swissmedic

Date: 22 December 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Talvey

International non-proprietary name: talquetamab

Pharmaceutical form: solution for injection

Dosage strength(s): 3 mg/1.5 mL, 40 mg/1.0 mL

Route(s) of administration: subcutaneous injection

Marketing authorisation holder: Janssen-Cilag AG

Marketing authorisation no.: 69049

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 30.10.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ASCT	Autologous stem cell transplantation
AUC	Area under the plasma concentration-time curve
BCMA	B-cell maturation antigen
CAR-T	Chimeric antigen receptor T-cell
CD3	Cluster of differentiation 3
CD38	Cluster of differentiation 38
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CRS	Cytokine release syndrome
CYP	Cytochrome P450
DCO	Data cut-off
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FDA	Food and Drug Administration (USA)
GPRC5D	G protein-coupled receptor class C group 5 member D
HC	Heavy chain
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
INN	International non-proprietary name
IRC	Independent review committee
IV	Intravenous
LoQ	List of Questions
mAb	Monoclonal antibody
MAH	Marketing Authorisation Holder
Max	Maximum
mFU	Median follow-up
Min	Minimum
MM	Multiple myeloma
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PFS	Progression-free survival
PI	Proteasome inhibitor
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
Q1W	Weekly
Q2W	Once every two weeks
RMP	Risk management plan
RP2D	Recommended phase 2 dose
RRMM	Relapsed or refractory multiple myeloma
SAE	Serious adverse event
SC	Subcutaneous(ly)
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event

TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for talquetamab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 23 August 2022.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Talvey is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

2.2.2 Approved indication

Talvey is indicated as monotherapy for treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on or after their last line of therapy.

This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of talquetamab is administered SC based on actual body weight (Table 1):

Table 1: Recommended Doses of Talquetamab

Dosing schedule	Phase	Day	Talquetamab Dose[a]
Weekly Dosing Schedule	Step-up Phase	Day 1	0.01 mg/kg
		Day 3[b]	0.06 mg/kg
		Day 5[b]	0.4 mg/kg
	Treatment Phase	Once a week thereafter[c]	0.4 mg/kg
Q2W Dosing Schedule	Step-up Phase	Day 1	0.01 mg/kg
		Day 3[b]	0.06 mg/kg
		Day 5[b]	0.4 mg/kg
		Day 7[b]	0.8 mg/kg
	Treatment Phase	Once every 2 weeks thereafter[c]	0.8 mg/kg

[a] Based on actual body weight.
[b] Dose may be administered between 2 to 4 days after the previous dose and may be given up to 7 days after the previous dose to allow for resolution of adverse reactions.
[c] Maintain a minimum of 6 days between weekly doses and a minimum of 12 days between once every-2-week doses.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	9 January 2023
Formal control completed	10 January 2023
Preliminary decision	11 May 2023
Response to preliminary decision	25 September 2023
Final decision	30 October 2023
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 1 to 2% of all cancers and is the second most common haematological malignancy, with an estimated incidence in Europe of approximately 5 to 6 cases per 100,000 people per year. The incidence increases with age, and the median age at onset of MM is approximately 70 years, with approximately two thirds of patients aged over 65 years. Although survival from the time of diagnosis of MM has improved since 2000, the prognosis of patients with relapsed or refractory MM (RRMM) following prior exposure to all three MM drug classes is poor, and the remaining therapeutic options are limited[1,2]. Most of these patients have triple-class refractory disease, and many have been exposed to all five drugs that have demonstrated single-agent effectiveness: bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab (so-called penta-exposed patients). Historically, this patient population achieved objective response rates (ORR) of approximately 30%, median progression-free survival (PFS) of approximately 3 to 6 months, and median overall survival (OS) of approximately 6 to 12 months[3].

[1] Dimopoulos MA et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2021;32:309-322 (including corrigendum 2022: https://doi.org/10.1016/j.annonc.2021.10.001).

[2] Cowan AJ et al. Diagnosis and Management of Multiple Myeloma – A Review. JAMA 2022;327:464-477.

[3] Gandhi UH et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia 2019;33:2266–2275

4 Quality aspects

4.1 Drug substance

INN: Talquetamab
Molecular mass: 147 kDa
Molecular structure:
Talquetamab is a humanised IgG4 bispecific antibody directed against G protein-coupled receptor class C group 5 member D (GPRC5D) and the cluster of differentiation 3 (CD3) receptors. Talquetamab consists of 2 heavy chains (HC) and 2 light chains (LC), joined by disulfide bonds. It is prepared by controlled reduction and oxidation of anti-GPRC5D monoclonal antibody (mAb) and anti-CD3 mAb resulting in an exchange of the Fab arms. The Fab arm exchange is facilitated by amino acid substitutions in the C_H3 domain of the parental anti-CD3 mAb HC to promote Fab-arm exchange and enhance stability of the heterodimer.

Manufacture:
Each parental antibody (anti-GPRC5D mAb and anti-CD3 mAb) is produced in a separate Chinese hamster ovary (CHO) cell line. For each production cell line, a respective 2-tiered cell banking system of master cell bank (MCB) and working cell bank (WCB) is in place. The parental antibodies are manufactured separately. After thawing of the respective WCB vial, the cells are grown in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The culture is harvested, and purification of the respective mAb is performed with a dedicated chromatography step. The 2 intermediates are stored and tested before being released for drug substance manufacturing. In a subsequent step, the 2 parental antibodies are combined and their HC-HC disulfide bonds are selectively reduced, followed by oxidation to produce the heterodimeric talquetamab antibody. The talquetamab drug substance is purified using a series of chromatography, ultrafiltration/diafiltration, virus inactivation, and virus removal filtration steps.
The entire manufacturing process for talquetamab drug substance is validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities.
Several changes were implemented during development of the manufacturing process of the drug substance, including changes to the manufacturing site and production scale. The analytical comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability between the different processes.

Specification:
The specifications for release and stability of the drug substance include relevant tests and acceptance criteria to control identity, purity and impurities, quantity and potency, and other general tests. Specifications are based on clinical experience, batch analysis data, and stability data, and comply with current compendial and regulatory guidelines.
Batch analysis data for clinical and process validation batches of the drug substance were provided. All batch release data comply with the commercial drug product specifications. All specific analytical methods are fully validated.

Stability:
The 2 intermediates and the drug substance are stored frozen. During storage, no significant changes were observed under the proposed storage conditions.

4.2 Drug product

Description and composition:
The 2 mg/mL drug product is supplied as a sterile liquid in a vial for subcutaneous administration. Each vial contains 3 mg of talquetamab in a 1.5 mL nominal fill volume.
The 40 mg/mL drug product is supplied as a sterile liquid in a vial for subcutaneous administration. Each vial contains 40 mg of talquetamab in a 1.0 mL nominal fill volume.

The 2 drug products contain no preservatives and are for single use only.
The excipients (sodium acetate trihydrate, glacial acetic acid, sucrose, polysorbate 20, EDTA disodium salt dihydrate, and water for injection) are of compendial grade and commonly used for the formulation of biopharmaceuticals.

Pharmaceutical development:
Several drug product dosage strengths, presentations, and filling facilities were used during clinical development. Comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability of the relevant quality attributes between the different processes supporting different presentations.
Compatibility studies were conducted to establish the in-use stability of the drug product with the intended materials and conditions of use.

Manufacture:
The manufacturing process for the 2 mg/mL and 40 mg/mL drug products consists of thawing of the drug substance, compounding and storage of the dilution buffer, compounding, sterile filtration, aseptic filling and stoppering of vials, capping, and optical inspection.
The drug product manufacturing process is validated with several consecutive batches of each dosage strength. The data demonstrated a consistent production.

Specification:
The specifications for release and stability of the drug products include relevant tests and acceptance criteria to control identity, purity and impurities, quantity and potency, and other general tests. The drug product specifications comply with current compendial and regulatory guidelines.
Batch analysis data for several batches of the drug products, including clinical and process performance qualification batches, were provided. All batch release data comply with the commercial drug product specifications. All specific analytical methods are fully validated.

Container closure system:
The container closure system used for the 2 mg/mL drug product is a 6 mL Type 1 glass vial closed with an elastomeric stopper and a 20-mm aluminium seal with a flip-off cap.
The container closure system used for the 40 mg/mL drug product is a 2 mL Type 1 glass vial closed with an elastomeric stopper and a 13-mm aluminium seal with a flip-off cap.
The materials of the Type I glass vial and rubber stopper meet compendial requirements.

Stability:
The vials are stored at 2°C to 8°C, protected from light. The stability data support a shelf life of 15 months.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.
Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

5 Nonclinical aspects

For the nonclinical testing strategy, the applicant considered the recommendations outlined in ICH S9 and S6(R1).

5.1 Pharmacology

The applicant provided several *in vitro* investigations and 1 *in vivo* study to characterise talquetamab; the *in vitro* results are shown in the following table:

Endpoint	***Results***
K_D (dissociation constant)	189 nM to human GPRC5D 15.1 nM to human CD3
T cell-dependent cytotoxicity with T cells from healthy donors	EC_{50} with multiple myeloma cell lines: 0.015 - 0.214 nM
T cell-dependent cytotoxicity with whole blood from healthy donors	EC_{50}: 0.389 nM for H929 cells
T-cell activation with T cells from healthy donors	EC_{50} values with multiple myeloma cell lines: 0.014 - 0.288 nM
T cell activation with whole blood from healthy donors	EC_{50}: 0.236 nM for H929 cells
T cell-dependent cytotoxicity and T cell activation with subject-derived CD138-positive MM bone marrow cell samples	EC_{50} for cytotoxicity: 0.127 nM EC_{50} for T cell activation: 0.061 nM.
T cell-dependent cytotoxicity and T cell activation with autologous CD138-expressing MM patient bone marrow cells	EC_{50} for cytotoxicity: 0.13 nM EC_{50} for T cell activation: 0.06 nM

There was no activity with the control antibodies or GPRC5D-negative cell lines. The investigators also confirmed the release of cytokines, which is well reflected in the RMP and the information for healthcare professionals, as it is a known risk for CD3 redirectors.
Taken together, the data show that talquetamab only binds to GPRC5D-positive cells and induces cytotoxicity and T cell activation in T cells and whole blood, as well as with subject-derived cells.

The *in vivo* activity of talquetamab was evaluated in a murine model engrafted with human peripheral blood mononuclear cells or human T cells and GPRC5D-expressing human multiple myeloma. The applicant showed tumour growth inhibition in mice treated with 1 µg and 10 µg/mouse of talquetamab in a prophylactic setting, whereas statistically significant antitumour efficacy was observed with 10 µg or 50 µg/mouse in a therapeutic setting. Significant body weight loss, overall decline in health, and/or mortality occurred due to graft-versus-host disease in the control as well as in talquetamab-treated and control antibody groups. Overall, the data provided support the proof of concept.

The applicant provided several investigations using immunohistochemistry and in-situ hybridisation to identify GPRC5D protein and mRNA expression in human tissue. Overall, GPRC5D is detected in plasma cells as expected and in anatomical sites with high numbers of resident normal plasma cells (i.e. tonsils, lymph nodes, spleen, bone marrow, salivary glands, and gastrointestinal tract). GPRC5D mRNA and protein expression was also confirmed in hair follicles and eccrine sweat glands of the skin as well as in keratinised structures (filiform papillae) of the human tongue. No relevant GPRC5D protein expression was reported for the brain. This distribution pattern is consistent with the oral toxicity and skin reactions observed in clinical studies.

The applicant could not identify a pharmacologically relevant species. Although the human full length GPRC5D protein is 96% identical to the cynomolgus monkey protein and 88% homology was found with the human sequence of CD3, talquetamab bound only poorly to cGPRC5D, with approximately 100-fold lower *in vitro* bioactivity against cGPRC5D-expressing cells compared with hGPRC5D-

expressing cells. In consequence, the applicant generated a tool molecule for hazard identification in cynomolgus monkeys, which consists of a cGPRC5D and hCD3 arm (EC_{50} cytotoxicity: 0.12 nM; EC_{50} T cell activation: 0.19 nM).

An *in vitro* human plasma membrane protein array screen with more than 6,000 human proteins did not identify any off-target binding for the GPRC5D binding arm of talquetamab at 5 µg/mL. Overall, the risk for off-target effects at clinically relevant exposure appears to be low.

The 1-month repeat dose study in cynomolgus monkeys included safety pharmacology endpoints for the cardiovascular, central nervous, and respiratory systems. Doses up to 30 mg/kg with the tool molecule did not reveal any adverse effects. As this study tested the tool molecule, a quantitative risk assessment with safety margins is not adequate.

Pharmacodynamic drug interaction studies with talquetamab were not conducted.

5.2 Pharmacokinetics

The applicant investigated the pharmacokinetic profile of talquetamab in cynomolgus monkeys following single and repeated IV administration (0.5 to 30 mg/kg). Serum exposure increased approximately proportional to dose and was comparable in male and female animals. The mean terminal half-life was between 8 and 12 days after a single dose, which is comparable to the half-life in patients. The low volume of distribution indicates limited distribution. The PK parameters are typical for a monoclonal antibody.
In line with ICH S6(R1), the applicant did not conduct studies on distribution, metabolism, and excretion.
There is potential for indirect drug-drug interaction via cytokine-mediated downregulation of CYP enzymes in cytokine release syndrome, an important identified clinical risk.

5.3 Toxicology

The toxicity programme consisted of three repeat-dose studies with weekly IV dosing of talquetamab or the tool molecule in cynomolgus monkeys over a maximum period of 1 month. The intravenous route did not represent the intended clinical route of administration, the frequency of administration was weekly and hence reflected the later treatment phase. The reproductive toxicity assessment is based on a weight-of-evidence approach and did not include any experimental data. Furthermore, the applicant provided *i.a.* a local tolerance study in rabbits.
Overall, the nonclinical data are of limited relevance and the use of the tool molecule allows only for hazard assessment. Risks related to CD3 interaction are known.

The repeat-dose toxicity programme consisted of a 4-week exploratory study with talquetamab and a 2- and 4-week study with the tool molecule in cynomolgus monkeys. The investigation with up to 30 mg/kg talquetamab did not show any significant pharmacodynamic or adverse effects. This is expected considering the 100-fold lower activity regarding cytotoxicity and T cell activation. However, the studies with the tool molecule with weekly IV doses up to 30 mg/kg also elicited only a minimal pharmacological response. The applicant explained this with low target expression and/or a low number of target cells in healthy cynomolgus monkeys. Furthermore, in the pivotal 4-week study, 10 out of 12 animals treated with the tool molecule tested positive for anti-drug antibodies (ADAs). These animals exhibited either lower drug exposure prior to the last dose or faster concentration decrease after the last dose. In all 3 studies, the high dose was also the no observed adverse effect level (NOAEL). As this study tested the tool molecule, a quantitative risk assessment with safety margins is not adequate. Swissmedic agrees with EMA and FDA decision to waive a 3-month study.

In accordance with ICH S9 and S6(R1), the applicant did not perform genotoxicity or carcinogenicity studies with talquetamab. Also, fertility and early embryonic development as well as pre- and post-

natal development studies are generally not required for products intended for the treatment of advanced cancer.
A weight-of-evidence reproductive risk assessment was provided to address embryofetal development instead of *in vivo* studies. The applicant argued that the disease generally affects elderly patients and is rare in women of childbearing potential. Furthermore, evidence was provided that GPRC5D has restricted expression in normal human tissues and has no known role in embryogenesis. From the technical point of view, the results of the repeat-dose studies with the tool molecule and the formation of ADAs in the majority of the treated animals do not support the conduct of meaningful *in vivo* studies. The effects of CD3 redirection pharmacology, such as cytokine release or tumour lysis syndrome, are known and may pose a potential risk to a pregnant mother and her unborn child. This is adequately addressed in the information for healthcare professionals.

The applicant provided a stand-alone local tolerance study in New Zealand White rabbits with the final market formulation. This study revealed no adverse effects at the injection site after subcutaneous administration.

The applicant provided a waiver granted by the EMA on the grounds that the disease multiple myeloma does not occur in paediatric patients from birth to 18 years.

Since talquetamab is a monoclonal antibody, there is no risk for the environment.

The Nonclinical Safety Specifications of the RMP adequately address the shortcomings of the above-mentioned studies in animals.

5.4 Nonclinical conclusions

The submitted pharmacology studies showed that talquetamab binds to both target structures, GPRC5D and CD3, causing cytotoxicity and T cell activation. The limited set of toxicity studies with the tool molecule did not identify any hazards; however, the relevance of these studies is considered low. From a nonclinical perspective, the application can be approved.

6 Clinical aspects

6.1 Clinical pharmacology

Pharmacokinetics

The PK information in support of this application is derived from the MonumenTAL-1 study (64007564MMY1001), with a data cutoff of 22 April 2022.

The available PK data were analysed in a popPK analysis. A total of 5,354 measurable talquetamab serum concentrations from 492 participants with at least 1 talquetamab dose and 1 measurable talquetamab serum concentration were included in the popPK analysis with n=100 IV and n=392 SC participants.

The observed serum concentration-time data of talquetamab were adequately described by a 2-compartment model with sequential zero-order and first-order absorption and 2 parallel linear clearances, 1 time-dependent and 1 time-independent. The overall talquetamab clearance consists of 2 components: The time-independent unspecific clearance component is thought to reflect the endogenous catabolic processes of IgG degradation. The time-dependent specific clearance component corresponds to the decrease in drug clearance as disease status improves over time, which is likely related to tumour burden or target amount.

There was no clinically meaningful impact (i.e. change of < 20%) for the covariates age (33 to 86 years), gender, race, weight, ADA status (n=91, 18.5% positive), region, drug product (commercial vs. clinical product), hepatic impairment (n=76, mild and moderate combined), and renal impairment (n=231 mild and n=142 moderate, based on modification of diet in renal disease (MDRD)).

Simulations based on the popPK model indicate that during the first 2 weeks after the full treatment dose, 0.8 mg/kg Q2W SC provides 66.4% higher C_{avg} than 0.4 mg/kg Q1W SC; the difference decreases to 32.7% for C_{avg} of the first 4 weeks. Starting from Week 3 until steady state, the 2 dosing schemes provide overlapping talquetamab exposure with clinically insignificant differences (<20%). From the first full dose, both dosing schemes maintain talquetamab C_{trough} above or around the threshold EC_{90} value of 353 ng/ml.

Accumulation ratios for the comparison of Cycle 1 Day 1 vs. Cycle 3 Day 1 of the Q1W dosing were 3.9- and 4.5-fold for C_{max} and AUC_{tau}, respectively. Similarly, accumulation ratios for the comparison of Cycle 1 Day 1 vs. Cycle 3 Day 1 of the Q2W dosing were 2.3- and 2.2-fold for C_{max} and AUC_{tau}, respectively

Based on available AUC_{tau} values at steady state from all IV and SC dosing cohorts, mean bioavailability following SC weekly administration for the treatment dose was 62%.

The volumes of distribution for the central compartment were 4.3 l (%CV, 22) and 5.8 l (%CV, 83), respectively.

The median terminal elimination half-life was 7.56 days following the first treatment and 12.2 days at steady-state.

Interaction potential

Talquetamab is not metabolised via cytochrome P450 (CYP) enzymes and is not expected to directly affect CYP enzymes. Therefore, no nonclinical or clinical drug-drug interaction studies were performed. The initial release of cytokines associated with the start of talquetamab treatment may, however, suppress CYP enzymes, which in turn may affect sensitive CYP substrates. Physiologically based PK (PBPK) simulations suggest that the highest potential for a drug-drug interaction is from the initiation of talquetamab step-up dose 1 up to 7 days after the first treatment dose or during a cytokine release syndrome (CRS) event for the 0.4 mg/kg Q1W SC dosing regimen, and from initiation of talquetamab step-up dose 1 up to 9 days after the first treatment dose or during a CRS event for the

0.8 mg/kg Q2W SC dosing regimen. Therefore, during this time period, toxicity or medicinal product concentrations (e.g. cyclosporine) should be monitored in patients who are receiving concomitant CYP substrates with a narrow therapeutic index. The dose of the concomitant medicinal product should be adjusted as needed.

QT/QTc interval prolongation potential
As a monoclonal antibody, talquetamab is too large to directly inhibit the human Ether-à-go-go-Related Gene (hERG) channel and is highly specific to the extracellular epitope of B-cell maturation antigen (BCMA). As such, talquetamab is unlikely to directly impact cardiac repolarisation and result in QTcF prolongation.

Mean QTcF (of triplicate readings) was ≤ 500 msec at any timepoint post-baseline for all subjects treated with either talquetamab IV or talquetamab SC in the MonumenTAL-1 study.

The ΔQTcF was ≤ 60 msec for all subjects. The QTcF and ΔQTcF over time showed no trend, indicating no time-dependent QT prolongation. Additionally, QTcF and ΔQTcF values showed no correlation with talquetamab serum concentrations collected at the same timepoint, suggesting no exposure-dependent QT prolongation.

Exposure-response (E-R) relationship
Efficacy: Near flat E-R relationships were observed between the ORR and the exposure metrics of $C_{avg,4weeks}$ and $C_{trough,1stdose}$. This near flat E-R relationship indicates that participants receiving both 0.4 mg/kg Q1W and 0.8 mg/kg Q2W reached maximum ORR effects across the derived pharmacokinetics exposure ranges. Similar relationships were observed for patients previously dosed with CAR-T cells or other bispecific antibodies.

Safety: There were no significant trends of increases in cytopenia occurrence rate with increasing exposure. Additionally, no trends were noted for Grade ≥ 3 infection, Grade ≥ 3 TEAEs, and TEAEs leading to dose modification including cycle delay, dose interruption, dose reduction, and drug discontinuation. The incidence rates of the safety endpoints including Grade ≥ 3 rash, Grade ≥ 3 hypo-gammaglobulinemia, Grade ≥ 3 tumour lysis, Grade ≥ 3 neurotoxicity, Grade ≥ 3 CRS, and Grade ≥ 2 nail loss were too low (0.0-1.7%) and therefore not applicable for E-R evaluation regarding safety.

6.2 Dose finding and dose recommendation

The applicant proposes two dose regimens with subcutaneous application route. The first dose regimen is a subcutaneous (SC) talquetamab dose of 0.4 mg/kg administered at weekly intervals (Q1W) and the second regimen is a bi-weekly dose (Q2W) of 0.8 mg/kg (see information for healthcare professionals for further details on step-up dosing).

The dose finding to support the doses was conducted during Part 1 (dose escalation) and Part 2 (dose expansion) of the MonumenTAL-1 study (64407564MMY1001). Both parts were Phase 1 studies designed to determine the recommended Phase 2 dose (RP2D) of talquetamab monotherapy. Parts 1 and 2 enrolled subjects with measurable multiple myeloma who had progressed on, or could not tolerate, all available established therapies.

The RP2D of talquetamab 0.4mg/kg Q1W was selected based on the pharmacokinetic, pharmacodynamic, safety, and efficacy data from the dose escalation part of the study. The alternative RP2D of 0.8 mg/kg Q2W was selected based on comparable pharmacokinetic, pharmacodynamic, safety, and efficacy data relative to the 0.4 mg/kg weekly SC RP2D.

To avoid incorrect dosing, separate dose recommendations for each dose regimen have been included in the information for healthcare professionals.

In summary, the dose-finding data support the selection of the 0.4 mg/kg weekly SC dose over other dose strengths evaluated in the Phase 1 part of the study. The 0.8 mg/kg bi-weekly dose was accepted because of similar pharmacokinetics and Phase 1 clinical efficacy and safety results.

6.3 Efficacy

The MonumenTAL-1 study (64407564MMY1001) is a single-arm, open-label, multicentre study of talquetamab administered as monotherapy to adult subjects with RRMM. The dose selection was based on the Phase 1 results of the pivotal study. The Phase 2 element of this study was added per clinical study protocol amendment and included several additional cohorts. **Cohort A** evaluated the efficacy and safety of the talquetamab 0.4 mg/kg Q1W SC dose schedule and included multiple myeloma patients who had previously received ≥3 prior lines of therapy including at least one proteasome inhibitor (PI), one immunomodulatory imide drug (IMiD), and an anti-CD38 monoclonal antibody, and had not been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies. **Cohort B** evaluated talquetamab 0.4 mg/kg Q1W SC in a more pre-treated population that included patients with exposure to T cell redirection therapies such as CAR-T or bispecific antibodies. **Cohort C** was added later on and evaluated talquetamab 0.8 mg/kg Q2W SC with the same study entry criteria as Cohort A. Regardless of study cohort, all study participants had to have documented progressive disease by the international myeloma working group (IMWG) 2016 criteria on or within 12 months of their last line of therapy. Also, subjects with documented evidence of progressive disease within the previous 6 months and who were refractory or non-responsive to their most recent line of therapy afterwards were eligible. Several eligibility restrictions were not considered representative for the intended population. These restrictions included the study entry criteria for hypercalcemia (corrected serum calcium ≤14 mg/dL or free calcium ≤6.5 mg/dL), renal function (creatinine clearance ≥40 mL/min/1.73 m^2), and anaemia (haemoglobin ≥8.0 g/dL). However, the applicant agreed to describe these study eligibility restrictions in the information for healthcare professionals.

Talquetamab was administered until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the study. Details on the premedication requirements are included in the attached information for healthcare professionals.

Adverse events and toxicities were primarily managed by dose delay. If a dose interruption was ≥28 days, treatment was to be permanently discontinued unless continuation was agreed in consultation with the sponsor after a review of safety and efficacy.

For step-up dosing days and the first full dose, patients were required to be hospitalised for at least 48 hours from the start of injection. At the first sign of cytokine release syndrome participants were to be immediately hospitalised for evaluation. See the information for healthcare professionals for further details on hospitalisation requirements.

Disease evaluations were performed at screening and prior to study drug administration at each 28-day cycle.

An Independent Review Committee (IRC) reviewed the data from study participants treated at the RP2D and determined disease response/progression.

The primary endpoint was confirmed overall response rate (at least partial response or better) of talquetamab as assessed by an IRC.

Study results

The applicant submitted the results from the primary analysis data cut-off (DCO) of 16 May 2022 and additionally provided updated analyses from the 12 September 2022 and 17 January 2023 DCOs.

At the primary analysis, the median follow-up (mFU) period in Cohort A (0.4 mg/kg Q1W) was 10.8 months and 64.8% of patients had discontinued the study drug in this cohort, mostly due to progressive disease (49.2%). In Cohort C (0.8 mg kg/Q2W), the median follow-up period during the primary analysis was 4.7 months and 28.4% of patients had discontinued the study drug in this cohort, mostly due to progressive disease (16.5%). In Cohort B (prior exposure to T cell redirection therapy), the median follow-up period was 7 months and 38.2% patients had discontinued the study in this cohort, mostly due to progressive disease (26.5%).

See the information for healthcare providers for the description of baseline demographic and disease characteristics. **Efficacy results**

The primary analysis was based on the results from data cut-off as of May 2022. For the assessment of the time to event analyses, the DCO from January 2023 was taken into consideration due to the short mFU that was provided with the primary analysis.

IRC assessed confirmed overall response rate according to May 2022 DCO:

In Phase 2 Cohort A (0.4 mg/kg Q1W; no prior exposure to T cell redirection therapies; n=122): 73% (CI95% 64.2%, 80.6%).

In Phase 2 Cohort C (0.8 mg/kg Q1W; no prior exposure to T cell redirection therapies; n=109): 50.5% (CI95% 40.7%, 60.2%).

In Phase 2 Cohort B (prior exposure to T cell redirection therapies, n=34): 64.7% (CI95% 46.5%, 80.3%).

Duration of response according to January 2023 DCO:

In Cohort A, the event rate among the 91 responders based on the latest DCO was 62.6%. The probability of these responders remaining in response at 6 months was approximately 66.8%. The median duration of response was 8.8 months.

In Cohort C, the event rate among the 81 responders based on the latest DCO was 17.7%. The probability of these responders remaining in response at 6 months was approximately 87.1%. The median duration of response was not estimable at the latest DCO.

In Cohort B, the event rate among the 25 responders based on the latest DCO was 52.0%. The probability of these responders remaining in response at 6 months was approximately 67.6%. The median duration of response was 11.9 months.

Progression-free survival (PFS) according to January 2023 DCO

In Cohort A, the median PFS was 7.5 months and 69.7% of patients had a PFS event. The probability of being PFS event-free at 6, 9, and 12 months was 57.0%, 42.6%, and 34.0%, respectively.

In Cohort C, the median PFS was not reached at the latest DCO and 36.7% of patients had a PFS event. The probability of being PFS event-free at 6, 9, and 12 months was 67.9%, 63.8%, and 60.7%, respectively.

In Cohort B, the median PFS was 6.8 months at the latest DCO and 61.8% of all patients had a PFS event. The probability of being PFS event-free at 6, 9, and 12 months was 50%, 44.1%, and 44.1%, respectively.

Overall survival (OS) according to January 2023 DCO

In Cohort A, the median OS was not reached and 36.1% of patients had an OS event. The probability of being OS event-free at 6, 9, and 12 months was 87.6%, 79.1%, and 73.9%, respectively.

In Cohort C, the median OS was not reached and 19.3% of patients had an OS event. The probability of being OS event-free at 6, 9, and 12 months was 86.2%, 84.3%, and 78.5%, respectively.

In Cohort B, the median OS was not reached and 29.4% of patients had an OS event. The probability of being OS event-free at 6, 9, and 12 months was 79.4%, 70.6%, and 70.6%, respectively.

6.4 Safety

The assessment of safety was based on the January 2023 DCO, which provided over 8 months of additional follow-up compared with the initial DCO from May 2022. All patients treated with RP2D reported at least one treatment emergent adverse event (TEAE). The most frequently reported TEAEs of any grade were (frequencies of adverse events are presented as rounded approximations based on results from different pools):

- Nervous system disorders (in 80-90%) such as dysgeusia (50-60%), headache (20%), and ageusia (10-20%);
- Blood and lymphatic disorders (in 70-80%) such as anaemia (45-50%), neutropenia (30-55%), lymphopenia (20-30%), thrombocytopenia (30-40%), and leukopenia (15-25%).
- Gastrointestinal disorders (in 75-90%) such as dry mouth (25-50%), diarrhoea (15-30%), dysphagia (25%), and constipation (15%-25%);
- Skin and subcutaneous disorders (in 80-90%) such as skin exfoliation (30-45%), dry skin (20-30%), nail disorders (20-30%), pruritus (20-30%), and rash (15-20%).;
- General disorders and administration (65-85%) such as pyrexia (30-40%), fatigue (25%-45%), asthenia (10-25%), chills (10-15%), peripheral oedema (10-15%), and injection site erythema (5-10%);
- Immune system disorders (in 75-80%), mainly cytokine release syndrome (75-80%):
- Metabolism and nutrition disorders (in 55-65%) such as decreased appetite (20-25%) and hypokalaemia (10-20%);
- Infections and infestations (in 60-75%), mainly COVID-19 (10-25%);
- Investigations (in 55-65%), mainly weight decreased (30-40%);
- Respiratory, thoracic, and mediastinal disorders (in 45-55%), mainly cough (20-30%):
- Vascular disorders (15-20%) such as hypertension (5-10%);
- Psychiatric disorders (20%) such as insomnia (10%).

Grade 3-4 TEAEs were reported in 77.6% of patients in the weekly RP2D safety pool (n=143), 77.9% of patients in the bi-weekly RP2D pool (n=145), and 91.2% of patients in the prior T cell redirection therapy pool (n=51). The most frequently reported grade 3-4 TEAEs were blood and lymphatic disorders (in 60-70%) such as neutropenia (30-55%), anaemia (30%), lymphopenia (15-25%), thrombocytopenia (20-30%), and leukopenia (10-20%); metabolism and nutrition disorders (in 5-30%), mainly hypophosphataemia (0-10%); infections and infestations (15%-30%), mainly pneumonia (2-5%) and COVID-19 (1-2%); and investigations (15-20%), mainly ALT increased (3-6%).

Serious TEAEs were reported in 53.1% in the weekly RP2D safety pool, 48.3% of patients treated with the bi-weekly RP2D pool, and 56.9% of patients in the prior T cell redirection therapy pool. The most frequently reported SAEs were:

- Infections and infestations (in 15-20%) such as pneumonia (1-4%), COVID-19 (1-3%), and urinary tract infections (1-2%);
- Immune system disorders (in 10-15%), mainly cytokine release syndrome (10-15%);
- Nervous system disorders (in 5-10%) such as immune effector cell-associated neurotoxicity syndrome (3-4%) and syncope (1-2%);
- General disorders and conditions (in 5-10%) such as pyrexia (5%);
- Blood and lymphatic disorders (in 5%) such as febrile neutropenia (up to 2%), neutropenia (up to 5%), and leukopenia (up to 2%).

TEAEs leading to study drug discontinuation were reported in 4.9 % of patients in the weekly RP2D pool, 8.3% of patients in the bi-weekly RP2D pool, and 7.8% of patients in the prior T cell redirection therapy pool. The most frequently reported TEAEs leading to study drug discontinuation were nervous system disorders (up to 3%), mostly immune effector cell-associated neurotoxicity syndrome (up to 2%) and dysgeusia (up to 1%), followed by skin and subcutaneous disorders (up to 1%).

Death events during the study were reported in 33.6% of patients in the weekly RP2D pool, 22.8% of patients in the bi-weekly RP2D pool, and 39.2% of patients in the prior T cell redirection therapy pool. Death due to disease progression was reported in 19.6%, 17.2%, and 37.3%, respectively.

Grade 5 TEAEs were reported in 3.5% of patients in the weekly RP2D pool, 4.1% of patients in the bi-weekly RP2D pool, and 0% of patients in the prior T cell redirection therapy pool. The most frequently reported grade 5 TEAEs in the weekly and bi-weekly RP2D pools were infections and infestations (in 1-2%) such as COVID-19 pneumonia and fungal sepsis, as well as respiratory, thoracic, and mediastinal disorders (in 1%) such as respiratory failure and pulmonary embolism.

6.5 Final clinical benefit-risk assessment

Talquetamab is a new active substance, an anti-CD3/GPRC5D bispecific antibody. In triple-class exposed, heavily pre-treated multiple myeloma (median of 5 lines of prior therapy) without prior T cell redirection therapies, talquetamab achieved an overall response rate (ORR) of up to almost 75%. Compared with historical results for this patient population (excluding anti-BCMA therapy, see “Medical context” section), ORR is increased and is in a comparable range to other BCMA T-cell redirection therapies[4]. Even in more pre-treated RRMM patients who received prior BCMA T-cell redirection therapies, a population for whom limited alternative therapies exist, talquetamab still demonstrated an ORR of almost 65% in the primary analysis (May 2022 DCO). However, the primary endpoint ORR is not considered an established surrogate parameter for OS[5].

At the January 2023 DCO, OS data were still immature in the submitted Phase 2 cohorts, even though the mFU ranged from 12 to 19 months. However, it is recognised that not achieving a mOS value after a mFU of up to 19 months across the submitted Phase 2 cohorts is supportive for the requested indication. Especially when evaluating these results in the context of published historical data.

The absence of a comparator arm is one of the major weaknesses of the MonumenTAL-1 study (64407564MMY1001), which hampers the interpretation of the efficacy of talquetamab. However, the results from the ongoing Phase 3 study MonumenTAL-3 (64407564MMY3002) would allow for a comparative assessment of talquetamab combination therapy versus daratumumab, pomalidomide, and dexamethasone (DPd) triplet therapy for RRMM. Although the indication targeted by this randomised clinical trial is different from the proposed indication, results from MonumenTAL-3 demonstrating a therapeutic benefit of talquetamab over the comparator arm could provide confirmatory evidence if accompanied by supportive results from MonumenTAL-1 after additional follow-up.

The most relevant risks associated with talquetamab therapy are infections (including fatal events), cytokine release syndrome, neurotoxicity (including immune effector cell-associated neurotoxicity syndrome), oral toxicity (in particular ageusia), weight loss, skin toxicity (such as skin exfoliation), and cytopenia. However, the safety profile appears to be comparable with BCMA-directed bispecific antibodies with exception of skin and oral toxicities that are likely related to the different receptor

[4] Gandhi UH et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia 2019;33:2266–2275

[5] Kumar S and Rajkumar SV. Surrogate endpoints in randomised controlled trials: a reality check. The Lancet 2019;394:281-283.

target of talquetamab (GPRC5D instead of BCMA). Nonetheless, the lack of controlled data in the safety pools also hampers the interpretation of safety, and limited duration of exposure and follow-up further reduces the interpretability of the safety results.

Taken together, the available evidence was considered insufficient for an authorisation without special conditions. Instead, a temporary authorisation *ex officio* supported by post-marketing requirements to provide additional data from the registrational MonumenTAL-1 study and the ongoing Phase 3 study MonumenTAL-3 is considered adequate in light of the medical need, promising efficacy results, and the overall manageable safety profile of talquetamab.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Talvey was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the *Undesirable effects* section for advice on the reporting of adverse reactions.
TALVEY has been authorised temporarily, see *Indications/Uses* section.

TALVEY®

Composition

Active substances

Talquetamab (genetically engineered in Chinese hamster ovary [CHO] cells)

Excipients

Sodium acetate trihydrate, Glacial acetic acid, Sucrose, Polysorbate 20, EDTA disodium salt dihydrate, Water for injection

Total sodium content: 0.4 mg of sodium in 1.5 mL vial; 0.3 mg of sodium in 1.0 mL vial

Pharmaceutical form and active substance quantity per unit

TALVEY is a colorless to light yellow solution for injection.
TALVEY is available in the following presentations:

- Each 1.5°mL vial contains 3°mg of talquetamab (2°mg of talquetamab per mL)
- Each 1.0°mL vial contains 40°mg of talquetamab (40°mg of talquetamab per mL)

Indications/Uses

TALVEY is indicated as monotherapy for treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on or after their last line of therapy.

This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

Dosage/Administration

TALVEY should only be administered under the guidance of medical personnel experienced in the treatment of malignant haematological diseases, cytokine release syndrome (CRS) and neurological toxicities including immune effector cell-associated neurotoxicity syndrome (ICANS).

Monitoring

Intensive monitoring of patients is recommended in the following cases:

- For 48 hours after each dose of TALVEY in the step-up phase (see table 1 for weekly and table 2 for biweekly dosing).
- For 36 hours following the next dose of TALVEY, if the patient experiences grade ≥ 2 ICANS or grade 2 CRS that does not resolve to baseline or does not improve to grade ≤1 within 48 hours or grade 3 CRS with the previous dose of TALVEY.

In these cases, inpatient monitoring should be provided in appropriately equipped centres that have multidisciplinary teams with sufficient experience to provide intensive medical treatment for even the most severe complications. In addition, patients should be monitored daily for signs and symptoms of cytokine release syndrome (CRS), and neurological and other toxicities up to 7 days after TALVEY administration (see *Dosage and Administration – Dose modifications for adverse reactions and Warnings and Precautions*).

TALVEY is administered via subcutaneous injection.

Administer pretreatment medications prior to each dose of TALVEY during the step-up phase (see *Dosage and Administration – Pretreatment medications*).
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

Administer TALVEY subcutaneously on a weekly or biweekly (every 2 weeks) dosing schedule according to Table 1 or Table 2.

Table 1: TALVEY Weekly Dosing Schedule

Dosing schedule	Day	Dose[a]	
Step-up dosing schedule	Day 1	Step-up dose 1	0.01 mg/kg
	Day 4[b]	Step-up dose 2	0.06 mg/kg
	Day 7[b]	First treatment dose	0.4 mg/kg
Weekly dosing schedule	One week after first treatment dose and weekly thereafter[c]	Subsequent treatment doses	0.4 mg/kg once weekly

[a] Based on actual body weight.

[b] Dose may be administered between 2 to 4 days after the previous dose and may be given up to 7 days after the previous dose to allow for resolution of adverse reactions.

[c] Maintain a minimum of 6 days between weekly doses.

Table 2: TALVEY Biweekly (Every 2 Weeks) Dosing Schedule

Dosing schedule	Day	Dose[a]	
Step-up dosing schedule	Day 1	Step-up dose 1	0.01 mg/kg
	Day 4[b]	Step-up dose 2	0.06 mg/kg
	Day 7[b]	Step-up dose 3	0.4 mg/kg
	Day 10[c]	First treatment dose	0.8 mg/kg

Biweekly (every 2 weeks) dosing schedule	Two weeks after the first treatment dose and every 2 weeks thereafter[d]	Subsequent treatment doses	0.8 mg/kg every 2 weeks

[a] Based on actual body weight.

[b] Dose may be administered between 2 to 4 days after the previous dose and may be given up to 7 days after the previous dose to allow for resolution of adverse reactions.

[c] Dose may be administered between 2 to 7 days after step-up dose 3.

[d] Maintain a minimum of 12 days between biweekly (every 2 weeks) doses.

Continue treatment until disease progression or unacceptable toxicity.

Pretreatment medications

Administer the following pretreatment medications 1 to 3 hours before each dose of TALVEY during the step-up phase to reduce the risk of CRS (see *Warnings and Precautions - Cytokine release syndrome*).

- Corticosteroid (oral or intravenous dexamethasone, 16 mg or equivalent)
- H1-Antihistamine (oral or intravenous diphenhydramine, 50 mg or equivalent)
- Antipyretics (oral or intravenous acetaminophen, 650 mg to 1'000 mg or equivalent)

Administration of pretreatment medications may be required prior to administration of subsequent doses of TALVEY in the following patients:

- Patients who repeat doses within the TALVEY step-up phase due to dose delays (see *Dosage and Administration – Dose delays*)
- Patients who experienced CRS following the prior dose of TALVEY (see *Dosage and Administration – Dose modifications for adverse reactions*)

Dose delays

If a dose of TALVEY is delayed, restart therapy based on recommendations in Table 3 and 4 and resume weekly or biweekly (every 2 weeks) dosing accordingly (see *Dosage and Administration-Usual dosage*). Administer pretreatment medications prior to restarting TALVEY and monitor patients following administration of TALVEY (see *Dosage and Administration – Pretreatment medications*).

Table 3: Recommendations for Restarting TALVEY after Dose Delay – Weekly Dosing Schedule

Last Dose Administered	Time from Last Dose Administered	TALVEY Recommendation*
0.01 mg/kg	More than 7 days	Restart TALVEY step-up dosing schedule at step-up dose 1 (0.01 mg/kg).
0.06 mg/kg	8 to 28 days	Repeat step-up dose 2 (0.06 mg/kg) and continue TALVEY step-up dosing schedule.
	More than 28 days	Restart TALVEY step-up dosing schedule at step-up dose 1 (0.01 mg/kg).
0.4 mg/kg	8 to 28 days	Continue TALVEY dosing schedule at treatment dose (0.4 mg/kg weekly)

	29 to 56 days	Restart TALVEY step-up dosing schedule at step-up dose 2 (0.06 mg/kg).
	More than 56 days	Consider permanent discontinuation and reassess the benefit risk of restarting TALVEY. If restarting TALVEY, begin with the step-up dosing schedule at step-up dose 1 (0.01 mg/kg).

* Administer pretreatment medications prior to restarting TALVEY. After restarting TALVEY, resume weekly dosing schedule accordingly *(see Dosage and Administration – Usual dosage)*.

Table 4: Recommendations for Restarting TALVEY after Dose Delay – Biweekly Dosing Schedule

Last Dose Administered	Time from Last Dose Administered	TALVEY Recommendation*
0.01 mg/kg	More than 7 days	Restart TALVEY step-up dosing schedule at step-up dose 1 (0.01 mg/kg).
0.06 mg/kg	8 to 28 days	Repeat step-up dose 2 (0.06 mg/kg) and continue TALVEY step-up dosing schedule.
	More than 28 days	Restart TALVEY step-up dosing schedule at step-up dose 1 (0.01 mg/kg).
0.4 mg/kg	8 to 28 days	Repeat step-up dose 3 (0.4 mg/kg) and continue TALVEY step-up dosing schedule.
	29 to 56 days	Restart TALVEY step-up dosing schedule at step-up dose 2 (0.06 mg/kg).
	More than 56 days	Restart TALVEY step-up dosing schedule at step-up dose 1 (0.01 mg/kg).
0.8 mg/kg	14 to 28 days	Continue TALVEY dosing schedule at treatment dose (0.8 mg/kg biweekly)
	29 to 56 days	Restart TALVEY step-up dosing schedule at step-up dose 3 (0.4 mg/kg).
	More than 56 days	Consider permanent discontinuation and reassess the benefit risk of restarting TALVEY. If restarting TALVEY, begin with the step-up dosing schedule at step-up dose 1 (0.01 mg/kg).

* Administer pretreatment medications prior to restarting TALVEY. After restarting TALVEY, resume biweekly (every 2 weeks) dosing schedule accordingly *(see Dosage and Administration – Usual dosage)*.

Dose modifications for adverse reactions

Dose delays may be required to manage toxicities related to TALVEY (see *Warnings and Precautions*).

See Tables 5, 6 and 7 for recommended actions for the management of CRS, ICANS and neurologic toxicity respectively. See Table 8 for recommended dose modifications for other adverse reactions.

Cytokine release syndrome (CRS)

Identify CRS based on clinical presentation (see *Warnings and Precautions - Cytokine release syndrome*). Evaluate and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, withhold TALVEY until CRS resolves, and manage according to the recommendations in Table 5. Administer supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS. Consider laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

Table 5: Recommendations for Management of Cytokine Release Syndrome

Grade[a]	Presenting Symptoms	Actions

Grade 1	Temperature ≥ 38°C[b]	• Withhold TALVEY until CRS resolves. • Manage CRS per consensus guidelines • Administer pretreatment medications prior to next dose of TALVEY
Grade 2	Temperature ≥ 38°C[b] with either: Hypotension responsive to fluids and not requiring vasopressors. or Oxygen requirement of low-flow nasal cannula[c] or blow-by.	• Withhold TALVEY until CRS resolves. • Manage CRS per consensus guidelines. • Administer pretreatment medications prior to next dose of TALVEY • If CRS does not resolve to baseline or does not improve to grade ≤1 within 48 hours patients should be monitored in an inpatient setting for at least 36 hours following the next dose of TALVEY *(see Dosage and Administration – Monitoring).*
Grade 3	Temperature ≥ 38°C[b] with either: Hypotension requiring one vasopressor with or without vasopressin. or Oxygen requirement of high-flow nasal cannula[c], facemask, non-rebreather mask, or Venturi mask.	Duration < 48 hours: • Withhold TALVEY until CRS resolves. • Manage CRS per consensus guidelines. • Administer pretreatment medications prior to next dose of TALVEY • Patients should be monitored in an inpatient setting for at least 36 hours following the next dose of TALVEY *(see Dosage and Administration – Monitoring).* Recurrent or Duration ≥ 48 hours Permanently discontinue TALVEY.
Grade 4	Temperature ≥ 38°C[b] with either: Hypotension requiring multiple vasopressors (excluding vasopressin). or Oxygen requirement of positive pressure (e.g., continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, and mechanical ventilation).	• Permanently discontinue TALVEY. • Manage CRS per consensus guidelines

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) grading for CRS (Lee et al 2019).
[b] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (e.g. corticosteroids).
[c] Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

Neurologic Toxicity including ICANS

At the first sign of neurologic toxicity, including ICANS, withhold TALVEY and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, including ICANS (see *Warnings and Precautions – Neurologic toxicity including ICANS*). Manage ICANS and neurologic toxicity according to the recommendations in Table 6 and Table 7 and consider further management per current practice guidelines.

Table 6: Recommendations for Management of ICANS

Grade[a]	Presenting Symptoms[b]	Actions
Grade 1	ICE score 7-9[c], or depressed level of consciousness[d]: awakens spontaneously.	• Withhold TALVEY until ICANS resolves.[e] • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. • Provide supportive therapy per consensus guidelines.
Grade 2	ICE score 3-6[c], or depressed level of consciousness[d]: awakens to voice.	• Withhold TALVEY until ICANS resolves. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. • Provide supportive therapy per consensus guidelines • Patients should be hospitalized for 36 hours following the next dose of TALVEY (*see Dosage and Administration - Monitoring)*.[e]
Grade 3	ICE score 0-2[c], (If ICE score is 0, but the patient is arousable (e.g., awake with global aphasia) and able to perform assessment) or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local edema on neuroimaging[d].	<u>First Occurrence of Grade 3 ICANS:</u> • Withhold TALVEY until ICANS resolves. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. • Provide supportive therapy, which may include intensive care, per consensus guidelines. • Patients should be hospitalized for 36 hours following the next dose of TALVEY (see *Dosage and Administration - Monitoring*).[e] <u>Recurrent Grade 3 ICANS:</u> • Permanently discontinue TALVEY. • Administer dexamethasone[f] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. • Provide supportive therapy, which may include intensive care, per consensus guidelines.
Grade 4	ICE score 0[c] (Patient is unarousable and unable to perform ICE assessment)	• Permanently discontinue TALVEY. • Administer dexamethasone[f] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.

	or depressed level of consciousness[d]: either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[d], either: • life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[d]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral edema[d], with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad.	• Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. • Provide supportive therapy, which may include intensive care, per consensus guidelines.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.

[b] Management is determined by the most severe event, not attributable to any other cause.

[c] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point; and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

[d] Attributable to no other cause.

[e] See Table 3 and Table 4 for recommendations on restarting TALVEY after dose delays (*see Dosage and Administration – Dose Delays)*.

[f] All references to dexamethasone administration are dexamethasone or equivalent.

Table 7: Recommendations for Management of Neurologic Toxicity (excluding ICANS)

Adverse Reaction	Severity[a]	Actions
Neurologic Toxicity[a] (excluding ICANS)	Grade 1	• Withhold TALVEY until neurologic toxicity symptoms resolve or stabilize.[b]
	Grade 2 Grade 3 (First occurrence)	• Withhold TALVEY until neurologic toxicity symptoms improve to Grade 1 or less.[b] • Provide supportive therapy.
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue TALVEY. • Provide supportive therapy, which may include intensive care.

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

[b] See Table 3 and Table 4 for recommendations on restarting TALVEY after dose delays (*see Dosage and Administration – Dose delays)*.

Other adverse reactions

The recommended dose modifications for other adverse reactions are provided in Table 8.

Table 8: Recommended Dose Modifications for Other Adverse Reactions

Adverse Reaction	Severity	Dose Modification
Serious Infections (see *Warnings and Precautions*)	All Grades	• Withhold TALVEY in the step-up phase until infection resolves

	Grade 3-4	• Withhold TALVEY during the treatment phase until infection improves to Grade 2 or better.
Cytopenias (see *Warnings and Precautions*)	Absolute neutrophil count less than 0.5×10^9/L	• Withhold TALVEY until absolute neutrophil count is 0.5×10^9/L or higher.
	Febrile neutropenia	• Withhold TALVEY until absolute neutrophil count is 1.0×10^9/L or higher and fever resolves.
	Hemoglobin less than 8 g/dL	• Withhold TALVEY until hemoglobin is 8 g/dL or higher.
	Platelet count less than 25,000/µL Platelet count between 25,000/µL and 50,000/µL with bleeding	• Withhold TALVEY until platelet count is 25,000/µL or higher and no evidence of bleeding.
Oral Toxicity (see *Warnings and Precautions*)	All grades	• Interrupt TALVEY or consider less frequent dosing (biweekly (every 2 weeks) instead of weekly, monthly instead of biweekly) until improvement.
Skin Reactions (see *Warnings and Precautions*)	Grade 3-4	• Withhold TALVEY until adverse reaction improves to Grade 1 or baseline.
Other Non-hematologic Adverse Reactions[a] (see*Undesirable Effects*)	Grade 3-4	• Withhold TALVEY until adverse reaction improves to Grade 1 or baseline.

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

Special dosage instructions

Patients with hepatic disorders

No formal studies of TALVEY in patients with hepatic impairment have been conducted.
Based on population pharmacokinetic analyses, no dose adjustment is recommended for patients with mild or moderate hepatic impairment (see *Pharmacokinetics*).

Patients with renal disorders

No formal studies of TALVEY in patients with renal impairment have been conducted.
Based on population pharmacokinetic analyses, no dose adjustment is recommended for patients with mild or moderate renal impairment (see *Pharmacokinetics*).

Elderly patients (65 years of age and older)

Of the 339 patients treated with TALVEY in MonumenTAL-1, 36% were 65 to less than 75 years of age, and 17% were 75 years of age or older. No clinically important differences in safety or effectiveness were observed in patients 65 to 75 years of age compared to younger patients. There are limited clinical data with talquetamab in patients 75 years of age or over. No dose adjustment is required (see *Pharmacokinetics*).

Pediatric population

TALVEY is not authorised for use in the paediatric population.

Contraindications

None.

Warnings and precautions

Cytokine release syndrome (CRS)

Cytokine release syndrome, including life-threatening or fatal reactions, may occur in patients receiving TALVEY (see *Undesirable Effects*). In the clinical trial, CRS occurred in 76.7 % of patients who received TALVEY at the recommended dosages, with Grade 1 CRS occurring in 58.7 % of patients, Grade 2 in 16.5 %, and Grade 3 in 1.5%. Recurrent CRS occurred in 31.0% of patients. Most events occurred during the step-up phase following the 0.01mg/kg dose (28.9%), the 0.06mg/kg dose (44.2%), the 0.3mg/kg dose (for patients who received biweekly dosing; 33.3%), or the initial treatment dose (0.4 mg/kg (29.6%) or 0.8 mg/kg (12.4%)). 3.5% of CRS events occurred from Week 5 onward; all events were Grade 1. The median time to onset of CRS was 2 (range: 1 to 22) days from the last dose, 90.9% of events occurred within 48 hours from the last dose, and the median duration was 2 (range: 1 to 29) days.
Clinical signs and symptoms of CRS may include but are not limited to pyrexia, hypotension, chills, hypoxia, headache, and tachycardia. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).
Initiate TALVEY therapy with step-up dosing and administer pre-treatment medications (corticosteroids, antihistamine, and antipyretics) prior to each dose of TALVEY during the step-up phase to reduce the risk of CRS. Monitor patients following administration of TALVEY accordingly. In patients who experience CRS, administer pre-treatment medications prior to the next TALVEY dose (see *Dosage and Administration – Monitoring, Usual dosage*, *Pretreatment medications*, and *Dose modifications for adverse reactions*).
Counsel patients to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care based on severity. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), during CRS was avoided during the clinical trial. Withhold TALVEY until CRS resolves or permanently discontinue based on severity (see *Dosage and Administration –Dose modifications for adverse reactions*).

Neurologic Toxicity including ICANS

TALVEY can cause serious or life-threatening neurologic toxicity, including ICANS, including fatal reactions (see *Undesirable effects*).
In the clinical trial, neurologic toxicity (including ICANS) occurred in 28.9% of patients who received TALVEY at the recommended dosages, with Grade 1 neurologic toxicity occurring in 16.5%, Grade 2 in 9.7% and Grade 3 and 4 in 2.7% of patients. The median time to onset of neurotoxicity (including

ICANS) was 2 days (range: 1 to 28) days after the most recent dose with a median duration of 4 (range: 1 to 618) days.
ICANS was reported in 9.8% of 265 patients where ICANS was collected and who received TALVEY at the recommended dosages (see *Undesirable effects*). Recurrent ICANS occurred in 3.0% of patients. Most patients experienced ICANS during the step-up phase following the 0.01 mg/kg dose (3.4%), the 0.06 mg/kg dose (3.0%), the 0.3mg/kg dose (for patients who received biweekly dosing; 1.8%), or the initial treatment dose (0.4 mg/kg (2.6%) and 0.8 mg/kg (3.7%)). The median time to onset of ICANS was 2 (range: 1 to 16) days after the most recent dose with a median duration of 2 (range: 1 to 22) days.
The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

Monitor patients for signs and symptoms of ICANS and treat promptly. Counsel patients to seek medical attention should signs or symptoms of ICANS occur. At the first sign of ICANS, immediately evaluate the patient and provide supportive care based on severity; withhold or discontinue TALVEY based on severity and follow management recommendations. (see *Dosage and Administration – Dose modifications for adverse reactions*).

Oral toxicity

Oral toxicities, including dysgeusia (72.3 %), dry mouth (36.0 %), dysphagia (24.2 %), and stomatitis (19.8%), may occur following treatment with TALVEY (see *Undesirable effects*). Seventy-eight percent (78%) of patients had Grade 1 or 2 events, with Grade 3 events occurring in 2% of patients. Monitor patients for signs and symptoms of oral toxicity. Counsel patients to seek medical attention should signs or symptoms of oral toxicity occur and provide supportive care. Supportive care may include saliva stimulating agents, steroid mouth wash, or consultation with a nutritionist. Interrupt TALVEY or consider less frequent dosing (see *Dosage and Administration – Dose modifications for adverse reactions*).

Weight loss

Over time, notable weight loss may occur (see *Undesirable effects*). Weight change should be monitored regularly during therapy. Clinically significant weight loss should be further evaluated.

Serious infections

Serious infections, including life-threatening or fatal infections, including opportunistic infections have been reported in patients receiving TALVEY (see *Undesirable effects*).
Opportunistic infections occurred in 4.7% of patients receiving TALVEY in the clinical trials, with Grade 3 or higher infections in 0.9%.

New or reactivated viral infections, occurred in clinical trials with TALVEY, including one case of fatal hepatitis B virus (HBV) reactivation in a clinical trial of talquetamab in combination with another antimyeloma therapy. Before starting treatment with TALVEY, screening for HBV infection, active HIV and active HCV infection should be performed according to clinical guidelines. Due to the possibility of fulminant courses, patients with positive HBV serology should be monitored during treatment with TALVEY and for at least six months after discontinuation for clinical symptoms and laboratory values that may be signs of HBV reactivation.
In patients who develop reactivation of HBV, active HCV infection or are known to be seropositive for HIV or acquired immune deficiency syndrome while on TALVEY treatment should be withheld as indicated in Table 8 and manage per local institutional guidelines (see *Dosage/Administration - Dose modifications for adverse reactions*).

Monitor patients for signs and symptoms of infection prior to and during treatment with TALVEY and treat appropriately. Administer prophylactic antimicrobials according to local guidelines. Withhold TALVEY as indicated (see *Dosing and Administration – Dose modifications for adverse reactions*).

Hepatotoxicity

TALVEY can cause hepatoxicity. Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TALVEY or consider permanent discontinuation of TALVEY based on severity and manage per local institutional guidelines (see *Dosage and Administration – Dose modifications for adverse reactions*).

Cytopenias

In the clinical trial, Grade 3 or 4 decreased neutrophils occurred in 36.4% of patients, and decreased platelets occurred in 23.4% of patients who received TALVEY. The median time to onset for Grade 3 or 4 neutropenia was 25 (range: 1 to 471) days, and the median time to resolution to Grade 2 or lower was 8 (range: 1 to 79) days. The median time to onset for Grade 3 or 4 thrombocytopenia was 13 (range: 2 to 477) days, and the median time to resolution to Grade 2 or lower was 10 (range: 1 to 64) days. Monitor complete blood counts during treatment and withhold TALVEY as warranted (see *Dosage and Administration – Dose modifications for adverse reactions*).

Skin reactions

Rash, including maculo-papular rash, erythema, and erythematous rash, occurred in patients who received TALVEY (see *Undesirable effects*). Monitor rash progression for early intervention and treatment with corticosteroids. Rashes should be managed with topical steroids and early consideration of a short course of oral steroids to reduce the risk of rash progression.

Vaccines

Immune response to vaccines may be reduced when taking TALVEY.

The safety of immunization with live viral vaccines during or following TALVEY treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 4 weeks prior to the start of treatment, during treatment, and at least 4 weeks after treatment.

Hypersensitivity reactions and other administration reactions

TALVEY can cause both systemic administration-related reactions and local injection-site reactions.

Systemic Reactions

In patients who received TALVEY at the recommended dose in the clinical trial, systemic-administration reactions occurred in 3.8 % of patients, with grade 1 in 3.2% and grade 2 and grade 3 in 0.3% (one patient each).

Local Reactions

In patients who received TALVEY at the recommended dose in the clinical trial, injection-site reactions occurred in 13.3 % of patients, with Grade 1 injection-site reactions in 12.7 % and Grade 2 in 0.6 %.
Withhold TALVEY or consider permanent discontinuation of TALVEY based on severity (see *Dosage and Administration, Other Adverse Reactions)*.

Excipients

TALVEY contains less than 1 mmol sodium (23 mg) per 1 vial, i.e. it is almost “sodium-free”.

Patient populations not studied in clinical trials

The following patient groups were excluded from the MonumenTAL-1 study:
Patients with hypercalcemia (>3.5 mmol/L), renal insufficiency (creatinine clearance <40 mL/min), anemia (hemoglobin <80 g/L), ECOG performance status >2, CNS involvement, infections (HIV, AIDS, HBV, HCV), cardiac disorders (congestive heart failure NYHA class III or IV, myocardial infarction or CABC ≤ 6 months prior to enrolment, history of clinically significant ventricular arrhythmia or unexplained syncope, history of severe non-ischemic cardiomyopathy), patients with stroke and seizure within the last 6 months, patients with allogenic stem cell transplant within 6 months and autologous stem cell transplant within 12 weeks before the first dose of TALVEY and patients who have received live, attenuated vaccines within 4 weeks prior to the first dose of TALVEY.

Interactions

No drug interaction studies have been performed with TALVEY.

Talquetamab causes release of cytokines (see *Properties/Effects – Pharmacodynamics*) that may suppress activity of cytochrome P450 (CYP) enzymes, potentially resulting in increased exposure of CYP substrates. The highest risk of drug-drug interaction is expected to occur from initiation of talquetamab step-up phase up to 9 days after the first treatment dose and during and after CRS (see

Warnings and Precautions – Cytokine release syndrome). Monitor for toxicity or concentrations of drugs that are CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5) substrates where minimal concentration changes may lead to serious adverse reactions. Adjust the dose of the concomitant CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5) substrate drugs as needed.

Pregnancy, lactation

Females and males of reproductive potential

Pregnancy testing

Verify pregnancy status of females of child-bearing potential prior to initiating TALVEY.

Contraception

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of TALVEY.
Advise male patients with a female partner of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of TRADENAME.

Pregnancy

There are no available data on the use of TALVEY in pregnant women or animal data to assess the risk of TALVEY in pregnancy. Human IgG is known to cross the placenta after the first trimester of pregnancy. Therefore, talquetamab has the potential to be transmitted from the mother to the developing fetus. The effects of TALVEY on the developing fetus are unknown. Pregnant women should be advised there may be risks to the fetus. TALVEY is not recommended for women who are pregnant or for women of childbearing potential not using contraception.

Breast-feeding

It is not known whether talquetamab is excreted in human or animal milk, affects breastfed infants, or affects milk production. Because the potential for serious adverse reactions in breastfed infants is unknown for TALVEY, advise patients not to breastfeed during treatment with TALVEY and for at least 3 months after the last dose.

Fertility

There are no data on the effect of TALVEY on fertility. Effects of TALVEY on male and female fertility have not been evaluated in animal studies.

Effects on ability to drive and use machines

Due to the potential for ICANS, patients receiving TALVEY are at risk of depressed level of consciousness (see *Warnings and Precautions*). Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during the step-up phase and for 48 hours after completion

of the step-up phase (see *Dosage and Administration – Usual Dosage*) and in the event of new onset of any neurological symptoms, until symptoms resolve**.**

Undesirable effects

Adverse reactions are adverse events that were considered to be reasonably associated with the use of talquetamab based on the comprehensive assessment of the available adverse event information. A causal relationship with talquetamab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Summary of the safety profile

The safety of TALVEY was evaluated in 339 adult patients with relapsed or refractory multiple myeloma, including patients exposed to prior T-cell redirection therapy, treated with TALVEY at the recommended dosing regimen in MonumenTAL-1. The median duration of treatment was 7.5 (range: 0.0 to 32.9) months.
The most frequent adverse reactions (≥ 20%) were CRS, dysgeusia, hypogammaglobulinemia, nail disorder, musculoskeletal pain, neutropenia, skin disorder, rash, fatigue, weight decreased, anemia, dry mouth, pyrexia, xerosis, thrombocytopenia, lymphopenia, dysphagia, diarrhea, and upper respiratory tract infection, pruritus, cough, pain, decreased appetite and headeache.
Serious adverse reactions reported in ≥ 2% of patients included CRS, pyrexia, ICANS, sepsis, COVID-19, bacterial infection, neutropenia, pneumonia, viral infection and pain.
Dose interruptions (dose delays and dose skips) of TALVEY due to adverse reactions occurred in 64.0% of patients. The most frequent adverse reactions (≥ 5 %) leading to dose interruptions were COVID-19 (13.3%), CRS (12.4%), pyrexia (9.7%), neutropenia (6.5%) and upper respiratory tract infection (6.2%).
Dose reduction of TALVEY due to adverse reaction occurred in 38 patients (11.2 %)
The most frequent adverse reactions leading to treatment discontinuation were ICANS (1.1%) and weight decreased (0.9%).

List of adverse reactions

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Table 9 summarizes adverse reactions reported in patients who received TALVEY.

Table 9: Adverse reactions in patients with multiple myeloma treated with TALVEY in MonumenTAL-1 (N=339)

System Organ Class Adverse Reaction	**Frequency category**	**Any Grade (%)**	**Grade 3 or 4 (%)**
Infections and infestations			
Bacterial infection*	Very common	40 (12%)	11 (3.2%)
Fungal infection*	Very common	39 (12%)	1 (0.3%)
COVID-19*#	Very common	63 (19%)	10 (2.9%)
Sepsis*#	Common	15 (4.4%)	14 (4.1%)
Pneumonia*	Common	23 (7%)	11 (3.2%)
Viral infection*	Common	23 (7%)	6 (1.8%)
Upper respiratory tract infection*	Very common	98 (29%)	7 (2.1%)
Blood and lymphatic system disorders			
Neutropenia*	Very common	120 (35%)	104 (31%)
Anaemia*	Very common	158 (47%)	99 (29%)
Thrombocytopenia	Very common	101 (30%)	71 (21%)
Lymphopenia	Very common	91 (27%)	83 (25%)
Leukopenia	Very common	62 (18%)	38 (11%)
Immune system disorders			
Cytokine release syndrome	Very common	260 (77%)	5 (1.5%)
Hypogammaglobulinemia[1]	Very common	227 (67%)	0
Metabolism and nutrition disorders			
Decreased appetite	Very common	76 (22%)	4 (1.2%)
Hypokalaemia	Very common	55 (16%)	12 (3.5%)
Hypophosphataemia*	Very common	49 (15%)	21 (6%)
Hypomagnesaemia	Very common	35 (11%)	0
Nervous system disorders			
Immune effector cell-associated neurotoxicity syndrome‡	Common	26 (10%)	6 (2.3%)
Encephalopathy[2]	Very common	36 (11%)	0
Headache*	Very common	69 (20%)	2 (0.6%)
Motor dysfunction[3]	Very common	38 (11%)	2 (0.6%)
Dizziness*	Very common	42 (12%)	8 (2.4%)
Sensory neuropathy[4]	Very common	34 (10%)	0
Respiratory, thoracic and mediastinal disorders			
Cough*	Very common	78 (23%)	0
Dyspnea[5#]	Very common	39 (12%)	5 (1.5%)
Oral Pain*	Very common	42 (12%)	0
Gastrointestinal disorders			
Dysgeusia‡[6]	Very common	245 (72%)	0

Dry mouth‡	Very common	122 (36%)	0
Dysphagia	Very common	82 (24%)	3 (0.9%)
Diarrhoea	Very common	84 (25%)	4 (1.2%)
Stomatitis[7]	Very common	67 (20%)	4 (1.2%)
Nausea	Very common	64 (19%)	0
Constipation	Very common	61 (18%)	0
Abdominal pain*	Very common	35 (10%)	1 (0.3%)
Vomiting	Very common	34 (10%)	2 (0.6%)
Skin and subcutaneous tissue disorders			
Rash*	Very common	132 (39%)	12 (3.5%)
Skin disorder*	Very common	145 (43%)	0
Xerosis[8]	Very common	109 (32%)	0
Pruritus	Very common	79 (23%)	1 (0.3%)
Nail disorder*	Very common	191 (56%)	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain*	Very common	164 (48%)	12 (3.5%)
General disorders and administrate site conditions			
Fatigue*	Very common	147 (43%)	12 (3.5%)
Weight decreased	Very common	134 (40%)	11 (3.2%)
Pyrexia*	Very common	113 (33%)	6 (1.8%)
Pain*	Very common	76 (22%)	7 (2.1%)
Oedema[9]	Very common	59 (17%)	0
Injection site reaction[10]	Very common	45 (13%)	0
Chills	Very common	39 (12%)	1 (0.3%)
Investigations			
Transaminase elevation[11]	Very common	48 (14%)	12 (3.5%)
Gamma-glutamyltransferase increased	Very common	36 (11%)	16 (4.7%)

Adverse events are coded using MedDRA Version 24.0.

‡ Per CTCAE v4.03, maximum toxicity grade for dysgeusia is 2 and maximum toxicity grade for dry mouth is 3.

* Grouped term

\# Contains fatal outcome(s)

1 Hypogammaglobulinaemia includes: hypogammaglobulinaemia and/or subjects with laboratory IgG levels below 500 mg/dL following treatment with talquetamab.

2 Encephalopathy includes: agitation, amnesia, aphasia, bradyphrenia, confusional state, delirium, disorientation, encephalopathy, hallucination, lethargy, memory impairment, restlessness, sleep disorder and somnolence.

3 Motor dysfunction includes: dysgraphia, dysphonia, gait disturbance, muscle spasms, muscular weakness and tremor.

4 Sensory neuropathy includes: dysaesthesia, hypoaesthesia, hypoaesthesia oral, neuralgia, peripheral sensory neuropathy, sciatica and vestibular neuronitis.

5 Dyspnoea includes: acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure and tachypnoea.

6 Dysgeusia includes: ageusia, dysgeusia, hypogeusia and taste disorder.

7 Stomatitis includes: cheilitis, glossitis, glossodynia, mouth ulceration, oral discomfort, oral mucosal erythema, oral pain, stomatitis, swollen tongue, tongue discomfort, tongue erythema, tongue oedema and tongue ulceration.

8 Xerosis includes: dry eye, dry skin and xerosis.

9 Oedema includes: fluid retention, gingival swelling, hypervolaemia, joint swelling, lip swelling, oedema, oedema peripheral, periorbital oedema, peripheral swelling and swelling.

10 Injection site reaction includes: injection site discomfort, injection site erythema, injection site haemorrhage, injection site inflammation, injection site irritation, injection site plaque, injection site pruritus, injection site rash and injection site reaction.

11 Transaminase elevation includes: alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased.

Description of specific adverse reactions and additional information

Cytokine release syndrome

In MonumenTAL-1 (N=339), CRS occurred in 76.7% of patients. 31.0% of patients experienced more than one CRS event. Clinical signs and symptoms of CRS may include but are not limited to pyrexia (76.1%), hypotension (14.7%), chills (12.4%), hypoxia (7.1%), headache (4.4%), tachycardia (5.0%) and elevated transaminases (aspartate aminotransferase (1.5%) and alanine aminotransferase (0.9%)).

Neurologic Toxicity including ICANS

In MonumenTAL-1 neurologic toxicities including ICANS occurred in 28.9% (n=98) of patients. Most events were Grade 1 (16.5%) or 2 (9.7%). The most frequent clinical manifestations of neurologic toxicity were ICANS (9.8%), headeache (9.1%), encephalopathy (3.8%), dizziness (3.5%), sensory neuropathy (2.9%) and paraesthesia (2.4%).32.2% were concurrent with CRS (during or within 7 days of CRS resolution).
One fatal ICANS event was reported in MonumenTAL-1.

Serious infections

In MonumenTAL-1 (N=339), Grade 3 or Grade 4 infections occurred in 18.6% of patients, and fatal infections occurred in 1.5% of patients.
Opportunistic infections occurred in 4.7% of patients receiving TALVEY in the clinical trials, with 0.9% of infections being Grade 3 or higher. New or reactivated viral infections that occurred with TALVEY in MonumenTAL-1 included cytomegalovirus (CMV) (0.3%).
In other studies of talquetamab used in combination with antimyeloma agents, 2 cases of HBV reactivation occurred.

Skin reactions

In MonumenTAL-1 (N=339), the majority of rash cases were Grade 1 or 2, with Grade 3 events occurring in 3.5% of patients. The median time to onset for rash was 22 days.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

The maximum tolerated dose of talquetamab has not been determined. In clinical trials, doses of up to 1.2 mg/kg once every 2 weeks and 1.6 mg/kg monthly have been administered.

Treatment

In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment should be instituted immediately.

Properties/Effects

ATC code

L01FX29

Mechanism of action

Talquetamab (also known as JNJ-64407564) is a humanized immunoglobulin G4 proline, alanine, alanine (IgG4 PAA) bispecific antibody directed against GPRC5D on multiple myeloma cells and the CD3 receptor on T-Cells.
Talquetamab promotes enhanced T-cell-mediated cytotoxicity through recruitment of CD3-expressing T-cells to GPRC5D-expressing cells. This leads to the activation of T-cells and induces subsequent lysis of GPRC5D-expressing cells mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T-cells. Based on the expression of GPRC5D, talquetamab targets multiple myeloma cells particularly, thus reducing potential off-target effects toward other cell lineages.

Pharmacodynamics

Within the first month of treatment with talquetamab, activation and redistribution of T-cells and induction of serum cytokines were observed.

Immunogenicity

In MonumenTAL-1, 260 patients treated with subcutaneous talquetamab monotherapy at 0.4 mg/kg weekly or 0.8 mg/kg biweekly (every 2 weeks) were evaluated for antibodies to talquetamab. Following treatment of 0.4 mg/kg weekly or 0.8 mg/kg biweekly (every 2 weeks), 64 of 260 patients (24.6%) developed anti-talquetamab antibodies. None of these participants were positive for neutralizing antibodies to talquetamab. There was no identified clinically significant effect of anti-talquetamab antibodies on the pharmacokinetics, efficacy, or safety (e.g., CRS, systemic administration-related reaction, and injection site reaction*).*

Clinical efficacy

The efficacy of TALVEY monotherapy was evaluated in patients with relapsed or refractory multiple myeloma in a single-arm, open-label, multicenter study, MMY1001 (MonumenTAL-1). The study included patients who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. The study included patients who received prior T-cell redirection therapy (N=34). The study excluded patients with hypercalcemia (>3.5 mmol/L), renal insufficiency (creatinine clearance <40 mL/min), anemia (hemoglobin <80 g/L), ECOG performance status >2, CNS involvement, infections (HIV, AIDS, HBV, HCVI), cardiac disorders (congestive heart failure NYHA class III or IV, myocardial infarction or CABC ≤ 6 months prior to enrollment, history of clinically significant ventricular arrhythmia or unexplained syncope, history of severe non-ischemic cardiomyopathy), patients with stroke and seizure within the last 6 months, patients with allogenic stem cell transplant within 6 months and autologous stem cell transplant within 12 weeks before the first dose of TALVEY and patients who have received live, attenuated vaccines within 4 weeks prior to the first dose of TALVEY. Patients received TALVEY 0.4 mg/kg subcutaneously weekly, following two step-up doses (0.01 and 0.06 mg/kg) in the first week of therapy, or TALVEY 0.8 mg/kg subcutaneously biweekly (every 2 weeks), following three step-up doses (0.01, 0.06 and 0.3 mg/kg), until disease progression or unacceptable toxicity. Patients were hospitalized for monitoring for at least 48 hours after each TALVEY dose during the step-up phase.
Of 122 patients treated with TALVEY 0.4 mg/kg weekly who were not exposed to prior T-cell redirection therapy, the median age was 67 (range: 47 to 86) years, 53% were male, 92% were White, and 7% were Black or African-American. Patients had received a median of 5 (range: 3 to 13) prior therapies, and 77% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-three percent (93%) of patients were refractory to their last therapy and 75% were refractory to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody. Of the 113 patients for whom baseline cytogenetic data were available, high-risk cytogenetic factors (presence of t(4:14), t(14:16), and/or del(17p)) were present in 35% of patients.
Of 109 patients treated with TALVEY 0.8 mg/kg biweekly (every 2 weeks) who were not exposed to prior T-cell redirection therapy, the median age was 67 (range: 38 to 82) years, 62% were male, 87% were White, and 6% were Black or African-American. Patients had received a median of 5 (range: 3 to 12) prior therapies, and 79% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-four percent (95%) of patients were refractory to their last therapy and 69% were refractory to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody. Of the 94 patients for whom baseline cytogenetic data were available, high-risk cytogenetic factors (presence of t(4:14), t(14:16), and/or del(17p)) were present in 33% of patients.
Efficacy results were based on overall response rate assessed by an Independent Review Committee using IMWG criteria (see table 10 and table 11, cut-off date 16 May 2022).

Table 10: Efficacy Results for MMY1001 (MonumenTAL-1) in Patients Receiving 0.4 mg/kg Weekly TALVEY

	0.4 mg/kg Weekly (N=122)
Overall response rate (ORR=sCR+CR+VGPR+PR)	89 (73.0%)
95% CI (%)	(64.2%, 80.6%)
Stringent complete response (sCR)	15.6%
Complete response (CR)	12.3%
Very good partial response (VGPR)	28.7%
Partial response (PR)	16.4%
Duration of Response (DOR)	
Number of responders	89
Median DOR (95% CI) (months)	8.3 (6.5, NE)
Patients with DOR ≥ 6 months	66.7%
Patients with DOR ≥ 9 months	48.2%
Time to First Response	
Number of responders	89
Median (range) (months)	1.2 (0.2; 5.0)
Progression-Free Survival (PFS)	
Median (95% CI) (months)	7.0 (5.7, 9.1)
6-month PFS rate % (95% CI)	56.8 (47.4, 65.2)
9-month PFS rate % (95% CI)	42.0 (33.0, 50.8)
Overall Survival (OS)	
Median (95% CI) (months)	NE
6-month OS rate % (95% CI)	87.6 (80.2, 92.3)
9-month OS rate % (95% CI)	78.7 (70.2, 85.1)

CI=confidence interval; NE=not estimable
Median duration of follow-up = 10.8 months.

Table 11: Efficacy Results for MMY1001 (MonumenTAL-1) in Patients Receiving 0.8 mg/kg Biweekly (Every 2 Weeks) TALVEY

	0.8 mg/kg Biweekly (Every 2 Weeks) (N=109)
Overall response rate (ORR=sCR+CR+VGPR+PR)	55 (50.5%)
95% CI (%)	(40.7%, 60.2%)
Stringent complete response (sCR)	4.6%
Complete response (CR)	5.5%
Very good partial response (VGPR)	23.9%
Partial response (PR)	16.5%
Duration of Response (DOR)	
Number of responders	55
Patients with DOR ≥ 6 months	NE
Patients with DOR ≥ 9 months	NE
Time to First Response	
Number of responders	55
Median (range) (months)	1.3 (0.2;3.3)
Progression-Free Survival (PFS)	
6-month PFS rate % (95% CI)	66.7 (52.5, 77.4)
9-month PFS rate % (95% CI)	NE
Overall Survival	
6-month OS rate % (95% CI)	88.4 (78.9, 93.7)
9-month OS rate % (95% CI)	NE

CI=confidence interval; NE=not estimable
Median duration of follow-up = 4.7 months.

At an updated clinical cut-off of on 17 January 2023 at a median follow-up of 18.7 months, in patients receiving TALVEY 0.4 mg/kg once weekly, the ORR was 74.6%, the median TTR was 1.15 months

(range: 0.2 to 10.9 months), the median DOR was 8.8 months (95 % CI: 6.5 to 12.7) and the median PFS was 7.5 months (95 % CI: 5.7 to 9.4). Estimated median OS was not mature.

At the updated clinical cut-off on 17 January 2023 at a median follow-up of 12.3 months, in patients receiving TALVEY 0.8 mg/kg biweekly, the ORR was 72.5%, the median TTR was 1.28 months (range: 0.2 to 9.2 months), the median DOR, the median PFS and the estimated median OS were not mature yet.

MMY1001 also included 34 patients who were exposed to prior T-cell redirection therapy and who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Patients received TALVEY 0.4 mg/kg subcutaneously once a week, following 2 step-up doses (0.01 and 0.06 mg/kg), until disease progression or unacceptable toxicity. The median age was 60 (range: 38 to 78) years, 60% were male, 97% were White, and 3% were Black or African-American. Patients had received a median of 6 (range: 3 to 15) prior therapies. Prior T-cell redirection therapy was CAR-T cell therapy for 82% of patients and bispecific antibody treatment for 24%.
At the clinical cut-ff on 16 May 2022 (N=34), the median duration of follow-up of 6.97 months, ORR per IRC assessment was 64.7%.
At the updated clinical cut-off on 17 January 2023, at a median follow-up of 14 months, the ORR was 73.5%, the median TTR was 1.15 months (range: 0.2 to 6.4 months), the median DOR was 11.9 months (95%CI: 3.7, NE) and the median PFS was 6.8 months (95 % CI: 3.4 to NE). Estimated median OS was not mature.

Pharmacokinetics

Absorption

0.4 mg/kg Weekly

Talquetamab exhibited approximately dose-proportional pharmacokinetics following subcutaneous administration across a dose ranging from 0.005 to 0.8 mg/kg weekly (0.0125 to 2 times the recommended 0.4 mg/kg weekly dose). The mean accumulation ratio between the 1st and 7th weekly dose of talquetamab 0.4 mg/kg was 3.9- and 4.5-fold for C_{max} and AUC_{tau}, respectively. Pharmacokinetic parameters of talquetamab following the 1st and 7th recommended weekly dose of 0.4 mg/kg are shown in Table 12.

Table 12: Pharmacokinetic Parameters of Talquetamab Following the First and Seventh Recommended 0.4 mg/kg Weekly Dose in Patients with Relapsed or Refractory Multiple Myeloma in MonumenTAL-1

Pharmacokinetic Parameters	1st dose of 0.4 mg/kg	7th dose of 0.4 mg/kg
T_{max} (days)	2.93 (0.98 - 7.75) (n=21)	2.01 (0.94 - 5.97) (n=13)

C_{max} (ng/mL)	1 568 ± 1 185 (n=21)	3 799 ± 2,411 (n=13)
C_{trough} (ng/mL)	178 ± 124 (n=19)	2 548 ± 1 308 (n=13)
AUC_{tau} (ng·h/mL)	178 101 ± 130 802 (n=17)	607 297 ± 371 399 (n=10)

T_{max} = Time to reach the C_{max}; C_{max} = Maximum observed serum talquetamab concentration; C_{trough} = Observed serum talquetamab concentration prior to next dose; AUC_{tau} = Area under the concentration-time curve over the weekly dosing interval. Data are presented as mean ± standard deviation, except for T_{max} which is presented as median (minimum, maximum).

0.8 mg/kg Biweekly (Every Two Weeks)

Talquetamab exhibited approximately dose-proportional pharmacokinetics following subcutaneous administration across a dose ranging from 0.8 mg/kg to 1.2 mg/kg biweekly (1.0 to 1.5 times the recommended 0.8 mg/kg biweekly dose). The mean accumulation ratio between the 1st and 5th biweekly dose of talquetamab 0.8 mg/kg was 2.3- and 2.2-fold for C_{max} and AUC_{ta}u, respectively. Pharmacokinetic parameters of talquetamab following the 1st and 5th recommended biweekly (every 2 weeks) dose of 0.8 mg/kg are shown in Table 13.

Table 13: Pharmacokinetic Parameters of Talquetamab Following the First and Fifth Recommended 0.8 mg/kg Biweekly (Every 2 Weeks) Dose in Patients with Relapsed or Refractory Multiple Myeloma in MonumenTAL-1

Pharmacokinetic Parameters	1st dose of 0.8 mg/kg	5th dose of 0.8 mg/kg
T_{max} (days)	2.83 (1.68 - 13.98) (n=33)	2.85 (0.96 - 7.82) (n=19)
C_{max} (ng/mL)	2 507 ± 1 568 (n=33)	4 161 ± 2 021 (n=19)
C_{trough} (ng/mL)	597 ± 437 (n=32)	1 831 ± 841 (n=17)
AUC_{tau} (ng·h/mL)	675 764 ± 399 680 (n=28)	1 021 059 ± 383 417 (n=17)

T_{max} = Time to reach the C_{max}; C_{max} = Maximum observed serum talquetamab concentration; C_{trough} = Observed serum talquetamab concentration prior to next dose; AUC_{tau} = Area under the concentration-time curve over the Q2W dosing interval. Data are presented as mean ± standard deviation, except for T_{max} which is presented as median (minimum, maximum).

Based on the population pharmacokinetic model, the typical value of the bioavailability of talquetamab was 62% when administered subcutaneously relative to intravenous dosing.

At 0.4 mg/kg weekly dose regimen, the median (range) T_{max} of talquetamab after the 1st and 7th treatment doses were 3 (1 to 8) days and 2 (1 to 6) days, respectively.

At 0.8 mg/kg biweekly (every 2 weeks) dose regimen, the median (range) T_{max} of talquetamab after the 1st and 5th treatment doses were 3 (2 to 14) days and 3 (1 to 8) days, respectively.

Distribution

Based on the population pharmacokinetic model, the typical value of the volume of distribution was 4.3 L (22% CV (coefficient of variation)) for the central compartment, and 5.8 L (83% CV) for the peripheral compartment.

Metabolism

No data.

Elimination

Talquetamab exhibited both linear time-independent and time-dependent clearance. Based on the population pharmacokinetic model, the typical total clearance is 2.08 L/day at initial treatment and 1.06 L/day at steady state for participants with IgG subtype of myeloma and ISS stage I. The time-dependent clearance accounted for 48.8% of total clearance at initial treatment and then decreased exponentially to <5% at around Week 16. The concentration-time profile at Week 16 would reach 90% of steady-state concentration for both 0.4 mg/kg weekly and 0.8 mg/kg biweekly regimens. The median terminal phase half-life based on the post hoc parameters of all SC population (N=392) was 7.56 days at initial treatment, and 12.2 days at steady state.

Kinetics in specific patient groups

Hepatic impairment

No formal studies of talquetamab in patients with hepatic impairment have been conducted.
Results of population pharmacokinetic analyses indicate that mild hepatic impairment (total bilirubin >1 to 1.5 times upper limit of normal (ULN) and any aspartate aminotransferase (AST), or total bilirubin ≤ULN and AST>ULN) and moderate hepatic impairment (total bilirubin 1.5 to 3 times ULN and any AST>ULN) did not significantly influence the pharmacokinetics of talquetamab. No data is available in patients with severe hepatic impairment.

Renal impairment

No formal studies of talquetamab in patients with renal impairment have been conducted.
Results of population pharmacokinetic analyses indicate that mild (60 mL/min/1.73 m^2 ≤ estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2) or moderate (30 mL/min/1.73 m^2 ≤ eGFR <60 mL/min/1.73 m^2) renal impairment did not significantly influence the pharmacokinetics of talquetamab. No data is available in patients with severe renal impairment.

Pediatrics ((17) years of age and younger)

The pharmacokinetics of TALVEY in pediatric patients aged 17 years and younger have not been investigated

Elderly ((65) years of age and older)

Results of population pharmacokinetic analyses indicate that age (33 to 86 years) did not influence the pharmacokinetics of talquetamab.

Preclinical data

No animal studies have been performed to assess the carcinogenic or genotoxic potential of talquetamab.
No animal studies have been conducted to evaluate the effects of talquetamab on reproduction and fetal development.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Chemical and physical in-use stability of the prepared syringes has been demonstrated for 24 hours at 2 - 8°C and subsequently for 24 hours at room temperature 15 – 30° C. For microbiological reasons, the prepared syringes should be used immediately. If this is not possible, in-use storage times and conditions are the responsibility of the user and should normally be no longer than 24 hours at 2 - 8°C.
If stored in the refrigerator, allow the solution to come to ambient temperature before administration.

Special precautions for storage

Store refrigerated at 2°C-8°C.
Store in the original carton in order to protect from light.
Do not freeze.
Do not shake.
Keep out of the sight and reach of children.

Instructions for handling

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Mode of administration

Administer TALVEY via subcutaneous injection.
TALVEY should be administered by a healthcare professional with adequate medical equipment and personnel to manage severe reactions, including cytokine release syndrome (see *Warnings and Precautions - Cytokine release syndrome*).
TALVEY 2 mg/mL vial and 40 mg/mL vial are supplied as ready-to-use solution for injection that do not need dilution prior to administration.
Do not combine TALVEY vials of different concentrations to achieve treatment dose.
Use aseptic technique to prepare and administer TALVEY.

Preparation of TALVEY

- Refer to the following reference tables for the preparation of TALVEY.

- Use Table 14 to determine total dose, injection volume, and number of vials required based on patient's actual body weight for the 0.01 mg/kg dose using TALVEY 2 mg/mL vial.

Table 14: 0.01 mg/kg Dose: Injection Volumes using TALVEY 2 mg/mL Vial

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.5 mL)
0.01 mg/kg Dose	35 to 39	0.38	0.19	1
	40 to 45	0.42	0.21	1
	46 to 55	0.5	0.25	1
	56 to 65	0.6	0.3	1
	66 to 75	0.7	0.35	1
	76 to 85	0.8	0.4	1
	86 to 95	0.9	0.45	1
	96 to 105	1.0	0.5	1
	106 to 115	1.1	0.55	1
	116 to 125	1.2	0.6	1
	126 to 135	1.3	0.65	1
	136 to 145	1.4	0.7	1
	146 to 155	1.5	0.75	1
	156 to 160	1.6	0.8	1

- Use Table 15 to determine total dose, injection volume, and number of vials required based on patient's actual body weight for the 0.06 mg/kg dose using TALVEY 2 mg/mL vial.

Table 15: 0.06 mg/kg Dose: Injection Volumes using TALVEY 2 mg/mL Vial

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.5 mL)
0.06 mg/kg Dose	35 to 39	2.2	1.1	1
	40 to 45	2.6	1.3	1
	46 to 55	3	1.5	1
	56 to 65	3.6	1.8	2
	66 to 75	4.2	2.1	2
	76 to 85	4.8	2.4	2
	86 to 95	5.4	2.7	2
	96 to 105	6	3	2
	106 to 115	6.6	3.3	3
	116 to 125	7.2	3.6	3
	126 to135	7.8	3.9	3
	136 to145	8.4	4.2	3
	146 to155	9	4.5	3
	156 to160	9.6	4.8	4

- Use Table 16 to determine total dose, injection volume, and number of vials required based on patient's actual body weight for the 0.4 mg/kg dose using TALVEY 40 mg/mL vial.

Table 16: 0.4 mg/kg Dose: Injection Volumes using TALVEY 40 mg/mL Vial

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.0 mL)
0.4 mg/kg Dose	35 to 39	14.8	0.37	1
	40 to 45	16	0.4	1
	46 to 55	20	0.5	1
	56 to 65	24	0.6	1
	66 to 75	28	0.7	1
	76 to 85	32	0.8	1
	86 to 95	36	0.9	1
	96 to 105	40	1	1
	106 to 115	44	1.1	2
	116 to 125	48	1.2	2

	126 to 135	52	1.3	2
	136 to 145	56	1.4	2
	146 to 155	60	1.5	2
	156 to 160	64	1.6	2

- Use Table 17 to determine total dose, injection volume, and number of vials required based on patient's actual body weight for the 0.8 mg/kg dose using TALVEY 40 mg/mL vial.

Table 17: 0.8 mg/kg Dose: Injection Volumes using TALVEY 40 mg/mL vial

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.0 mL)
0.8 mg/kg Dose	35 to 39	29.6	0.74	1
	40 to 45	34	0.85	1
	46 to 55	40	1	1
	56 to 65	48	1.2	2
	66 to 75	56	1.4	2
	76 to 85	64	1.6	2
	86 to 95	72	1.8	2
	96 to 105	80	2	2
	106 to 115	88	2.2	3
	116 to 125	96	2.4	3
	126 to 135	104	2.6	3
	136 to 145	112	2.8	3
	146 to 155	120	3	3
	156 to 160	128	3.2	4

- Check that the TALVEY solution for injection is colorless to light yellow. Do not use if the solution is discolored, cloudy, or if foreign particles are present.
- Remove the appropriate strength TALVEY vial(s) from refrigerated storage (2°C to 8°C) and equilibrate to ambient temperature (15°C to 30°C) for at least 15 minutes. Do not warm TALVEY in any other way.
- Once equilibrated, gently swirl the vial for approximately 10 seconds to mix. Do not shake.
- Withdraw the required injection volume of TALVEY from the vial(s) into an appropriately sized syringe using a transfer needle.
  - Each injection volume should not exceed 2.0 mL. Divide doses requiring greater than 2.0 mL equally into multiple syringes.
- TALVEY is compatible with stainless steel injection needles and polypropylene or polycarbonate syringe material.
- Replace the transfer needle with an appropriately sized needle for injection.

Administration of TALVEY

- Inject the required volume of TALVEY into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, TALVEY may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, TALVEY injections should be at least 2 cm apart.
- Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.

- Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Authorisation number

69049 (Swissmedic)

Packs

Carton with 1 vial of 3 mg/1.5 mL (Step-up Dose) [A].
Carton with 1 vial of 40 mg/1.0 mL (Treatment Dose) [A].

Marketing authorisation holder

Janssen-Cilag AG, Zug

Date of revision of the text

July 2023