European Union Risk Management Plan
Teclistamab

Data lock point for current RMP	28 Feb 2023	Version number	3.2

CHMP Opinion Date: 12 October 2023

QPPV Sign-off Date: 20 September 2023
RMP Version Number: 3.2
Supersedes Version: 2.3
EDMS Number: EDMS-RIM-1140537; 1.0

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	3.2
Rationale for submitting an updated RMP (if applicable)	To address PRAC comments on the PSUR, related to ICANS data. To address PRAC comments on the PSUR, related to the addition of ICANS to the Patient Card.
Summary of significant changes in this RMP:	Added information on ICANS from clinical trials with teclistamab alone or in combination and from postmarketing data, and updated the symptoms of ICANS. Changed the important identified risk from "Neurologic toxicity" to "Neurologic toxicity, including ICANS". Expanded the Patient Card to include details on "Neurologic toxicity, including ICANS".

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:	2.3
Approved within procedure	EMEA/H/C/005865/II/0006
Date of approval (Competent authority opinion date)	16 August 2023 (EC Decision)

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Teclistamab
Pharmacotherapeutic group(s) (ATC Code)	Other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX24
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)	TECVAYLI
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: humanized immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) bispecific antibody
	Summary of mode of action: Teclistamab is a full-size, IgG4-PAA bispecific antibody that targets the cluster of differentiation 3 (CD3) receptor expressed on the surface of T cells and B cell maturation antigen (BCMA), which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. With its dual binding sites, teclistamab is able to draw $CD3^+$ T cells in close proximity to $BCMA^+$ cells, resulting in T cell activation and subsequent lysis and death of $BCMA^+$ cells, which is mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells. This effect occurs without regard to T cell receptor specificity or reliance on major histocompatability complex (MHC) Class 1 molecules on the surface of antigen presenting cells.
	Important information about its composition: Teclistamab is a humanized IgG4-PAA bispecific antibody directed against the BCMA and CD3 receptors, produced in a mammalian cell line (Chinese hamster ovary [CHO]) using 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: Teclistamab 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="4">Current:
The recommended doses of teclistamab are 1.5 mg/kg by subcutaneous injection weekly, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg, as shown in the following table. In patients who have a complete response or better for a minimum of 6 months, a reduced dosing frequency of 1.5 mg/kg SC every 2 weeks may be considered.</td></tr>
<tr><td></td><td>Dosing schedule</td><td colspan="2">Day</td><td>Dose[a]</td></tr>
<tr><td></td><td colspan="4">All patients</td></tr>
<tr><td></td><td rowspan="3">Step-up dosing schedule[e]</td><td>Day 1</td><td>Step-up dose 1</td><td>0.06 mg/kg SC single dose</td></tr>
<tr><td></td><td>Day 3[b]</td><td>Step-up dose 2</td><td>0.3 mg/kg SC single dose</td></tr>
<tr><td></td><td>Day 5[c]</td><td>First maintenance dose</td><td>1.5 mg/kg SC single dose</td></tr>
<tr><td></td><td>Weekly dosing schedule[e]</td><td>One week after first maintenance dose and weekly thereafter[d]</td><td>Subsequent maintenance doses</td><td>1.5 mg/kg SC once weekly</td></tr>
<tr><td></td><td colspan="4">Patients who have a complete response or better for a minimum of 6 months</td></tr>
<tr><td></td><td>Biweekly (every 2 weeks) dosing schedule[e]</td><td colspan="3">Consider reducing the dosing frequency to 1.5 mg/kg SC every 2 weeks</td></tr>
<tr><td></td><td colspan="4">[a] Dose is based on actual body weight and should be administered subcutaneously.
[b] Step-up dose 2 may be given between 2 to 7 days after Step-up dose 1.
[c] First maintenance dose may be given between 2 to 7 days after Step-up dose 2. This is the first full treatment dose (1.5 mg/kg).
[d] Maintain a minimum of 5 days between weekly maintenance doses.
[e] See Table 2 in the SmPC for recommendations on restarting teclistamab after dose delays.</td></tr>
<tr><td></td><td colspan="4">Proposed: Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td colspan="4">Current: Teclistamab is available as a solution for injection and is provided in a 3 mL-vial containing 30 mg of teclistamab (10 mg/mL) or a 1.7 mL-vial containing 153 mg of teclistamab (90 mg/mL).</td></tr>
<tr><td></td><td colspan="4">Proposed: Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td colspan="2">☑ Yes</td><td colspan="2">☐ No</td></tr>
</table>

PART II: SAFETY SPECIFICATION

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

Indication: Multiple Myeloma

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 European Union (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 (European Cancer Information System [ECIS] 2021). The estimated number of new cases for the EU overall was 35,842. Similarly, the annual age-adjusted incidence rate was 6.8 per 100,000 in the United Kingdom (UK) with 4,440 cases (Haematological Malignancy Research Network [HMRN] 2021). 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 2020 using 10 years of collected or projected data, as described by Kantar Health's CancerMPact® 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	2020	10-year	24,076	3.7	CancerMPact® 2021
Germany	2020	10-year	32,755	3.9	CancerMPact® 2021
Italy	2020	10-year	24,426	4.0	CancerMPact® 2021
Spain	2020	10-year	12,000	2.6	CancerMPact® 2021
United Kingdom	2016	10-year	19,340	3.0	HMRN 2021
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 United States (US) in 2018, the incidence rates are 8.8 per 100,000 in men versus 5.7 per 100,000 in women (SEER 2021).

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 monoclonal gammopathy of undetermined significance (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% confidence interval [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, and doxorubicin);
- Histone deacetylase inhibitors (panobinostat);
- Monoclonal antibodies (daratumumab, isatuximab, and elotuzumab);
- Immunomodulatory agents (ImiDs including thalidomide, lenalidomide, or pomalidomide);
- Proteasome inhibitors (Pis including bortezomib, ixazomib, and carfilzomib);
- Nuclear export inhibitor (selinexor);
- Anti-BCMA targeted treatment (idecabtagene vicleucel, belantamab mafodotin);
- Corticosteroids (dexamethasone, methylprednisone, prednisone).

In US and European guidelines, treatment approaches depend on patient fitness and risk of toxicities (National Comprehensive Cancer Network [NCCN] 2021; Dimopoulos 2021). The initial evaluation of patients includes an assessment of eligibility for high-dose therapy and autologous stem cell transplantation (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. 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 and is characterized by patterns of remissions and relapses until death. With each successive relapse and new line of treatment, the chance of response, duration of response, and median overall survival (OS) typically decreases (Gandhi 2019). A recent prospective observational study evaluated the outcomes of 246 patients with relapsed or refractory multiple myeloma who were triple class exposed (Moreau 2021). 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, 75% were triple class refractory, and 93% were refractory to the last line

of therapy. The overall response rate (ORR) was 28%. With a median duration of follow up of 7.8 months, the median duration of response was 5.1 months, the median progression-free survival (PFS) was 4.4 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 a plasma cell dyscrasia (Kyle 2018). Plasma cell dyscrasias are a spectrum of progressively more severe monoclonal gammopathies, which range from pre-malignant conditions, such as MGUS and smoldering multiple myeloma (SMM), to paraneoplastic conditions, like amyloid light chain (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, especially among patients with an immunoglobulin M (IgM) MGUS. (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 (Langren 2009).

Another plasma cell dyscrasia preceding active multiple myeloma is SMM, an asymptomatic stage of disease without end organ damage. Smoldering multiple myeloma (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 European Union countries, with an age-standardized mortality rate of 4.8 per 100,000 (ECIS 2021). The 5-year relative survival for multiple myeloma patients is 48% in the UK in 2016 and ranged from 45.6% to 60.3% in Nordic countries (HMRN 2021; 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 overall survival was approximately 4.6 years in the Swedish Myeloma Registry in 2016.

Multiple factors are considered in risk stratification for multiple myeloma. The International Staging System [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 revised ISS (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). 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 elevated calcium, renal failure, anemia, or lytic bone lesions (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.

Anemia can arise as a result of myelosuppression, where the clonal plasma cells crowd out the normal blood cells or reduce production of blood cells and platelets. Ongoing anemia can lead to arrhythmias, heart failure, dyspnea, fatigue, and dizziness. Baseline renal impairment can worsen, largely as a result of M-protein build-up in the kidneys, hypercalcemia, or hyperuricemia, and result in end stage renal disease (Dimopoulos 2008). Additionally, hypercalcemia can result in nausea/vomiting, constipation, confusion, and hypercalcemic crisis.

Other conditions related to the disease are also anticipated. Hyperviscosity syndrome and cryoglobulinemia can arise due to increased circulating serum immunoglobulins in multiple myeloma (Talamo 2010). In addition to causing anemia, myelosuppression due to the clonal plasma cells in the bone marrow can lead to leukopenia, especially neutropenia, and thrombocytopenia.

Neutropenia is present at diagnosis in approximately 6% of patients and is associated with a higher risk of infection (Augustson 2005; Palumbo 2012). According to a study of 9,253 patients with multiple myeloma and 34,931 matched controls without hematologic malignancy conducted in Sweden between 2004 and 2007, patients with multiple myeloma have a 7-fold higher risk of infections due to clonal plasma cells affecting immune system activities (Blimark 2015). The risk of infections was 11-fold greater during the first year following diagnosis. The most common infections were meningitis, septicemia, pneumonia, osteomyelitis, cellulitis, and pyelonephritis. The risk of viral infections was 10-fold higher overall and 18-fold higher during the first year. Influenza infection and herpes zoster were the most frequent viral infections. Patients with multiple myeloma display a 7.5 times higher hazard of deep vein thrombosis and pulmonary embolism within the first year of disease than the general matched Swedish population (Kristinsson 2010).

Additional plasma cell dyscrasias that did not exist at diagnosis may also arise during multiple myeloma, including plasmacytomas, plasma cell leukemia, AL amyloidosis, and Waldenstrom macroglobulinemia. The rate of extramedullary disease (EMD) in the first 3 years following diagnosis was 3% (Short 2011).

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, ulcers, mild liver disease, chronic pulmonary disease, diabetes mellitus with chronic complications, metastatic solid tumors, and lymphoma (Gregersen 2017). 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

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
A 5-week repeat dose toxicity study in cynomolgus monkeys was performed administering teclistamab intravenously, once weekly. No toxicities were observed in any measured parameter.	The lack of pharmacodynamic (eg, cytokine release or transient lymphocyte decreases) or toxicological response to teclistamab was attributed to a combination of lower number of plasma cells (and consequently low expression of BCMA) in a healthy cynomolgus monkey compared with a multiple myeloma patient and limited cross-reactivity of teclistamab to cynomolgus monkey BCMA relative to human BCMA. Translation to human usage may be limited. Based on expression of BCMA on a subset of mature B cells and plasma cells, depletion of these cells is expected which may result in increased risk of infection and hypogammaglobulinemia.
Reproductive toxicity	
No reproductive toxicity studies were conducted with teclistamab. Reproductive toxicity studies (eg. Fertility and early embryonic development studies) are generally not applicable to therapies for advanced cancer indications (ICH S9).	Expression of BCMA in reproductive tissues was studied in an examination of 33 tissues for BCMA protein by immunohistochemistry using a commercially available polyclonal antibody. B cell maturation antigen (BCMA) was not detected in female reproductive organs such as uterus, fallopian tubes, ovary, and placenta, or in male reproductive organs such as prostate and testis (Carpenter 2013). No test-article related microscopic findings were noted in the histopathology examination of the pivotal repeat dose toxicity study, including juvenile male (epididymis, prostate, and testis) and juvenile female (cervix, uterus, and vagina) reproductive tissues.
Developmental toxicity	
No developmental toxicity studies were conducted with teclistamab. Developmental toxicity studies (pre- and postnatal development studies) are generally not applicable to therapies for advanced cancer indications (ICH S9); however, an assessment of embryo-fetal development toxicity are needed to support marketing applications [ICH S5(R3) and ICH M3(R2)].	Developmental toxicity, including pregnancy and lactation, was not considered essential to inform risk to pregnant women based on the intended patient population and BCMA target biology including data from genetically modified mice that lack BCMA. Therefore, it was not assessed in nonclinical studies. Immunoglobulin G (IgG) antibodies are known to cross the human placenta during pregnancy and have been detected in the serum of infants born to patients treated with therapeutic antibodies (Hyrich 2014).

Key Safety Findings	Relevance to Human Usage
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).	Teclistamab is not expected to be genotoxic.
Carcinogenicity	
No standard carcinogenicity studies were conducted with teclistamab. Standard carcinogenicity studies are generally not applicable to therapies for advanced cancer indications (ICH S9).	Teclistamab is not expected to be carcinogenic.
Safety pharmacology:	
Cardiovascular system (including potential for QT interval prolongation)	
No cardiovascular effects were identified in the 5-week cynomolgus monkey study.	Based on the nonclinical data, teclistamab is not expected to affect cardiovascular function or induce QT prolongation. While there is restricted expression of BCMA on B-lineage cells, cytokine release syndrome (CRS), a known toxicity associated with T cell activating therapies, may affect safety pharmacology parameters (Lee 2014; Lee 2019).
Nervous system	
No nervous system effects were identified in the 5-week cynomolgus monkey study.	Based on nonclinical data, no BCMA protein expression could be detected in normal human adult brain and teclistamab is not expected to affect the nervous system function; however, neurotoxicity (eg, immune effector cell-associated neurotoxicity syndrome [ICANS] and other neurotoxicities) is a known potential toxicity with bispecific antibodies that engage T cells (Salvaris 2021)
Nephrotoxicity	
No nephrotoxicity was identified in the clinical and anatomic pathology assessment in the 5-week cynomolgus monkey study.	Based on the nonclinical data, teclistamab is not expected to be nephrotoxic. Renal injury could occur as a manifestation of CRS (Shimabukuro-Vornhagen 2018). Renal insufficiency is common in multiple myeloma (Dimopoulos 2008).
Hepatotoxicity	
No hepatotoxicity was identified in the clinical and anatomic pathology assessments in the 5-week cynomolgus monkey study.	Based on the nonclinical data, teclistamab is not expected to be hepatotoxic. However, CRS, a known toxicity associated with T cell activating therapies, may present with hepatotoxicity (Shimabukuro-Vornhagen 2018).

Key Safety Findings	Relevance to Human Usage
Other toxicity-related information or data	
Immunogenicity	
In a repeat dose toxicity study, 21 out of 30 cynomolgus monkeys developed measurable anti-drug antibodies (ADAs) at 1, 10, and 30 mg/kg/week following 5 weeks of dosing, of which 7 animals exhibited a faster decrease in teclistamab concentration. No cynomolgus monkeys had ADA-related toxicity.	The relationship between immunogenicity in animals and humans is not well established and results in animals are not expected to be predictive of the human immunogenic response.
Cytokine Release Assay	
Teclistamab was evaluated for potential to stimulate release of cytokines in an in vitro soluble format 48 hour diluted whole blood model system using blood from human donors. Teclistamab induced statistically significant but low-level release of interleukin (IL)-8, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α compared to that of the negative control (phosphate buffered saline) at concentrations greater than or equal to 82 ng/mL.	Consistent with the mechanism of action, cytokine release is expected with T-cell redirecting therapies and the risk mitigation strategy has been implemented clinically.

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 teclistamab (JNJ-64007957) in the multiple myeloma population is supported by one clinical trial in this EU RMP, ie, Trial 64007957MMY1001 (also known as MajesTEC-1; hereafter referred to as MMY1001).

Trial MMY1001 is an ongoing Phase 1/2, open-label, multicenter trial of teclistamab administered as monotherapy to adult subjects with relapsed or refractory multiple myeloma. Phase 1 included Part 1 (dose escalation) and Part 2 (dose expansion) and evaluated the safety, PK, and pharmacodynamics of teclistamab, as well as selection and preliminary evaluation of the proposed recommended Phase 2 doses (RP2Ds). The RP2D to be further evaluated was determined to be 1.5 mg/kg of teclistamab administered subcutaneously (SC) weekly, preceded by step-up doses of 0.06 and 0.3 mg/kg.

During Phase 2 (Part 3), the pivotal RP2D was evaluated in cohorts of subjects that differed by prior therapies. Cohort A is the patient population that aligns with the intended indication, and includes patients with multiple myeloma who are triple class exposed (PI, ImiD, and an anti-CD38 monoclonal antibody) and have previously received ≥3 prior lines of therapy.

The RMP includes data from subjects who received the pivotal RP2D (hereafter referred to as RP2D), either in Phase 1 or in Cohort A of Phase 2. The clinical cutoff date for clinical trial exposure is 4 January 2023. As of that data cutoff date, this includes 165 subjects.

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 teclistamab in the all clinical trials population is summarized in Tables SIII.1 through SIII.4 for all subjects 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: Cumulative Exposure by Duration; All Clinical Trials Population

	Persons	Person-Months
Duration of exposure		
Multiple Myeloma		
1.5 mg/kg SC:		
Cumulative up to 3 months	52	61.0
Cumulative up to 6 months	66	120.4
Cumulative up to 9 months	82	243.7
Cumulative up to 12 months	94	368.0
Cumulative up to 18 months	111	629.2
Cumulative up to 24 months	146	1388.7
Cumulative up to 30 months	163	1824.6
Total	165	1888.7

Note: 1 month equals 365.25/12 days. Study MMY1001 subjects who received 1.5 mg/kg SC in Phase 1 or Cohort A of Phase 2 are included.

[tsiexp01a.rtf] [jnj-64007957/mmy1001_p3/dbr_biweekly_csr_feb2023/re_rmp_june2023/tsiexp01a.sas] 26JUN2023, 10:18

Table SIII.2: Exposure by Age Group and Gender: All Clinical Trials Population

	Men		Women	
	Persons	Person-Months	Persons	Person-Months
Age Group				
Multiple Myeloma				
1.5 mg/kg SC:				
<30 years	0	0	0	0
30-54 years	18	254.9	13	143.6
55-64 years	32	353.3	23	275.8
65-74 years	33	360.7	22	265.1
75-84 years	13	122.8	11	112.4
>=85 years	0	0	0	0
Total	96	1091.7	69	797.0

Note: 1 month equals 365.25/12 days. Study MMY1001 subjects who received 1.5 mg/kg SC in Phase 1 or Cohort A of Phase 2 are included.

[tsiexp02a.rtf] [jnj-64007957/mmy1001_p3/dbr_biweekly_csr_feb2023/re_rmp_june2023/tsiexp02a.sas] 26JUN2023, 10:18

Table SIII.3: Exposure by Dose: All Clinical Trials Population

	Persons	Person-Months
Dose of exposure		
Multiple Myeloma		
1.5 mg/kg SC	165	1888.7

Note: 1 month equals 365.25/12 days. Study MMY1001 subjects who received 1.5 mg/kg SC in Phase 1 or Cohort A of Phase 2 are included.

[tsiexp03a.rtf] [jnj-64007957/mmy1001_p3/dbr_biweekly_csr_feb2023/re_rmp_june2023/tsiexp03.sas] 26JUN2023, 10:18

Table SIII.4: Exposure by Special Populations: All Clinical Trials Population

	Persons	Person-Months
Population		
Multiple Myeloma		
Ethnicity		
Hispanic or Latino	15	146.5
Not-Hispanic or Latino	144	1704.4
Not Reported	5	33.8
Unknown	1	3.9
Total	165	1888.7
Race		
White	134	1597.1
Black or African American	21	219.6
Asian	3	31.4
American Indian or Alaska Native	0	0
Not Reported	4	22.1
Multiple[a]	1	8.5
Other	2	9.9
Total	165	1888.7
Renal impairment at baseline (e-GFR mL/min/1.73 m^2)		
Normal (>= 90 mL/min)	75	768.4
Mild (60 to < 90 mL/min)	64	922.8
Moderate (30 to < 60 mL/min)	26	197.4
Severe (< 30 mL/min)	0	0
Missing	0	0
Total	165	1888.7
Hepatic impairment at baseline[b]		
Normal	143	1695.9
Mild	22	192.8
Moderate	0	0
Severe	0	0
Missing	0	0
Total	165	1888.7

[a] Multiple=one or more category was selected
[b] Normal hepatic function (per NCI organ dysfunction criteria): total bilirubin ≤ ULN and AST ≤ ULN; Mild: (total bilirubin ≤ ULN and AST >ULN) or (ULN < total bilirubin ≤ 1.5 x ULN); Moderate: 1.5 x ULN < total bilirubin ≤ 3 x ULN; Severe: total bilirubin > 3 x ULN.
Key: AST = Aspartate Aminotransferase; e-GFR=estimated Glomerular Filtration Rate; NCI = National Cancer Institute; ULN = Upper Limit Normal.
Note: 1 month equals 365.25/12 days. Study MMY1001 subjects who received 1.5 mg/kg SC in Phase 1 or Cohort A of Phase 2 are included.

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

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

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Pregnant or breast-feeding**
Reason for being an exclusion criterion	Per ICH guidelines, pregnant women should normally be excluded from clinical trials. 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 teclistamab is excreted in human or animal milk or affects milk production.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Pregnancy and breast-feeding is uncommon in this heavily pretreated patient population, and thus use in these patients is not considered missing information. SmPC Section 4.6 states that teclistamab is not recommended for women who are pregnant, and that women of child-bearing potential should use effective contraception during treatment and for 5 months after the final dose of teclistamab.
Criterion 2	**Known to be seropositive for human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (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)	This is consistent with standard of care.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 3	**Active Hepatitis B Virus (HBV) or Hepatitis C Virus (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)	It is consistent with standard of care to not treat patients with active infections. The SmPC states that patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation while receiving teclistamab, and for at least 6 months following the end of treatment.
Criterion 4	**The following cardiac conditions:** • **New York Heart Association stage III or IV congestive heart failure** • **Myocardial infarction or coronary artery bypass graft (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)	There are no specific data on the use of teclistamab in patients with significant cardiac disease. 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, type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing** • **Psychiatric conditions (eg, alcohol or drug abuse), 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. Neurologic toxicities have been reported with bispecific T-cell redirectors. 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
Rationale (if not included as missing information)	The SmPC includes a recommendation to delay the initial doses of teclistamab until any active infection has resolved. There are no specific data on the use of teclistamab in patients with autoimmune disease or recent stroke or seizure. 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 6	**Known active central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma**
Reason for being an exclusion criterion	Neurologic toxicities have been reported with bispecific T-cell redirectors. 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)	There are no specific data on the use of teclistamab in patients with active CNS involvement. 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 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 to be 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 to allow a minimal interval of time since prior therapies, in order to avoid overlapping toxicities from anticancer therapies.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	This is consistent with standard of care.

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
Breast-feeding women	Not included in the clinical development program
Population with relevant different ethnic origin	Of 165 subjects in the all clinical trials population, 134 subjects (81.2%) were White, 21 subjects (12.7%) were Black or African American, and 3 subjects (1.8%) were Asian. The remaining 7 subjects (4.2%) had race reported as "multiple," "other," or data were not reported.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects must have had alanine transaminase (ALT) and aspartate transaminase (AST) ≤3 x the upper limit of normal (ULN) at screening to be eligible for trial participation. Of 165 subjects in the all clinical trials population, there were 22 subjects (13.3%) with mild hepatic impairment at baseline (total bilirubin ≤ULN and AST >ULN, or ULN < total bilirubin ≤ 1.5 x ULN; [Ramalingam 2010]); no subjects had moderate (1.5 x ULN < total bilirubin ≤ 3 x ULN) or severe (total bilirubin >3 x ULN) hepatic impairment at baseline.
Patients with renal impairment	Subjects must have had e-GFR of ≥40 mL/min/1.73 m^2 at screening to be eligible for trial participation. Of 165 subjects in the all clinical trials population, there were 64 subjects (38.7%) with mild renal impairment at baseline (e-GFR 60 to <90 mL/min/1.73 m^2), 26 subjects (15.7%) with moderate renal impairment (e-GFR 30 to <60 mL/min/1.73 m^2), and no subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2).
Patients with cardiovascular impairment	Patients with the following conditions were excluded from the clinical development program: New York Heart Association stage 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

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time medication is distributed until it is used by a patient.

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. Region specific bodyweight has been used to calculate exposure.

At the time of the RMP data lock point (28 February 2023), the recommended dosing was 1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule. For step-up dosing, an average duration of 3 days is considered based on the statement "Two to 4 days after Step-up Dose". Considering this, the average is 53 doses/per year (ie, 2 step-up doses and 51 treatment doses) assuming a compliance rate of 100%. The dosing schedules have been provided as:

- European Union: 70.8 kg=5,441.7 mg per year
- North America: 80.7 kg=4,765.3 mg per year
- Rest of world: 62 kg=6,202.6 mg per year

SV.1.2. Exposure

The interval/cumulative exposure to teclistamab by region is presented below.

Interval/Cumulative Exposure to Teclistamab (01 September 2022 to 28 February 2023)

Region	Total Milligrams	Person-Years
EU	796,785	146
NA[a]	896,730	188
ROW	31,025	5
Total[b]	**1,724,540**	**339**

Note: Post-marketing exposure may include supply used in EAPs
Key: EAP=Expanded Access Programme; EU=European Union; NA=North America; ROW=Rest of World
a: Sales were only reported for the United States.
b: The distribution was first observed in October 2022.

Based on the 1,724,540 milligrams distributed worldwide from 01 September 2022 to 28 February 2023, the estimated exposure to teclistamab is 339 person-years.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Teclistamab 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:
Not applicable
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
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 redirector therapy including bispecific antibodies that bind to CD3. While CRS may be life-threatening or fatal, the majority of CRS events in the clinical trial were Grade 1 or Grade 2. All events of CRS were effectively managed with available treatments. 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 Studies MMY1001 and 64007957MMY3001 (hereafter referred to as MMY3001) 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. Overall, the risk-benefit balance is positive for the product considering the severity of the proposed indication, the demonstrated efficacy for patients treated with teclistamab, and the low grade severity of CRS observed in the clinical trial.
Neurologic toxicity	Neurologic toxicity, primarily ICANS, is a known class effect associated with T-cell redirector therapies. While neurologic toxicities, including ICANS, may be life-threatening or fatal, all ICANS events in the teclistamab clinical trial as of the 16 March 2022 cutoff date were Grade 1 or Grade 2. Neurologic toxicities were effectively managed with available treatments. Detailed guidance for how to manage and mitigate ICANS is provided in the SmPC and PL. Follow-up data from Studies MMY1001 and MMY3001 will provide further information on the risk of neurologic toxicity. Overall, the risk-benefit balance is positive for the product considering the severity of the proposed indication, the demonstrated efficacy for patients treated with teclistamab, and the low grade severity of neurologic toxicities observed in clinical trials.
Serious infections	Serious infections including pneumonia and sepsis have been reported in the teclistamab clinical trial. Teclistamab is expected to reduce B cells which may lead to hypogammaglobulinemia, resulting in the increase of serious infection including HBV reactivation. 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 Studies MMY1001 will provide further information on the risk of serious infections. Serious infection also will be monitored in the planned phase 3 trial (MMY3001) with comparators to further evaluate the causality of serious infection with teclistamab.

	The SmPC and PL provide information on how to manage the risk of infection. Overall, the risk benefit balance is positive for the product considering the severity of the proposed indication, the ability to manage infections, and the demonstrated efficacy for patients treated with teclistamab.
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 teclistamab. Follow-up data from Study MMY1001 will provide further information on the long-term safety profile of the product.

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

Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 was used to classify the clinical trial adverse event information that is summarized in this section. Data in this section are based on a data cutoff date of 16 March 2022.

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

Important Identified Risk: Cytokine release syndrome

Potential Mechanisms:

Teclistamab targets the CD3 receptor on T cells and BCMA on B cells and subsequently promotes T cell activation and causes cytokines to be released, which may result in CRS. The increase in

multiple cytokines, in particular IL-10, IL-6, and IL-2R, was noted during step-up dosing and the first cycle of teclistamab.

Evidence Source(s) and Strength of Evidence:

Cytokine release syndrome is a known class effect associated with T-cell redirector therapy including bispecific antibodies that bind to CD3. Cytokine release syndrome has been reported in subjects treated in the teclistamab 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 teclistamab.

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

Characterization of the Risk:

Cytokine Release Syndrome: Frequency, Seriousness, Outcomes, and Severity in Clinical Trials

	All Clinical Trials
	Teclistamab 1.5 mg/kg
Multiple Myeloma	
Number of subjects treated	165
Frequency[a]	119 (72.1%)
Seriousness	14 (8.5%)
Outcomes	
Fatal	0
Not recovered/Not Resolved	0
Recovered with sequelae	0
Recovered/Resolved	119 (72.1%)
Recovering/Resolving	0
Unknown[b]	0
Severity (toxicity grade)	
Worst Grade=1	83 (50.3%)
Worst Grade=2	35 (21.2%)
Worst Grade=3	1 (0.6%)
Worst Grade=4	0
Worst Grade=5	0
Missing	0

Note: Study MMY1001 subjects who received 1.5 mg/kg SC in Phase 1 or Cohort A of Phase 2 are included.
[a] Includes subjects who had one or more occurrences of treatment-emergent adverse events that coded to the following MedDRA terms: cytokine release syndrome and cytokine release storm; the subject 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 24.0.
Note: The denominators are total number of subjects treated.
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Clinical signs and symptoms of CRS may include but are not limited to fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes. Potentially life-threatening

complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal or hepatic failure, and disseminated intravascular coagulation.

At RP2D in Trial MMY1001, CRS was reported for 72.1% of subjects. One subject had a Grade 3 event and all other events were Grade 1 or Grade 2. The median time from last teclistamab injection to new onset of CRS was 2 days (range: 1 to 6 days). The median duration of CRS was 2 days, with duration ranging from 1 to 9 days. All events of CRS resolved.

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:

Teclistamab should be initiated using step-up dosing to reduce the incidence and severity of CRS. The step-up dosing schedule should not be started in patients with active infection. Pretreatment medication should be administered for all patients prior to each dose in the Step-up dosing schedule (which includes the first full maintenance dose). Patients should be instructed to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of all doses in the step-up dosing schedule. At the first sign of CRS, patients should be evaluated for hospitalization, and treatment (which may include tocilizumab and/or corticosteroids) should be started. For any patient who has experienced CRS, pretreatment medication should be administered prior to their next dose of teclistamab and they should remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration. Specific guidelines for the management of CRS by severity are provided in the SmPC. 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 redirector therapy including bispecific antibodies that bind to CD3. While CRS may be life-threatening or fatal, the majority of CRS events in the clinical trial were Grade 1 or Grade 2. All events of CRS were effectively managed with available treatments. 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 Studies MMY1001 and MMY3001 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. Overall, the risk-benefit balance is positive for the product considering the severity of the proposed indication, the demonstrated efficacy for patients treated with teclistamab, and the 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 (Preferred term [PT])

Important Identified Risk: Neurologic toxicity, including ICANS

Potential Mechanisms:

Neurologic toxicity, including ICANS, has been reported with other T-cell redirectors; 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 redirectors. Neurologic toxicity, including ICANS, has been reported in subjects treated with teclistamab in the clinical trial and ICANS was identified as an adverse reaction. The risk for neurologic toxicity, including ICANS, and information regarding this adverse reaction, are described in the SmPC for teclistamab.

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

Characterization of the Risk:

As the clinical manifestations of neurological toxicity, including ICANS, varied from nervous system disorders to psychiatric disorders, the system organ classes (SOCs) of Nervous System Disorders and Psychiatric Disorders were used for this important identified risk. However, the major safety concern for teclistamab is ICANS as a class effect associated with bispecific T-cell redirectors. One case of reversible movement disorder was also reported, which could be drug induced. Other neurological findings were non-specific and were consistent with neurologic toxicity observed with bispecific T-cell redirectors.

Neurologic Toxicity, including ICANS: Frequency, Seriousness, Outcomes, and Severity in Clinical Trials

	All Clinical Trials
	Teclistamab 1.5 mg/kg
Multiple Myeloma	
Number of subjects treated	165
Frequency[a]	95 (57.6%)
Seriousness	13 (7.9%)
Outcomes	
Fatal	0
Not recovered/Not Resolved	20 (12.1%)
Recovered with sequelae	1 (0.6%)
Recovered/Resolved	65 (39.4%)
Recovering/Resolving	9 (5.5%)
Unknown[b]	0
Severity (toxicity grade)	
Worst Grade=1	46 (27.9%)
Worst Grade=2	43 (26.1%)
Worst Grade=3	4 (2.4%)
Worst Grade=4	2 (1.2%)
Worst Grade=5	0
Missing	0

Note: Study MMY1001 subjects who received 1.5 mg/kg SC in Phase 1 or Cohort A of Phase 2 are included.
[a] Includes subjects who had one or more occurrences of treatment-emergent adverse events that coded to the following Body system: nervous system disorders, psychiatric disorders; the subject 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 24.0.
Note: The denominators are total number of subjects treated.
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Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported for 5 subjects (3.0%) in Trial MMY1001 (n=165), and the severity was Grade 1 or Grade 2 for all events. The median time from last injection of teclistamab to new onset of ICANS was 4 days (range: 2 to 5 days) and the median duration of ICANS was 3 days (range: 1 to 20 days). All events of ICANS resolved, with none leading to discontinuation or death.

Grade 3 and higher ICANS events (<1%) were reported in clinical trials with teclistamab alone and in combination with other medicinal products (16 March 2023 cutoff date) and from postmarketing data (22 February 2023 cutoff date); the median observed time to onset of ICANS events (any grade) was 3 days (range: 0 to 21 days) after the most recent dose.

The most frequent clinical manifestations of ICANS were confusional state, decreased level of consciousness, disorientation, dysgraphia, aphasia, apraxia, and somnolence.

Of subjects treated at RP2D in Trial MMY1001, 57.6% were reported to have at least 1 event in the Nervous System Disorders or Psychiatric Disorders SOC (defined as neurologic toxicity, including ICANS, above); most events were Grade 1 or Grade 2. Thirteen subjects (7.9%) were

reported to have serious events. One subject had a serious event of neurotoxicity that was considered related to teclistamab treatment; preferred terms included cogwheel rigidity, hypokinesia, lethargy, muscle rigidity, tremor, and apathy. These events have either resolved or are resolving, and the subject remains on trial at the time of clinical cutoff.

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:

Patients should be monitored for symptoms of neurologic toxicity, including ICANS, and treated promptly. At the first sign of ICANS, patients should be evaluated and treated with consideration for neurologic evaluation. Teclistamab should be withheld until resolution of any Grade 1, Grade 2, or first occurrence of a Grade 3 event of ICANS, and should be permanently discontinued for any recurrent Grade 3 or any Grade 4 ICANS event. In the case of any Grade 2 or first occurrence of a Grade 3 ICANS event, patients should remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of the next dose of teclistamab. Specific guidelines for the management of ICANS by severity are provided in the SmPC. Part V.2 of the RMP includes an additional risk minimization measure (ie, Patient Card) to further mitigate the risk of neurologic toxicity, including ICANS.

Impact on the Risk-Benefit Balance of the Product:

Neurologic toxicity, including ICANS, is a known class effect associated with T-cell redirector therapies. While neurologic toxicities including ICANS may be life threatening or fatal, all ICANS events in the teclistamab clinical trial were Grade 1 or Grade 2.

Neurologic toxicities, including ICANS, were effectively managed with available treatments. Detailed guidance for how to manage and mitigate ICANS is provided in the SmPC and PL. Follow-up data from Studies MMY1001 and MMY3001 will provide further information on the risk of neurologic toxicity, including ICANS. A Patient Card is included as an additional risk minimization measure to further mitigate this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the proposed indication, the demonstrated efficacy for patients treated with teclistamab, and the low-grade severity of neurologic toxicities, 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:

Nervous System Disorders (SOC)

Important Identified Risk: Serious infections

Potential Mechanisms:

Multiple myeloma is a bone marrow disorder of immune system cells (plasma cells) with impaired immune function resulting in infection. B cell maturation antigen (BCMA) is expressed in B cell lineage. Teclistamab is expected to reduce B cells which may lead to hypogammaglobulinemia.

Evidence Source(s) and Strength of Evidence:

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

Based on the findings from the clinical trial, serious infections are considered an important identified risk for teclistamab. Further data are needed to establish whether a causal relationship exists.

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.

All Infections: Frequency, Seriousness, Outcomes, and Severity in Clinical Trials

	All Clinical Trials
	Teclistamab 1.5 mg/kg
Multiple Myeloma	
Number of subjects treated	165
Frequency[a]	126 (76.4%)
Seriousness	67 (40.6%)
Outcomes	
Fatal	15 (9.1%)
Not recovered/Not Resolved	13 (7.9%)
Recovered with sequelae	3 (1.8%)
Recovered/Resolved	83 (50.3%)
Recovering/Resolving	11 (6.7%)
Unknown[b]	1 (0.6%)
Severity (toxicity grade)	
Worst Grade=1	4 (2.4%)
Worst Grade=2	47 (28.5%)
Worst Grade=3	49 (29.7%)
Worst Grade=4	11 (6.7%)
Worst Grade=5	15 (9.1%)
Missing	0

Note: Study MMY1001 subjects who received 1.5 mg/kg SC in Phase 1 or Cohort A of Phase 2 are included.
[a] Includes subjects who had one or more occurrences of treatment-emergent adverse events that coded to the following Body system: infections and infestations, independent of their seriousness; the subject 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 24.0.
Note: The denominators are total number of subjects treated.
[tsfae03.rtf] [jnj-64007957/mmy1001_p3/dbr_asco_ash_ema/re_rmp_may2022/tsfae03.sas] 25MAY2022, 08:54

At RP2D in Trial MMY1001, infections were considered serious for 40.6% of subjects. The most commonly reported serious infections were COVID-19 infection (24 subjects [14.5%]) and pneumonia (17 subjects [10.3%]). Grade 5 infections were reported for 15 subjects (9.1%), of which 12 died from COVID-19, and 1 subject each died from pneumonia, pneumonia streptococcal, and progressive multifocal leukoencephalopathy.

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. In addition, B-cell aplasia and subsequent hypogammaglobulinemia are on-target, off-tumor toxicities for teclistamab, which could result in increased susceptibility to infection including reactivation of latent hepatitis B infection.

Preventability:

Patients with active infection should not be started on the teclistamab step-up dosing schedule until the infection resolves. For subsequent dosing (ie, after step-up dosing), if patients develop an infection of Grade 3 or 4, then teclistamab should be withheld until the infection improves to Grade 2 or better. Patients should be monitored for signs and symptoms of infection prior to and during treatment with teclistamab and should be treated appropriately. Prophylactic antimicrobials should be administered according to local institutional guidelines. Hepatitis B virus reactivation can occur in patients treated with medicinal products directed against B cells. Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation while receiving teclistamab, and for at least 6 months following the end of treatment. Hypogammaglobulinemia has been reported in patients receiving teclistamab. Immunoglobulin levels should be monitored during teclistamab treatment and hypogammaglobulinemia should be treated 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 teclistamab clinical trial. Teclistamab is expected to reduce B cells which may lead to hypogammaglobulinemia, resulting in the increase of serious infection including HBV reactivation. 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 Studies MMY1001 will provide further information on the risk of serious infections. Serious infection also will be monitored in the planned Phase 3 trial (MMY3001) with comparators to further evaluate the causality of serious infection with teclistamab. 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, the ability to manage infections, and the demonstrated efficacy for patients treated with teclistamab.

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 teclistamab.
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 study (64007957MMY1001). Updated data based on a later data cutoff date will increase understanding of the long-term safety profile of the product.

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	Not applicable
Missing Information	Long-term safety

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

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

Specific Adverse Reaction Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description	Milestones
PSUR reporting	To closely monitor immune-mediated adverse events, newly diagnosed and/or worsening peripheral neuropathies and extrapyramidal neurotoxicity, and tumor lysis syndrome.	Routine PSUR submissions following initial approval, in accordance with the EURD list

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities	
Study	
Study name and title	64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma
Rationale and study objectives	Rationale: Teclistamab may be associated with delayed adverse events. The primary objective in Part 1 (dose escalation) is to identify the proposed RP2D(s) and schedule assessed to be safe for teclistamab. The primary objective in Part 2 (dose expansion) is to characterize the safety and tolerability of teclistamab at the proposed RP2D.
Safety concern(s) addressed	CRS, neurologic toxicity, including ICANS, serious infections, long-term safety
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, and ImiD, and an anti-CD38 monoclonal antibody.
Milestones	Updated Safety Report: Q1 2024 Final Report: Q4 2028

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				
64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma	The primary objective in Part 1 (dose escalation) is to identify the proposed RP2D(s) and schedule assessed to be safe for teclistamab. The primary objective in Part 2 (dose expansion) is to characterize the safety and tolerability of teclistamab at the proposed RP2D.	CRS Neurologic toxicity, including ICANS Serious infections Long-term safety	Updated Safety Report Final Report	Q1 2024 Q4 2028
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				
64007957MMY3001: A Phase 3 Randomized Study Comparing Teclistamab in Combination with Daratumumab SC (Tec-Dara) versus Daratumumab SC, Pomalidomide, and Dexamethasone (DPd) or Daratumumab SC, Bortezomib, and Dexamethasone (DVd) in Participants with Relapsed or Refractory Multiple Myeloma Ongoing	The primary objective is to compare the efficacy of Tec Dara with that of an investigator's choice of DPd or DVd as assessed by PFS. Secondary objectives are: • to assess the safety profile of Tec-Dara (including further characterization of the safety concerns of CRS, neurologic toxicity, including ICANS, and serious infections), • to assess the immunogenicity of teclistamab and daratumumab, • to further compare the efficacy of Tec-Dara with DPd/DVd; • to characterize the PK of teclistamab, • to compare the patient-reported outcomes (PROs) of Tec Dara with DPd/DVd, and • to evaluate the efficacy of teclistamab in high-risk molecular subgroups.	Long-term efficacy	Protocol submission Interim report Final report	Jan 2022 Sep 2025 Mar 2028

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:** • Usage of a step-up dosing schedule (ie, Step-up dose 1, Step-up dose 2, and initial maintenance dose) to reduce the incidence and severity of CRS is described in SmPC Sections 4.2 and 4.4. • Instructions that pretreatment medications (corticosteroid, antihistamine, antipyretics) must be administered prior to each dose in the step-up dosing schedule to reduce the risk of CRS are provided in SmPC Sections 4.2 and 4.4. • Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of all doses in the step-up dosing schedule is provided in SmPC Sections 4.2 and 4.4. • Recommendation to withhold teclistamab until any Grade 1, Grade 2, or Grade 3 (<48 hours' duration) CRS event resolves is provided in SmPC Section 4.2 and Section 4.4. • Recommendation to permanently discontinue teclistamab for any Grade 3 (recurrent or >48 hours' duration) or Grade 4 CRS event is provided in SmPC Section 4.2. • Recommendation to administer pretreatment medication prior to the next dose for any patient with a CRS event of Grade 1, Grade 2, or Grade 3 (<48 hours' duration) is provided in SmPC Section 4.2 and in SmPC Section 4.4. • For patients who have a CRS event of Grade 2 or Grade 3 (<48 hours' duration), instruction that they should remain within the proximity of a healthcare facility and be monitored daily for 48 hours after the next dose is provided in SmPC Sections 4.2 and 4.4. • Recommendations that patients should be counselled to seek medical attention if signs and symptoms of CRS occur, that patients should be

	immediately evaluated for hospitalization at the first sign of CRS, and that treatment should be instituted, are provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors, particularly GM-CSF, during CRS is provided in SmPC Section 4.4. • Recommendations that CRS should be identified based on clinical presentation, and that other causes of fever, hypoxia, and hypotension should be evaluated and treated, are provided in SmPC Section 4.4. • Recommendation to administer supportive care as appropriate is provided in SmPC Section 4.4. • Recommendation that laboratory testing should be considered to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function is provided in SmPC Section 4.4. • Specific guidelines for the management of CRS with tocilizumab and/or corticosteroids, depending on toxicity grade and symptoms, is provided in tabular format in SmPC Section 4.4. • Patients should get medical help right away if signs of CRS occur, as described in PL Section 2 and Section 4. **Other routine risk minimization measures beyond the Product Information:** 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 (where the 10 mg/mL vial should be used). 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 to withhold teclistamab until any Grade 1, Grade 2, or first occurrence of a Grade 3 ICANS event resolves is provided in SmPC Section 4.2. • Recommendation to permanently discontinue teclistamab in the case of any recurrent Grade 3 or any Grade 4 ICANS event is provided in SmPC Section 4.2. • Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of the next dose of teclistamab following any Grade 2 or first occurrence of a Grade 3 ICANS event is provided in SmPC Sections 4.2 and 4.4.

	• Recommendation to monitor patients for signs and symptoms of neurologic toxicity and to treat promptly is provided in SmPC Section 4.4. • Recommendation to counsel patients to seek medical attention if signs or symptoms of neurologic toxicity occur is described in SmPC Section 4.4. • At the first sign of neurologic toxicity, including ICANS, recommendation to immediately evaluate and treat patients, consider neurologic evaluation, and rule out other causes of neurologic symptoms is provided in SmPC Section 4.4. • Recommendation to provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities is provided in SmPC Section 4.4. • Detailed guidelines on the management of ICANS, by severity, symptoms, and whether patients have concurrent CRS, including the use of tocilizumab, corticosteroids, and anti-seizure medications, are provided in tabular format in SmPC Section 4.4. • Recommendation to avoid driving and operating heavy or potentially dangerous machinery during and for 48 hours after completion of the teclistamab step-up dosing schedule, and in the event of new onset of any neurological symptoms, is provided in SmPC Sections 4.4 and 4.7. • Patients should get medical help right away if symptoms of ICANS or other neurologic toxicities occur, as described in PL Section 2 and Section 4. **Other routine risk minimization measures beyond the Product Information:** Not applicable
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 to consider antiviral prophylaxis for the prevention of herpes zoster virus reactivation per local institutional guidelines is provided in SmPC Section 4.2. • Recommendation to not administer teclistamab step-up dosing schedule in patients with active infection (any grade) until the infection has resolved is provided in SmPC Section 4.2. • Recommendation that for subsequent dosing (ie, after step-up dosing), if patients develop an infection of Grade 3 or 4, then teclistamab should be withheld until the infection improves to Grade 2 or better is provided in SmPC Section 4.2.

	• Recommendations that patients should be monitored for signs and symptoms of infection prior to and during teclistamab treatment and treated appropriately, and that prophylactic antimicrobials should be administered according to local institutional guidelines, are described in SmPC Section 4.4. • Recommendation that teclistamab should not be administered in patients with active infection and should be withheld for subsequent dosing based on severity of infection is provided in SmPC Section 4.4. • Recommendation that patients with positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during and for at least 6 months after teclistamab treatment is provided in SmPC Section 4.4. • Recommendation that for patients who develop reactivation of HBV, teclistamab should be withheld and this should be managed per local institutional guidelines is provided in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels during teclistamab treatment and treat hypogammaglobulinemia according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement, is included in SmPC Section 4.4. • Recommendations that patients with neutropenia should be monitored for signs of infection, treatment should be withheld based on severity, and blood cell counts should be monitored at baseline and periodically during treatment with supportive care provided per local institutional guidelines, are included in SmPC Section 4.4. • Patients should tell their doctor or nurse if they have any signs of infection, as described in PL Sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Not applicable
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:** Not applicable.

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 associated with teclistamab and increase awareness of symptoms requiring immediate medical attention. To advise patients to stay close to the location where they received teclistamab for 48 hours after each dose of 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/carers who are expected to use teclistamab
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.

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 • Usage of a step-up dosing schedule (ie Step-up dose 1, Step-up dose 2, and initial maintenance dose) to reduce the incidence and severity of CRS is described in SmPC Sections 4.2 and 4.4. • Instructions that pretreatment medications (corticosteroid, antihistamine, antipyretics) must be administered prior to each dose in the step-up dosing schedule to reduce the risk of CRS are provided in SmPC Sections 4.2 and 4.4. • Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of all doses in the step-up dosing schedule is provided in SmPC Sections 4.2 and 4.4. • Recommendation to withhold teclistamab until any Grade 1, Grade 2, or Grade 3 (<48 hours' duration) CRS event resolves is provided in SmPC Section 4.2 and Section 4.4. • Recommendation to permanently discontinue teclistamab for any Grade 3 (recurrent or >48 hours' duration) or Grade 4 CRS event is provided in SmPC Section 4.2. • Recommendation to administer pretreatment medication prior to the next dose for any patient with a CRS event of Grade 1, Grade 2, or Grade 3 (<48 hours' duration) is provided in SmPC Section 4.2 and in SmPC Section 4.4. • For patients who have a CRS event of Grade 2 or Grade 3 (<48 hours' duration),	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma Final report: Q4 2028

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	instruction that they should remain within the proximity of a healthcare facility and be monitored daily for 48 hours after the next dose is provided in SmPC Sections 4.2 and 4.4. • Recommendations that patients should be counselled to seek medical attention if signs and symptoms of CRS occur, that patients should be immediately evaluated for hospitalization at the first sign of CRS, and that treatment should be instituted are provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors, particularly GM-CSF, during CRS is provided in SmPC Section 4.4. • Recommendations that CRS should be identified based on clinical presentation, and that other causes of fever, hypoxia, and hypotension should be evaluated and treated, are provided in SmPC Section 4.4. • Recommendation to administer supportive care as appropriate is provided in SmPC Section 4.4. • Recommendation that laboratory testing should be considered to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function is provided in SmPC Section 4.4. • Specific guidelines for the management of CRS with tocilizumab and/or corticosteroids, depending on toxicity grade and symptoms, is provided in tabular format in SmPC Section 4.4. • Patients should get medical help right away if signs of CRS occur, as described in PL Section 2 and Section 4. • 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 (where the 10 mg/mL vial should be used. Step-up dosing is designed to mitigate the severity of CRS.	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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 to withhold teclistamab until any Grade 1, Grade 2, or first occurrence of a Grade 3 ICANS event resolves is provided in SmPC Section 4.2. • Recommendation to permanently discontinue teclistamab in the case of any recurrent Grade 3 or any Grade 4 ICANS event is provided in SmPC Section 4.2. • Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of the next dose of teclistamab following any Grade 2 or first occurrence of a Grade 3 ICANS event is provided in SmPC Sections 4.2 and 4.4. • Recommendation to monitor patients for signs and symptoms of neurologic toxicity and to treat promptly is provided in SmPC Section 4.4. • Recommendation to counsel patients to seek medical attention if signs or symptoms of neurologic toxicity occur is described in SmPC Section 4.4. • At the first sign of neurologic toxicity, including ICANS, recommendation to immediately evaluate and treat patients, consider neurologic evaluation, and rule out other causes of neurologic symptoms is provided in SmPC Section 4.4. • Recommendation to provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities is provided in SmPC Section 4.4. • Detailed guidelines on the management of ICANS, by severity, symptoms, and whether	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma Final report: Q4 2028

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	patients have concurrent CRS, including the use of tocilizumab, corticosteroids, and anti-seizure medications, are provided in tabular format in SmPC Section 4.4. • Recommendation to avoid driving and operating heavy or potentially dangerous machinery during and for 48 hours after completion of the teclistamab step-up dosing schedule, and in the event of new onset of any neurological symptoms, is provided in SmPC Sections 4.4 and 4.7. • Patients should get medical help right away if symptoms of ICANS or other neurologic toxicities occur, as described in PL Section 2 and Section 4. **Additional risk minimization measures:** • Patient Card	
Serious infections	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Recommendation to consider antiviral prophylaxis for the prevention of herpes zoster virus reactivation per local institutional guidelines is provided in SmPC Section 4.2. • Recommendation to not administer teclistamab step-up dosing schedule in patients with active infection (any grade) until the infection has resolved is provided in SmPC Section 4.2. • Recommendation that for subsequent dosing (ie, after step-up dosing), if patients develop an infection of Grade 3 or 4, then teclistamab should be withheld until the infection improves to Grade 2 or better is provided in SmPC Section 4.2. • Recommendations that patients should be monitored for signs and symptoms of infection prior to and during teclistamab treatment and treated appropriately, and that prophylactic antimicrobials should be administered according to local institutional	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma Final report: Q4 2028

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	guidelines, are described in SmPC Section 4.4. • Recommendation that teclistamab should not be administered in patients with active infection and should be withheld for subsequent dosing based on severity of infection is provided in SmPC Section 4.4. • Recommendation that patients with positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during and for at least 6 months after teclistamab treatment is provided in SmPC Section 4.4. • Recommendation that for patients who develop reactivation of HBV, teclistamab should be withheld and this should be managed per local institutional guidelines is provided in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels during teclistamab treatment and treat hypogammaglobulinemia according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement, is included in SmPC Section 4.4. • Recommendations that patients with neutropenia should be monitored for signs of infection, treatment should be withheld based on severity, and blood cell counts should be monitored at baseline and periodically during treatment with supportive care provided per local institutional guidelines, are included in SmPC Section 4.4. • Patients should tell their doctor or nurse if they have any signs of infection, as described in PL Sections 2 and 4. **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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		Additional pharmacovigilance activities: 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma Final report: Q4 2028

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for teclistamab

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

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

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

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

1. The Medicine and What it is Used For

TECVAYLI 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 (see SmPC for the full indication). It contains teclistamab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of TECVAYLI's benefits can be found in TECVAYLI'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 TECVAYLI, together with measures to minimize such risks and the proposed studies for learning more about TECVAYLI'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 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.

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

- Patient card

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

II.A. List of Important Risks and Missing Information

Important risks of TECVAYLI 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 TECVAYLI. 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 (CRS) Neurologic toxicity, including ICANS Serious infections
Important potential risks	Not applicable
Missing information	Long-term safety

II.B. Summary of Important Risks

Important Identified Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	CRS is a known class effect associated with T-cell redirector therapy including bispecific antibodies that bind to CD3. CRS has been reported in subjects treated in the TECVAYLI 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 TECVAYLI. Based on the strength of evidence from the clinical trial data and information from the literature, CRS is considered an important identified risk for TECVAYLI.

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 • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Usage of a step-up dosing schedule (ie, Step-up dose 1, Step-up dose 2, and initial maintenance dose) to reduce the incidence and severity of CRS is described in SmPC Sections 4.2 and 4.4. • Instructions that pretreatment medications (corticosteroid, antihistamine, antipyretics) must be administered prior to each dose in the step-up dosing schedule to reduce the risk of CRS are provided in SmPC Sections 4.2 and 4.4. • Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of all doses in the step-up dosing schedule is provided in SmPC Sections 4.2 and 4.4. • Recommendation to withhold TECVAYLI until any Grade 1, Grade 2, or Grade 3 (<48 hours' duration) CRS event resolves is provided in SmPC Section 4.2 and Section 4.4. • Recommendation to permanently discontinue TECVAYLI for any Grade 3 (recurrent or >48 hours' duration) or Grade 4 CRS event is provided in SmPC Section 4.2. • Recommendation to administer pretreatment medication prior to the next dose for any patient with a CRS event of Grade 1, Grade 2, or Grade 3 (<48 hours' duration) is provided in SmPC Section 4.2 and in SmPC Section 4.4. • For patients who have a CRS event of Grade 2 or Grade 3 (<48 hours' duration), instruction that they should remain within the proximity of a healthcare facility and be monitored daily for 48 hours after the next dose is provided in SmPC Sections 4.2 and 4.4. • Recommendations that patients should be counselled to seek medical attention if signs and symptoms of CRS occur, that patients should be immediately evaluated for hospitalization at the first sign of CRS, and that treatment should be instituted are provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors, particularly GM-CSF, during CRS is provided in SmPC Section 4.4.

	• Recommendations that CRS should be identified based on clinical presentation, and that other causes of fever, hypoxia, and hypotension should be evaluated and treated, are provided in SmPC Section 4.4. • Recommendation to administer supportive care as appropriate is provided in SmPC Section 4.4. • Recommendation that laboratory testing should be considered to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function is provided in SmPC Section 4.4. • Specific guidelines for the management of CRS with tocilizumab and/or corticosteroids, depending on toxicity grade and symptoms, is provided in tabular format in SmPC Section 4.4. • Patients should get medical help right away if signs of CRS occur, as described in PL Sections 2 and 4. • 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 (where the 10 mg/mL vial should be used). Step-up dosing is designed to mitigate the severity of CRS. Additional risk minimization measures • Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA 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 redirectors. Neurologic toxicity, including ICANS, has been reported in subjects treated with TECVAYLI in the clinical trial and ICANS was identified as an adverse reaction. The risk for neurologic toxicity, including ICANS, and information regarding this adverse reaction, are described in the SmPC for TECVAYLI. Based on the known class effect and the evidence from clinical trial data, neurologic toxicity, including ICANS, is considered an important identified risk for TECVAYLI.
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 to withhold TECVAYLI until any Grade 1, Grade 2, or first occurrence of a Grade 3 ICANS event resolves is provided in SmPC Section 4.2. • Recommendation to permanently discontinue TECVAYLI in the case of any recurrent Grade 3 or any Grade 4 ICANS event is provided in SmPC Section 4.2. • Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of the next dose of TECVAYLI following any Grade 2 or first occurrence of a Grade 3 ICANS event is provided in SmPC Sections 4.2 and 4.4. • Recommendation to monitor patients for signs and symptoms of neurologic toxicity and to treat promptly is provided in SmPC Section 4.4. • Recommendation to counsel patients to seek medical attention if signs or symptoms of neurologic toxicity occur is described in SmPC Section 4.4. • At the first sign of neurologic toxicity, including ICANS, recommendation to immediately evaluate and treat patients, consider neurologic evaluation, and rule out other causes of neurologic symptoms is provided in SmPC Section 4.4. • Recommendation to provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities is provided in SmPC Section 4.4. • Detailed guidelines on the management of ICANS, by severity, symptoms, and whether patients have concurrent CRS, including the use of tocilizumab, corticosteroids, and anti-seizure medications, are provided in tabular format in SmPC Section 4.4. • Recommendation to avoid driving and operating heavy or potentially dangerous machinery during and for 48 hours after completion of the TECVAYLI step-up dosing schedule, and in the event of new onset of any neurological symptoms, is provided in SmPC Sections 4.4 and 4.7. • Patients should get medical help right away if symptoms of ICANS or other neurologic toxicities occur, as described in PL Sections 2 and 4.

	Additional risk minimization measures • Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA 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 subjects treated with TECVAYLI in the clinical trial and serious infections such as pneumonia and sepsis have been identified as an adverse reaction. The risk for serious infection and information regarding this adverse reaction are described in the SmPC for TECVAYLI. Based on the findings from the clinical trial, serious infections are considered an important identified risk for TECVAYLI. Further data are needed to establish whether a causal relationship exists.
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. In addition, B-cell aplasia and subsequent hypogammaglobulinemia are on-target, off-tumor toxicities for TECVAYLI, which could result in increased susceptibility to infection including reactivation of latent hepatitis B infection.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4

	• Recommendation to consider antiviral prophylaxis for the prevention of herpes zoster virus reactivation per local institutional guidelines is provided in SmPC Section 4.2. • Recommendation to not administer TECVAYLI step-up dosing schedule in patients with active infection (any grade) until the infection has resolved is provided in SmPC Section 4.2. • Recommendation that for subsequent dosing (ie, after step-up dosing), if patients develop an infection of Grade 3 or 4, then TECVAYLI should be withheld until the infection improves to Grade 2 or better is provided in SmPC Section 4.2. • Recommendations that patients should be monitored for signs and symptoms of infection prior to and during TECVAYLI treatment and treated appropriately, and that prophylactic antimicrobials should be administered according to local institutional guidelines, are described in SmPC Section 4.4. • Recommendation that TECVAYLI should not be administered in patients with active infection and should be withheld for subsequent dosing based on severity of infection is provided in SmPC Section 4.4. • Recommendation that patients with positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during and for at least 6 months after TECVAYLI treatment is provided in SmPC Section 4.4. • Recommendation that for patients who develop reactivation of HBV, TECVAYLI should be withheld and this should be managed per local institutional guidelines is provided in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels during TECVAYLI treatment and treat hypogammaglobulinemia according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement, is included in SmPC Section 4.4. • Recommendations that patients with neutropenia should be monitored for signs of infection, treatment should be withheld based on severity, and blood cell counts should be monitored at baseline and periodically during treatment with supportive care provided per local institutional guidelines, are included in SmPC Section 4.4. • Patients should tell their doctor or nurse if they have any signs of infection, as described in PL Sections 2 and 4. Additional risk minimization measures • None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA 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	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA 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:

64007957MMY3001: A Phase 3 Randomized Study Comparing Teclistamab in Combination with Daratumumab SC (Tec-Dara) versus Daratumumab SC, Pomalidomide, and Dexamethasone (DPd) or Daratumumab SC, Bortezomib, and Dexamethasone (DVd) in Participants with Relapsed or Refractory Multiple Myeloma

Purpose of the study: The primary objective is to compare the efficacy of teclistamab in combination with daratumumab SC with that of an investigator's choice of DPd or DVd as assessed by progression-free survival (PFS). Secondary objectives are:

- to assess the safety profile of Tec-Dara (including further characterization of the safety concerns of CRS, neurologic toxicity, including ICANS, and serious infections),
- to assess the immunogenicity of teclistamab and daratumumab,
- to further compare the efficacy of Tec-Dara with DPd/DVd;
- to characterize the PK of teclistamab,
- to compare the patient-reported outcomes (PROs) of Tec Dara with DPd/DVd, and
- to evaluate the efficacy of teclistamab in high-risk molecular subgroups.

64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA 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 identify the proposed RP2D(s) and schedule assessed to be safe for teclistamab. The primary objective in Part 2 (dose expansion) is to characterize the safety and tolerability of teclistamab at the proposed 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 TECVAYLI is marketed, all patients/carers who are expected to use teclistamab 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 teclistamab.

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
- The prescribing physician’s contact details