Multiple Myeloma			
Number of participants treated	186	153	339
Frequency[a]	146 (78.5%)	114 (74.5%)	260 (76.7%)
Seriousness	30 (16.1%)	15 (9.8%)	45 (13.3%)
Outcomes			
Fatal	0	0	0
Not recovered/Not Resolved	1 (0.7%)	0	1 (0.4%)
Recovered with sequelae	0	0	0
Recovered/Resolved	145 (99.3%)	114 (100.0%)	259 (99.6%)
Recovering/Resolving	0	0	0
Unknown[b]	0	0	0
Severity (toxicity grade)			
Worst Grade=1	113 (77.4%)	86 (75.4%)	199 (76.5%)
Worst Grade=2	29 (19.9%)	27 (23.7%)	56 (21.5%)
Worst Grade=3	4 (2.7%)	1 (0.9%)	5 (1.9%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing	0	0	0

Key: Q2W: once every 2 weeks.
Note: Trial MMY1001 participants who received 0.4 mg/kg weekly or 0.8 mg/kg Q2W in Phase 1 and participants in Phase 2 Cohorts A, B, and C are included.
[a] Includes participants who had one or more occurrences of treatment-emergent adverse events that coded to the following MedDRA terms: cytokine release syndrome; the participant is counted only once regardless of the number of events or the number of occurrences.
[b] AE records with missing outcome in current data.
Note: The worst "outcome" or "grade" are used in case of multiple events.
Note: Adverse Events were coded using MedDRA Version 25.0.
Note: The denominators are the total number of treated participants, except for the outcome and severity for which the denominators are the number of treated participants who had at least one event.

[TSFAE01.RTF] [PROD/JNJ-64407564/MMY1001_P3/DBR_SBLA/RE_RMP/TSFAE01.SAS] 30MAR2023, 10:02

Clinical signs and symptoms of CRS may include but are not limited to pyrexia, hypotension, chills, hypoxia, headache, tachycardia, and elevated transaminases. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal or hepatic failure, and disseminated intravascular coagulation.

At the RP2Ds in Trial MMY1001, CRS was reported for 76.7% of participants. For most participants with CRS (98.1%), the severity was Grade 1 or 2; 1.9% of participants had Grade 3 events and there were no Grade 4 or 5 events. Most events occurred during the step-up phase following the 0.01 mg/kg dose (28.9%), the 0.06 mg/kg dose (44.2%), the 0.3 mg/kg dose (for participants who received biweekly [every 2 weeks] dosing; 33.3%), or the initial treatment dose (0.4 mg/kg [29.6%] or 0.8 mg/kg [12.4%]). Less than 4% of CRS events occurred from Week 5 onward; all events were Grade 1. Most events of CRS (92.3%) occurred within 48 hours of the last talquetamab dose; the median time to onset was 27 hours (range: 0.1 to 333 hours [1 to 14 days]).

The median duration of CRS was 17 hours, ranging from 0 to 622 hours (1 to 26 days). As of the clinical cutoff date, 99.6% of participants with CRS had recovered; CRS was unresolved for 1 participant.

Risk Factors and Risk Groups:

The risk factors of CRS are not fully identified; however, active infection may increase the severity of CRS. Active infection was an exclusionary criterion in clinical trials.

Preventability:

Specific guidance in the SmPC Sections 4.2 and 4.4 is provided to minimize and manage the risk of CRS. To reduce the risk of CRS, talquetamab should be initiated using step-up dosing, and pretreatment medicinal products should be administered during the step-up phase. As the majority of CRS events occur within the first 48 hours after dosing, patients should be instructed to remain within the proximity of a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase. At the first sign of CRS, patients should be evaluated for hospitalization, and treatment should be started. For patients who experience CRS, pretreatment medicinal products should be administered before their next dose. Part V.2 of the RMP includes an additional risk minimization measure (ie, Patient Card) to further mitigate the risk of CRS.

Impact on the Risk-Benefit Balance of the Product:

Cytokine release syndrome is a known class effect associated with T cell redirection therapy. While CRS may be life-threatening or fatal, the majority of CRS events in the clinical trial were Grade 1 or Grade 2. The risk of CRS was mitigated by the use of step-up dosing and pretreatment medicinal products. Detailed guidance for how to manage and mitigate this risk is provided in the SmPC and PL and reflects the guidance followed by investigators in the clinical trial. A Patient Card is included as an additional risk minimization measure to further mitigate the risk of CRS, by increasing patient awareness of signs and symptoms requiring medical attention. Overall, the risk-benefit balance is positive for the product considering the severity of the proposed indication, the demonstrated efficacy for patients treated with talquetamab, and the primarily low-grade severity of CRS observed in the clinical trial.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Cytokine release syndrome (PT)

Important Identified Risk: Neurologic toxicity including ICANS

Potential Mechanisms:

Neurologic toxicity, particularly ICANS, has been reported with other T cell redirection therapies; however, the precise mechanism is unclear.

Evidence Source(s) and Strength of Evidence:

Neurologic toxicity, primarily ICANS, is a known class effect associated with bispecific T cell redirection therapy. Neurologic toxicity has been reported in participants treated with talquetamab in the clinical trial and several neurologic events were identified as adverse reactions. The risk for neurologic toxicity including ICANS is described in the SmPC for talquetamab.

Based on the known class effect and the evidence from clinical trial data, neurologic toxicity including ICANS is considered an important identified risk for talquetamab.

Characterization of the Risk:

Clinical manifestations of neurologic toxicity varied from Nervous System Disorders to Psychiatric Disorders. Thus, TEAEs included in this important identified risk were those in the System Organ Classes (SOCs) of Nervous System Disorders or Psychiatric Disorders (excluding preferred terms of dysgeusia, ageusia, hypogeusia, and taste disorder) that were considered by the investigator to be related to talquetamab. However, the major safety concern for talquetamab is ICANS as a class effect associated with bispecific T cell redirection therapies.

Investigators graded events of ICANS prospectively according to ASTCT criteria (Lee 2019). Because Phase 1 started before the ASTCT criteria were implemented, ICANS could not be identified or excluded prospectively for participants in Phase 1. Therefore, ICANS data in this section are presented for Phase 2 only.

Neurologic toxicity including ICANS: Frequency, Seriousness, Outcomes, and Severity (Multiple Myeloma); All Clinical Trials Population

	All Clinical Trials		
	Talquetamab SC 400ug/kg Q1W	Talquetamab SC 800ug/kg Q2W	All
Multiple Myeloma			
Number of subjects treated	186	153	339
Frequency[a]	52 (28.0%)	46 (30.1%)	98 (28.9%)
Seriousness	7 (3.8%)	7 (4.6%)	14 (4.1%)
Outcomes			
Fatal	0	0	0
Not recovered/Not Resolved	18 (34.6%)	17 (37.0%)	35 (35.7%)
Recovered with sequelae	0	0	0
Recovered/Resolved	33 (63.5%)	26 (56.5%)	59 (60.2%)
Recovering/Resolving	1 (1.9%)	2 (4.3%)	3 (3.1%)
Unknown[b]	0	1 (2.2%)	1 (1.0%)
Severity (toxicity grade)			
Worst Grade=1	32 (61.5%)	24 (52.2%)	56 (57.1%)
Worst Grade=2	18 (34.6%)	15 (32.6%)	33 (33.7%)
Worst Grade=3	2 (3.8%)	6 (13.0%)	8 (8.2%)
Worst Grade=4	0	1 (2.2%)	1 (1.0%)
Worst Grade=5	0	0	0
Missing	0	0	0

Key: Q1W: weekly, Q2W: bi-weekly.
Note: Study MMY1001 subjects who received 400ug/kg Q1W or 800ug/kg Q2W in phase 1 and subjects in phase 2 cohorts A, B, and C are included.
[a] Includes subjects who had one or more occurrences of treatment-emergent adverse events that coded to the following MedDRA System Organ Class: Nervous System Disorders or Psychiatric Disorders (excluding preferred terms of dysgeusia, ageusia, hypogeusia, and taste disorder) that were considered by the investigator to be related to talquetamab.
[b] AE records with missing outcome in current data.
Note: The worst "outcome" or "grade" are used in case of multiple events.
Note: Adverse Events were coded using MedDRA Version 25.0.
Note: The denominators are the total number of treated subjects, except for the outcome and severity for which the denominators are the number of treated subjects who had at least one event.
[TSFAE07.RTF] [PROD/JNJ-64407564/MMY1001_P3/DBR_SBLA/RE_RMP/TSFAE07.SAS] 16JUN2023, 07:50

At the RP2Ds in Trial MMY1001, neurologic toxicity including ICANS was reported for 28.9% of participants as of the clinical cutoff date. The maximum severity of events was Grade 1 or 2 for 90.8% of participants and Grade 3 or 4 for 9.2% of participants. As of the clinical cutoff date, 63.3% of participants with neurologic toxicity including ICANS had recovered or were recovering and 35.7% of participants had not yet recovered.

At the RP2Ds in Trial MMY1001, ICANS was reported for 9.8% of participants in Phase 2 of the trial as of the clinical cutoff date. Of participants with ICANS, the severity was Grade 1 or 2 for 76.9% of participants and Grade 3 or 4 for 23.1% of participants. The majority of ICANS events (68.0%) occurred within 48 hours of the last talquetamab dose; the median time to onset was 28 hours (range: 3 to 355 hours [1 to 15 days]). The median duration of ICANS events was 9 hours (range: 2 to 194 hours [1 to 8 days]). As of the clinical cutoff date, 84.6% of participants with ICANS had recovered or were recovering and 15.4% of participants had not yet recovered.

Although not in scope for the RMP analyses, one fatal event of ICANS was reported for a participant enrolled at an investigative site in China. The event occurred within 30 days of the last dose of talquetamab and was considered related to talquetamab treatment.

Risk Factors and Risk Groups:

Risk factors have not been fully identified. Patients with CNS disorders may be at higher risk for neurological adverse events.

Preventability:

As the majority of ICANS events occur within the first 2 days after dosing, patients should be instructed to remain within the proximity of a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase. At the first sign of neurologic toxicity including ICANS, patients should be evaluated and treated with consideration for neurologic evaluation. Talquetamab should be withheld until resolution of any Grade 1, Grade 2, or first occurrence of a Grade 3 event of ICANS. Patients should be permanently discontinued for any recurrent Grade 3 or any Grade 4 ICANS event. In the case of any Grade 2 or higher ICANS event, patients should remain within the proximity of a healthcare facility and be monitored for 48 hours after administration of the next dose of talquetamab. Specific guidelines for the management of neurologic toxicity including ICANS are provided in the SmPC. Part V.2 of the RMP includes additional risk minimization measures (ie, Patient Card, HCP Educational Materials) to further mitigate the risk of neurologic toxicity including ICANS.

Impact on the Risk-Benefit Balance of the Product:

Neurologic toxicity, primarily ICANS, is a known class effect associated with T cell redirection therapy. While these events may be life threatening or fatal, the majority of events in the talquetamab clinical trial were Grade 1 or 2. Detailed guidance for how to manage and mitigate neurologic toxicity including ICANS is provided in the SmPC and PL. Follow-up data from Trial MMY1001 and results from Trial MMY3002 will provide further information on this risk. Additional risk minimization measures to further mitigate the risk of neurologic toxicity including ICANS include a Patient Card and HCP Educational Materials. Overall, the risk-benefit balance is positive for the product considering the severity of the proposed indication, the demonstrated efficacy for patients treated with talquetamab, and the primarily low-grade severity of neurologic toxicity including ICANS observed in the clinical trial.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

ICANS (PT)

Important Identified Risk: Serious infections

Potential Mechanisms:

Patients with multiple myeloma are susceptible to infection due to underlying disease causing hypogammaglobulinemia and immunosuppression (Terpos 2015). GPRC5D is expressed on normal plasma cells in addition to multiple myeloma cells. Thus, normal plasma cells are also expected to be targeted by talquetamab, which may cause hypogammaglobulinemia and infection.

Evidence Source(s) and Strength of Evidence:

Serious bacterial, fungal, and viral infections, including life-threatening or fatal infections, have been reported for participants treated with talquetamab in the clinical trial and serious infections such as pneumonia and sepsis have been identified as adverse reactions. Based on this, serious infections are considered an important identified risk for talquetamab. The risk for serious infection and information regarding this adverse reaction are described in the SmPC for talquetamab.

Characterization of the Risk:

Note: Although the important identified risk is serious infections, all adverse events identified by the SOC of infections and infestations are captured in the following table, independent of their seriousness.

Infections: Frequency, Seriousness, Outcomes, and Severity (Multiple Myeloma); All Clinical Trials Population

	All Clinical Trials		
	Talquetamab SC 0.4 mg/kg Weekly	Talquetamab SC 0.8 mg/kg Q2W	All
Multiple Myeloma			
Number of participants treated	186	153	339
Frequency[a]	115 (61.8%)	102 (66.7%)	217 (64.0%)
Seriousness	34 (18.3%)	26 (17.0%)	60 (17.7%)
Outcomes			
Fatal	3 (2.6%)	2 (2.0%)	5 (2.3%)
Not recovered/Not Resolved	20 (17.4%)	15 (14.7%)	35 (16.1%)
Recovered with sequelae	2 (1.7%)	1 (1.0%)	3 (1.4%)
Recovered/Resolved	89 (77.4%)	83 (81.4%)	172 (79.3%)
Recovering/Resolving	1 (0.9%)	1 (1.0%)	2 (0.9%)
Unknown[b]	0	0	0
Severity (toxicity grade)			
Worst Grade=1	10 (8.7%)	13 (12.7%)	23 (10.6%)
Worst Grade=2	63 (54.8%)	63 (61.8%)	126 (58.1%)
Worst Grade=3	37 (32.2%)	19 (18.6%)	56 (25.8%)
Worst Grade=4	2 (1.7%)	5 (4.9%)	7 (3.2%)
Worst Grade=5	3 (2.6%)	2 (2.0%)	5 (2.3%)
Missing	0	0	0

Key: Q2W: once every 2 weeks.
Note: Trial MMY1001 participants who received 0.4 mg/kg weekly or 0.8 mg/kg Q2W in Phase 1 and participants in Phase 2 Cohorts A, B, and C are included.
[a] Includes participants who had one or more occurrences of treatment-emergent adverse events that coded to the following MedDRA System Organ Class: Infections and infestations; the participant is counted only once regardless of the number of events or the number of occurrences.
[b] AE records with missing outcome in current data.
Note: The worst "outcome" or "grade" are used in case of multiple events.
Note: Adverse Events were coded using MedDRA Version 25.0.
Note: The denominators are the total number of treated participants, except for the outcome and severity for which the denominators are the number of treated participants who had at least one event.

[TSFAE03.RTF] [PROD/JNJ-64407564/MMY1001_P3/DBR_SBLA/RE_RMP/TSFAE03.SAS] 30MAR2023, 10:02

At the RP2Ds in Trial MMY1001, infections were reported for 64.0% of participants and were considered serious for 17.7% of participants. The severity was Grade 5 for 2.3% of participants, Grade 4 for 3.2% of participants, and Grade 3 for 25.8% of participants. The 5 fatal events were COVID-19 pneumonia (2 participants), and septic shock, fungal sepsis, and infection (unknown etiology) (1 participant each). None of the fatal events were considered related to study drug.

Risk Factors and Risk Groups:

There are multiple factors that may increase the risk of infectious complications. Patients with multiple myeloma are at risk of infection due to the overproduction of ineffective monoclonal antibodies from the underlying disease, which causes immune dysfunction. Multiple myeloma patients have as much as a 15-fold increase in risk of infections, particularly pneumonia. In addition, the functional status and medical fragility of the patient may be a risk factor. Studies have shown that hospitalized patients, those with poor functional status or comorbid conditions, and older adults are more likely to develop infection complications. Another risk factor is the

concomitant use of other immunosuppressive medications with synergistic adverse immunologic effects. The use of multiple chemotherapy and immunosuppressive treatments (eg, corticosteroids), and neutropenia as a complication of the treatments, increases the risk of infection.

Preventability:

Talquetamab should be withheld during the step-up phase until the infection resolves, and should be withheld during the treatment phase until the infection improves to Grade 2 or better. Talquetamab should not be administered in patients with active serious infection. Prior to starting talquetamab, prophylaxis should be considered for the prevention of infections (including antiviral prophylaxis for prevention of herpes zoster virus reactivation), per local institutional guidelines. Patients should be monitored for signs and symptoms of infection prior to and during treatment with talquetamab and should be treated appropriately. Prophylactic antimicrobials should be administered according to local institutional guidelines.

Impact on the Risk-Benefit Balance of the Product:

Serious infections including pneumonia and sepsis have been reported in the talquetamab clinical trial. Multiple myeloma is a bone marrow disorder of immune system cells (plasma cells) with impaired immune function, thus the incidence of serious infection in this refractory and relapsing population is expected to be high. Follow-up data from Trial MMY1001 and results from Trial MMY3002 will provide further information on the risk of serious infections. The SmPC and PL provide information on how to manage the risk of serious infection. Overall, the risk benefit balance is positive for the product considering the severity of the proposed indication and the demonstrated efficacy for patients treated with talquetamab.

Public Health Impact:

All usage will be well controlled by the healthcare professional. No public health impact is anticipated.

Annex 1 MedDRA Term:

Infections and Infestations (SOC)

SVII.3.2. Presentation of the Missing Information

Missing information: Long-term safety
Evidence source: To date, there are no data on the long-term safety (ie, >2 years) of talquetamab.
Population in need of further characterization: A risk associated with long-term use cannot be defined based on available evidence. Delayed onset adverse events will be collected as part of the ongoing pivotal trial (64407564MMY1001). Updated data based on a later data cutoff date will increase understanding of the long-term safety profile of the product.
Missing information: Safety in patients with prior CAR-T cell therapy
Evidence source: To date, there are limited safety data from patients with prior CAR-T cell therapy.
Population in need of further characterization: A risk associated with prior CAR-T cell therapy cannot be defined based on available evidence. Additional follow-up data from Trial MMY1001 will provide further information.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Cytokine release syndrome
	Neurologic toxicity including ICANS
	Serious infections
Important Potential Risks	None
Missing Information	Long-term safety
	Safety in patients with prior CAR-T cell therapy

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization 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
Not applicable	

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Study	
Study name and title	64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma
Rationale and study objectives	Rationale: Talquetamab may be associated with delayed adverse events. The primary objective in Part 1 (dose escalation) is to characterize the safety of talquetamab and recommend the Phase 2 dose and schedule. The primary objective in Part 2 (dose expansion) is to further characterize the safety of talquetamab at the recommended Phase 2 dose (RP2D).
Safety concern(s) addressed	CRS, Neurologic toxicity including ICANS, Serious infections, Long-term safety; Safety in patients with prior CAR-T cell therapy
Study design	Open-label Phase 1/2 trial
Study population	Adult patients with relapsed or refractory multiple myeloma who have previously received at least 3 prior lines of therapy including a PI, an IMiD, and an anti-CD38 monoclonal antibody.
Milestones	Updated Safety Report: Q2 2025

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** (in DD/MM/YYYY format)
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				
64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma	The primary objective in Part 1 (dose escalation) is to characterize the safety of talquetamab and recommend the Phase 2 dose and schedule. The primary objective in Part 2 (dose expansion) is to further characterize the safety of talquetamab at the recommended Phase 2 dose (RP2D).	CRS Neurologic toxicity including ICANS Serious infections Long-term safety Safety in patients with prior CAR-T cell therapy	Updated Safety Report	Q2 2025
Category 3 – Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization 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 (in DD/MM/YYY format)
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
64407564MMY3002: A Phase 3 Randomized Study Comparing Talquetamab SC in Combination With Daratumumab SC and Pomalidomide (Tal-DP) or Talquetamab SC in Combination With Daratumumab SC (Tal-D) Versus Daratumumab SC, Pomalidomide and Dexamethasone (DPd), in Participants With Relapsed or Refractory Multiple Myeloma who Have Received at Least 1 Prior Line of Therapy	The primary objective is to compare the efficacy of Tal-DP and Tal-D, respectively, with DPd. Secondary objectives are: • to further compare the efficacy of Tal-DP and Tal-D, respectively, with DPd; • to assess the safety profile of Tal-DP and Tal-D (including further characterization of the safety concerns of CRS, neurologic toxicity including ICANS, and serious infections); • to characterize the PK of talquetamab; • to assess the immunogenicity of talquetamab and daratumumab; and • to assess changes in PROs with Tal-DP, DPd, and Tal-D.	Long-term efficacy	Protocol submission	Q1 2023
			Interim report	April 2027
			Final report	June 2030

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
Cytokine release syndrome	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Instructions that talquetamab should be administered by a healthcare professional with adequate medical equipment and personnel to manage severe reactions, including CRS, is included in SmPC Section 4.2. • Instructions for step-up dosing and pretreatment medicinal products (corticosteroids, antihistamines, antipyretics) to reduce the risk of CRS are included in SmPC Section 4.2. • Recommendation that patients should remain close to a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase is provided in SmPC Section 4.2. • Recommendations for the management of CRS by severity, and including actions to be taken (eg, withholding, discontinuation) and treatment, are included in SmPC Section 4.2. • Recommendations for the monitoring, evaluation, and treatment of CRS (including hospitalization, supportive care, medicinal products, etc) is provided in SmPC Section 4.4. • Guidance for patients to recognize symptoms of CRS and get medical help right away are included in PL Sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** • Legal status • The design of the packaging has been chosen to appropriately differentiate between the product strengths to ensure the medicine is used correctly during step-up dosing. Step-up dosing is designed to mitigate the severity of CRS.
Neurologic toxicity including ICANS	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4

	• SmPC Section 4.7 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation that patients should remain close to a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase is provided in SmPC Section 4.2. • Recommendations for the management of neurologic toxicity (excluding ICANS) by severity, and including actions to be taken (eg, withholding, discontinuation) and treatment, are included in SmPC Section 4.2. • Recommendations for management of ICANS (including neurology consultation, corticosteroids, and anti-seizure medicinal products) is provided in SmPC Section 4.2. • Recommendations for the monitoring, evaluation, and treatment of neurologic toxicity, including ICANS, is provided in SmPC Section 4.4. • Recommendation for restrictions on driving and operating machines due to the potential for ICANS is provided in SmPC Sections 4.4 and 4.7 and PL Section 2. • Guidance for patients to recognize symptoms of neurologic toxicity including ICANS and get medical help right away are included in PL Sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** • Legal status
Serious Infections	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation that talquetamab should not be started and should be withheld during the step-up phase until the infection resolves, and should be withheld during the treatment phase until the infection improves to Grade 2 or better, is provided in SmPC Section 4.2. • Recommendation that prior to starting talquetamab, prophylaxis should be considered for the prevention of infections (including antiviral prophylaxis for prevention of herpes zoster virus reactivation), per local institutional guidelines, is provided in SmPC Section 4.2. • Recommendations for the management and treatment of serious infections, as well as guidance that the step-up dosing schedule should not

	be administered in patients with active infection, is provided in SmPC Section 4.4. • Guidance that talquetamab should not be administered in patients with active serious infection is provided in SmPC Section 4.4. • Guidance that patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur is provided in SmPC Section 4.4. • Guidance for patients to recognize symptoms of serious infection is included in PL Sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** • Legal status
Long-term safety	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • None
Safety in patients with prior CAR-T cell therapy	**Routine risk communication:** • SmPC Section 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Guidance that heightened caution should be exercised when administering talquetamab to patients who experienced Grade 3 or higher CRS with prior CAR-T cell therapy is provided in SmPC Section 4.4. **Other routine risk minimization measures beyond the Product Information:** • None

V.2. Additional Risk Minimization Measures

Additional Risk Minimization Activity 1

Additional Risk Minimization Activity 1 Patient Card	
Objective(s):	To minimize the important identified risks of CRS and neurologic toxicity including ICANS.
Rationale for the additional risk minimization activity:	To inform patients of CRS and neurologic toxicity including ICANS associated with talquetamab and increase awareness of symptoms requiring immediate medical attention. To advise patients to stay close to the location where they received talquetamab for 48 hours after administration of all doses within the step-up dosing schedule. To provide a Patient Card that advises patients to carry it at all times and share it with any HCP providing care (including emergency) so the patient can be evaluated and treated for CRS or neurologic toxicity including ICANS in a timely manner.
Target audience and planned distribution path:	All patients/caregivers who are expected to use talquetamab.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Plan to evaluate the effectiveness: CRS and neurologic toxicity including ICANS reporting trend analyses from postmarketing safety data will be included in the PBRER/PSUR. Criteria for success: Stable reporting trend analyses (after 2 years post-approval) are the criteria for success.

Additional Risk Minimization Activity 2

Additional Risk Minimization Activity 2 Health Care Professional (HCP) Educational Materials	
Objective(s):	To minimize the important identified risk of neurologic toxicity including ICANS
Rationale for the additional risk minimization activity:	To increase awareness of neurologic toxicity including ICANS and its appropriate monitoring, prevention, and management before treating a patient. To facilitate patient counseling relevant information. To provide guidance on reporting these serious adverse reactions associated with talquetamab.
Target audience and planned distribution path:	HCPs who prescribe or administer talquetamab.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Neurologic toxicity including ICANS reporting trend analyses from postmarketing safety data per PBRER/PSUR period. Stable reporting trend analysis (after 18 months post-approval) are the criteria for success.

V.2.1. Removal of Additional Risk Minimization Activities

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
Cytokine release syndrome	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Instructions that talquetamab should be administered by a healthcare professional with adequate medical equipment and personnel to manage severe reactions, including CRS, is included in SmPC Section 4.2. • Instructions for step-up dosing and pretreatment medicinal products (corticosteroids, antihistamines, antipyretics) to reduce the risk of CRS are included in SmPC Section 4.2. • Recommendation that patients should remain close to a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase is provided in SmPC Section 4.2. • Recommendations for the management of CRS by severity, and including actions to be taken (eg, withholding, discontinuation) and treatment, are included in SmPC Section 4.2. • Recommendations for the monitoring, evaluation, and treatment of CRS (including hospitalization, supportive care, medicinal products, etc) is provided in SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma Updated report: Q2 2025

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Guidance for patients to recognize symptoms of CRS and get medical help right away are included in PL Sections 2 and 4. • Legal status • The design of the packaging has been chosen to appropriately differentiate between the product strengths to ensure the medicine is used correctly during step-up dosing. Step-up dosing is designed to mitigate the severity of CRS. **Additional risk minimization measures:** • Patient Card	
Neurologic toxicity including ICANS	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • PL Section 2 • PL Section 4 • Recommendation that patients should remain close to a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase is provided in SmPC Section 4.2. • Recommendations for the management of neurologic toxicity (excluding ICANS) by severity, and including actions to be taken (eg, withholding, discontinuation) and treatment, are included in SmPC Section 4.2. • Recommendations for management of ICANS (including neurology consultation, corticosteroids, and anti-seizure medicinal products) is provided in SmPC Section 4.2. • Recommendations for the monitoring, evaluation, and treatment of neurologic toxicity, including ICANS, is provided in SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma Updated report: Q2 2025

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Recommendation for restrictions on driving and operating machines due to the potential for ICANS is provided in SmPC Sections 4.4 and 4.7 and PL Section 2. • Guidance for patients to recognize symptoms of neurologic toxicity including ICANS and get medical help right away are included in PL Sections 2 and 4. • Legal status **Additional risk minimization measures:** • Patient Card • HCP Educational Materials	
Serious infections	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Recommendation that talquetamab should not be started and should be withheld during the step-up phase until the infection resolves, and should be withheld during the treatment phase until the infection improves to Grade 2 or better, is provided in SmPC Section 4.2. • Recommendation that prior to starting talquetamab, prophylaxis should be considered for the prevention of infections (including antiviral prophylaxis for prevention of herpes zoster virus reactivation), per local institutional guidelines, is provided in SmPC Section 4.2. • Recommendations for the management and treatment of serious infections, as well as guidance that the step-up dosing schedule should not be administered in patients with	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma Updated report: Q2 2025

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	active infection, is provided in SmPC Section 4.4. • Guidance that talquetamab should not be administered in patients with active serious infection is provided in SmPC Section 4.4. • Guidance that patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur is provided in SmPC Section 4.4. • Guidance for patients to recognize symptoms of serious infection is included in PL Sections 2 and 4. • Legal status **Additional risk minimization measures:** • None	
Long-term safety	**Routine risk minimization measures:** • None **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma Updated report: Q2 2025
Safety in patients with prior CAR-T cell therapy	**Routine risk minimization measures:** • SmPC Section 4.4 • Guidance that heightened caution should be exercised when administering talquetamab to patients who experienced Grade 3 or higher CRS with prior CAR-T cell therapy is provided in SmPC Section 4.4. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma Updated report: Q2 2025

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for talquetamab

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

Talquetamab's SmPC and its package leaflet give essential information to healthcare professionals and patients on how talquetamab should be used.

This summary of the RMP for talquetamab 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 EPAR.

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

I. The Medicine and What it is Used For

Talquetamab is authorized as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (see SmPC for the full indication). It contains talquetamab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of talquetamab's benefits can be found in talquetamab's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of talquetamab, together with measures to minimize such risks and the proposed studies for learning more about talquetamab'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 talquetamab, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including 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 talquetamab is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of talquetamab 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 talquetamab. 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	Cytokine release syndrome Neurologic toxicity including ICANS Serious infections
Important potential risks	None
Missing information	Long-term safety Safety in patients with prior CAR-T cell therapy

II.B. Summary of Important Risks

Important Identified Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	Cytokine release syndrome is a known class effect associated with T cell redirection therapy. Cytokine release syndrome has been reported in participants treated in the talquetamab clinical trial and was identified as an adverse reaction. The risk for CRS and information regarding this adverse reaction are described in the SmPC for talquetamab. Based on the strength of evidence from the clinical trial data and information from the literature, CRS is considered an important identified risk for talquetamab.
Risk factors and risk groups	The risk factors of CRS are not fully identified; however, active infection may increase the severity of CRS. Active infection was an exclusionary criterion in clinical trials.
Risk minimization measures	Routine risk minimization measures

Important Identified Risk: Cytokine release syndrome	
	• SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Instructions that talquetamab should be administered by a healthcare professional with adequate medical equipment and personnel to manage severe reactions, including CRS, is included in SmPC Section 4.2. • Instructions for step-up dosing and pretreatment medicinal products (corticosteroids, antihistamines, antipyretics) to reduce the risk of CRS are included in SmPC Section 4.2. • Recommendation that patients should remain close to a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase is provided in SmPC Section 4.2. • Recommendations for the management of CRS by severity, and including actions to be taken (eg, withholding, discontinuation) and treatment, are included in SmPC Section 4.2. • Recommendations for the monitoring, evaluation, and treatment of CRS (including hospitalization, supportive care, medicinal products, etc) is provided in SmPC Section 4.4. • Guidance for patients to recognize symptoms of CRS and get medical help right away are included in PL Sections 2 and 4. Additional risk minimization measures • Patient Card
Additional pharmacovigilance activities`	Additional pharmacovigilance activities: 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Neurologic toxicity including ICANS	
Evidence for linking the risk to the medicine	Neurologic toxicity, primarily ICANS, is a known class effect associated with bispecific T cell redirection therapy. Neurologic toxicity has been reported in participants treated with talquetamab in the clinical trial and several neurologic events were identified as adverse reactions. The risk for neurologic toxicity including ICANS is described in the SmPC for talquetamab.

	Based on the known class effect and the evidence from clinical trial data, neurologic toxicity including ICANS is considered an important identified risk for talquetamab.
Risk factors and risk groups	Risk factors have not been fully identified. Patients with CNS disorders may be at higher risk for neurological adverse events.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • PL Section 2 • PL Section 4 • Recommendation that patients should remain close to a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase is provided in SmPC Section 4.2. • Recommendations for the management of neurologic toxicity (excluding ICANS) by severity, and including actions to be taken (eg, withholding, discontinuation) and treatment, are included in SmPC Section 4.2. • Recommendations for management of ICANS (including neurology consultation, corticosteroids, and anti-seizure medicinal products) is provided in SmPC Section 4.2. • Recommendations for the monitoring, evaluation, and treatment of neurologic toxicity, including ICANS, is provided in SmPC Section 4.4. • Recommendation for restrictions on driving and operating machines due to the potential for ICANS is provided in SmPC Sections 4.4 and 4.7 and PL Section 2. • Guidance for patients to recognize symptoms of neurologic toxicity including ICANS and get medical help right away are included in PL Sections 2 and 4. Additional risk minimization measures • Patient Card • HCP Educational Materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Serious bacterial, fungal, and viral infections, including life-threatening or fatal infections, have been reported for participants treated with talquetamab in the clinical trial and serious infections such as pneumonia and sepsis have been identified as adverse reactions. Based on this, serious infections are considered an important identified risk for talquetamab. The risk for serious infection and information regarding this adverse reaction are described in the SmPC for talquetamab.
Risk factors and risk groups	There are multiple factors that may increase the risk of infectious complications. Patients with multiple myeloma are at risk of infection due to the overproduction of ineffective monoclonal antibodies from the underlying disease, which causes immune dysfunction. Multiple myeloma patients have as much as a 15-fold increase in risk of infections, particularly pneumonia. In addition, the functional status and medical fragility of the patient may be a risk factor. Studies have shown that hospitalized patients, those with poor functional status or comorbid conditions, and older adults are more likely to develop infection complications. Another risk factor is the concomitant use of other immunosuppressive medications with synergistic adverse immunologic effects. The use of multiple chemotherapy and immunosuppressive treatments (eg, corticosteroids), and neutropenia as a complication of the treatments, increases the risk of infection.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Recommendation that talquetamab should not be started and should be withheld during the step-up phase until the infection resolves, and should be withheld during the treatment phase until the infection improves to Grade 2 or better, is provided in SmPC Section 4.2. • Recommendation that prior to starting talquetamab, prophylaxis should be considered for the prevention of infections (including antiviral prophylaxis for prevention of herpes zoster virus reactivation), per local institutional guidelines, is provided in SmPC Section 4.2. • Recommendations for the management and treatment of serious infections, as well as guidance that the step-up dosing schedule should not be administered in patients with active infection, is provided in SmPC Section 4.4. • Guidance that talquetamab should not be administered in patients with active serious infection is provided in SmPC Section 4.4.

	• Guidance that patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur is provided in SmPC Section 4.4. • Guidance for patients to recognize symptoms of serious infection is included in PL Sections 2 and 4. Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety	
Risk minimization measures	Routine risk minimization measures • None Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Safety in patients with prior CAR-T cell therapy	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • Guidance that heightened caution should be exercised when administering talquetamab to patients who experienced Grade 3 or higher CRS with prior CAR-T cell therapy is provided in SmPC Section 4.4. Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x

	CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

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

The following studies are conditions of the marketing authorization:

64407564MMY3002: A Phase 3 Randomized Study Comparing Talquetamab SC in Combination With Daratumumab SC and Pomalidomide (Tal-DP) or Talquetamab SC in Combination With Daratumumab SC (Tal-D) Versus Daratumumab SC, Pomalidomide and Dexamethasone (DPd), in Participants With Relapsed or Refractory Multiple Myeloma who Have Received at Least 1 Prior Line of Therapy

Purpose of the study: The primary objective is to compare the efficacy of Tal-DP and Tal-D, respectively, with DPd. Secondary objectives are:

- to further compare the efficacy of Tal-DP and Tal-D, respectively, with DPd;
- to assess the safety profile of Tal-DP and Tal-D (including further characterization of the safety concerns of CRS, neurologic toxicity including ICANS, and serious infections);
- to characterize the PK of talquetamab;
- to assess the immunogenicity of talquetamab and daratumumab; and
- to assess changes in PROs with Tal-DP, DPd, and Tal-D.

64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma

Purpose of the study: The primary objective in Part 1 (dose escalation) is to characterize the safety of talquetamab and recommend the Phase 2 dose and schedule. The primary objective in Part 2 (dose expansion) is to further characterize the safety of talquetamab at the recommended Phase 2 dose (RP2D).

II.C.2. Other Studies in Postauthorization Development Plan

Not applicable

PART VII: ANNEXES

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities

Additional Risk Minimization Measure 1

Patient Card

The MAH shall ensure that in each Member State where talquetamab is marketed, all patients/caregivers who are expected to use talquetamab have access to/are provided with the Patient Card which will inform and explain to patients the risks of CRS and neurologic toxicity including ICANS. The Patient Card also includes a warning message for healthcare professionals treating the patient that the patient is receiving talquetamab.

The Patient Card will contain the following key messages:

- A description of the key signs and symptoms of CRS and neurologic toxicity including ICANS
- A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or neurologic toxicity including ICANS present themselves
- A reminder that patients should stay close to a healthcare facility for 48 hours after administration of all doses within the step-up dosing schedule
- The prescribing physician's contact details

Additional Risk Minimization Measure 2

Health Care Professional (HCP) Educational Materials

This proposed additional risk minimization measure addresses the important identified risk of neurologic toxicity including ICANS.

Prior to the launch of talquetamab in each Member State, the MAH must agree on the content and format of the educational materials with the National Competent Authority.

The MAH shall ensure that in each Member State where talquetamab is marketed, all HCPs who are expected to prescribe or administer talquetamab shall be provided with medical education material to:

- ensure awareness of the risk of neurologic toxicity including ICANS and recommendations to help minimize the risk, including information on frequency, severity, and time to onset observed in patients who received treatment with talquetamab
- facilitate identification of neurologic toxicity including ICANS
- facilitate management of neurologic toxicity including ICANS
- facilitate monitoring of neurologic toxicity including ICANS
- ensure that adverse reactions are adequately and appropriately reported