Summary of the Risk Management Plan (RMP) for TALVEY® (Talquetamab)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of TALVEY® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, eg. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of TALVEY® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of TALVEY®.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for talquetamab

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

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

This summary of the RMP for talquetamab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

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

I. The Medicine and What it is Used For

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

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

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

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

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

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

Together, these measures constitute routine risk minimization measures.

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

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

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

II.A. List of Important Risks and Missing Information

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

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

II.B. Summary of Important Risks

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

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

Important Identified Risk: Neurologic toxicity including ICANS

Evidence for linking the risk to the medicine	Neurologic toxicity, primarily ICANS, is a known class effect associated with bispecific T cell redirection therapy. Neurologic toxicity has been reported in participants treated with talquetamab in the clinical trial and several neurologic events were identified as adverse reactions. The risk for neurologic toxicity including ICANS is described in the SmPC for talquetamab. Based on the known class effect and the evidence from clinical trial data, neurologic toxicity including ICANS is considered an important identified risk for talquetamab.
Risk factors and risk groups	Risk factors have not been fully identified. Patients with CNS disorders may be at higher risk for neurological adverse events.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • PL Section 2 • PL Section 4 • Recommendation that patients should remain close to a healthcare facility and be monitored for 48 hours after administration of all doses within the step-up phase is provided in SmPC Section 4.2. • Recommendations for the management of neurologic toxicity (excluding ICANS) by severity, and including actions to be taken (eg, withholding, discontinuation) and treatment, are included in SmPC Section 4.2. • Recommendations for management of ICANS (including neurology consultation, corticosteroids, and anti-seizure medicinal products) is provided in SmPC Section 4.2. • Recommendations for the monitoring, evaluation, and treatment of neurologic toxicity, including ICANS, is provided in SmPC Section 4.4. • Recommendation for restrictions on driving and operating machines due to the potential for ICANS is provided in SmPC Sections 4.4 and 4.7 and PL Section 2. • Guidance for patients to recognize symptoms of neurologic toxicity including ICANS and get medical help right away are included in PL Sections 2 and 4. Additional risk minimization measures • Patient Card • HCP Educational Materials
Additional pharmacovigilance	Additional pharmacovigilance activities:

activities	64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

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

	herpes zoster virus reactivation), per local institutional guidelines, is provided in SmPC Section 4.2. • Recommendations for the management and treatment of serious infections, as well as guidance that the step-up dosing schedule should not be administered in patients with active infection, is provided in SmPC Section 4.4. • Guidance that talquetamab should not be administered in patients with active serious infection is provided in SmPC Section 4.4. • Guidance that patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur is provided in SmPC Section 4.4. • Guidance for patients to recognize symptoms of serious infection is included in PL Sections 2 and 4. Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64407564MMY1001: A Phase ½, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

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

Missing Information: Safety in patients with prior CAR-T cell therapy	
Risk minimization measures	Routine risk minimization measures

	• SmPC Section 4.4 • Guidance that heightened caution should be exercised when administering talquetamab to patients who experienced Grade 3 or higher CRS with prior CAR-T cell therapy is provided in SmPC Section 4.4. Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64407564MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

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

The following studies are conditions of the marketing authorization:

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

- Purpose of the study: The primary objective is to compare the efficacy of Tal-DP and Tal-D, respectively, with DPd. Secondary objectives are:
- to further compare the efficacy of Tal-DP and Tal-D, respectively, with DPd;
- to assess the safety profile of Tal-DP and Tal-D (including further characterization of the safety concerns of CRS, neurologic toxicity including ICANS, and serious infections);
- to characterize the PK of talquetamab;
- to assess the immunogenicity of talquetamab and daratumumab; and
- to assess changes in PROs with Tal-DP, DPd, and Tal-D.

64407564MMY1001: A Phase ½, First-in-Human, Open-Label, Dose Escalation Study of Talquetamab, a Humanized GPRC5D x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma

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

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

Not applicable.