ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

TALVEY 2 mg/mL solution for injection
TALVEY 40 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TALVEY 2 mg/mL solution for injection
One 1.5 mL vial contains 3 mg of talquetamab (2 mg/mL).

TALVEY 40 mg/mL solution for injection
One 1 mL vial contains 40 mg of talquetamab (40 mg/mL).

Talquetamab is a humanised immunoglobulin g4-proline, alanine, alanine (IgG4-PAA) bispecific antibody directed against G protein-coupled receptor family C group 5 member D (GPRC5D) and the CD3 receptors, produced in Chinese hamster ovary cells by recombinant DNA technology.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is colourless to light yellow, with pH of 5.2 and osmolality of 287-290 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with TALVEY should be initiated and supervised by physicians experienced in the treatment of multiple myeloma.

TALVEY should be administered by a healthcare professional with adequately-trained medical personnel and appropriate medical equipment to manage severe reactions, including cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS).

Posology

Pre-treatment medicinal products should be administered prior to each dose of TALVEY during the step-up phase (see below).
TALVEY should be administered subcutaneously on a weekly or biweekly (every 2 weeks) dosing schedule according to Table 1. Patients who receive talquetamab according to the 0.4 mg/kg weekly

dosing schedule and have attained an adequate clinical response that is confirmed in at least two consecutive disease assessments can be considered for switch to the 0.8 mg/kg biweekly dosing schedule.

Table 1: Recommended TALVEY dose

Dosing schedule	Phase	Day	TALVEY 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
Biweekly (every 2 weeks) 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 and administered subcutaneously.

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

[c] Maintain a minimum of 6 days between weekly doses and a minimum of 12 days between biweekly (every 2 weeks) doses.

Patients should be instructed to remain within proximity of a healthcare facility and monitored for 48 hours after administration of all doses within the TALVEY step-up phase for signs and symptoms of CRS and ICANS (see section 4.4).

Duration of treatment
Patients should be treated with TALVEY until disease progression or unacceptable toxicity.

Pre-treatment

The following pre-treatment medicinal products must be administered 1 to 3 hours before each dose of TALVEY during the step-up phase to reduce the risk of CRS (see section 4.4).

- Corticosteroid (oral or intravenous dexamethasone 16 mg or equivalent)
- Antihistamine (oral or intravenous diphenhydramine 50 mg or equivalent)
- Antipyretics (oral or intravenous paracetamol 650 mg to 1 000 mg or equivalent)

Pre-treatment medicinal products should be administered prior to subsequent doses for patients who repeat doses within the TALVEY step-up phase due to dose delays (see Table 2) or for patients who experienced CRS (see Table 3).

Prevention of infection
Prior to starting treatment with TALVEY, prophylaxis should be considered for the prevention of infections, per local institutional guidelines.

Dose delays

If a dose of TALVEY is delayed, therapy should be restarted based on recommendations in Table 2, and weekly or biweekly dosing should be resumed accordingly (see Posology above). Pre-treatment medicinal products should be administered prior to restarting TALVEY, and patients should be monitored accordingly (see section 4.2).

Table 2: Recommendations for restarting TALVEY after dose delay

Dosing schedule	Last dose administered	Time from last dose administered	TALVEY recommendation*
Weekly dosing schedule	0.01 mg/kg	More than 7 days	Restart at 0.01 mg/kg
	0.06 mg/kg	8 to 28 days	Repeat 0.06 mg/kg
		More than 28 days	Restart at 0.01 mg/kg
	0.4 mg/kg	8 to 35 days	Repeat 0.4 mg/kg
		36 to 56 days	Restart at 0.06 mg/kg
		More than 56 days	Restart at 0.01 mg/kg
Biweekly (every 2 weeks) dosing schedule	0.01 mg/kg	More than 7 days	Restart at 0.01 mg/kg
	0.06 mg/kg	8 to 28 days	Repeat 0.06 mg/kg
		More than 28 days	Restart at 0.01 mg/kg
	0.4 mg/kg	8 to 35 days	Repeat 0.4 mg/kg
		36 to 56 days	Restart at 0.06 mg/kg
		More than 56 days	Restart at 0.01 mg/kg
	0.8 mg/kg	14 to 35 days	Repeat 0.8 mg/kg
		36 to 56 days	Restart at 0.4 mg/kg
		More than 56 days	Restart at 0.01 mg/kg

* Administer pretreatment medicinal products prior to restarting TALVEY. After restarting TALVEY, resume weekly or biweekly (every 2 weeks) dosing accordingly (see section 4.2).

Dose modifications for adverse reactions

Dose delays may be required to manage toxicities related to TALVEY (see section 4.4). See Table 2 for recommendations on restarting TALVEY after a dose delay.

See Tables 3 and 4 for recommended actions for the management of CRS and ICANS. See Table 6 for recommended dose modifications for other adverse reactions.

Cytokine release syndrome (CRS)

CRS should be identified based on clinical presentation (see section 4.4). Other causes of fever, hypoxia, and hypotension should be evaluated and treated. If CRS is suspected, TALVEY should be withheld until CRS resolves and should be managed according to the recommendations in Table 3. Supportive therapy for CRS should be administered, which may include intensive care for severe or life-threatening CRS. Laboratory testing should be considered to monitor for disseminated intravascular coagulation (DIC), haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

Table 3: Recommendations for management of CRS

CRS Grade[a]	TALVEY actions	Tocilizumab[b]	Corticosteroids[c]
Grade 1 Temperature ≥ 38°C[d]	Withhold TALVEY until CRS resolves. Administer pre-treatment medicinal product prior to next dose of TALVEY.	May be considered.	Not applicable

Grade 2 Temperature ≥ 38°C[d] with either: • Hypotension responsive to fluids and not requiring vasopressors, or • Oxygen requirement of low-flow nasal cannula[e] or blow-by.	Withhold TALVEY until CRS resolves. Administer pre-treatment medicinal products prior to next dose of TALVEY. Monitor patient for 48 hours following the next dose of TALVEY. Instruct patients to remain within proximity of a healthcare facility during monitoring.	Administer tocilizumab[c] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement within 24 hours of starting tocilizumab, administer methylprednisolone 1 mg/kg intravenously twice daily, or dexamethasone 10 mg intravenously every 6 hours. Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days.
Grade 3 Temperature ≥ 38°C[d] with either: • Hypotension requiring one vasopressor, with or without vasopressin, or • Oxygen requirement of high-flow nasal cannula[e], facemask, non-rebreather mask, or Venturi mask	<u>Duration < 48 hours</u> Per Grade 2. <u>Recurrent or Duration ≥ 48 hours</u> Permanently discontinue TALVEY.	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily or dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Temperature ≥ 38°C[d] 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.	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above or administer methylprednisolone 1 000 mg intravenously per day for 3 days, per physician discretion. If no improvement or if condition worsens, consider alternate immunosuppressants.[c]

[a] Based on ASTCT grading for CRS (Lee et al 2019).

[b] Refer to tocilizumab prescribing information for details.

[c] Treat unresponsive CRS per institutional guidelines.

[d] 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., tocilizumab or corticosteroids).

[e] 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, TALVEY should be withheld and neurology evaluation should be considered. Other causes of neurologic symptoms should be ruled out.

Supportive therapy should be provided, which may include intensive care, for severe or life-threatening ICANS (see section 4.4). Management recommendations for ICANS are summarised in Table 4.

Table 4: Recommendations for management of ICANS

<table>
<tr><th>ICANS Grade[a, b]</th><th>Concurrent CRS</th><th>No concurrent CRS</th></tr>
<tr><td rowspan="2">Grade 1

ICE[c] score 7-9

or depressed level of consciousness[d]: awakens spontaneously.</td><td>Management of CRS per Table 3.

Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.</td><td>Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.</td></tr>
<tr><td colspan="2">Withhold TALVEY until ICANS resolves.

Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.</td></tr>
<tr><td rowspan="2">Grade 2

ICE[c] score 3-6

or depressed level of consciousness[d]: awakens to voice.</td><td>Administer tocilizumab per Table 3 for management of CRS.

If no improvement after starting tocilizumab, administer dexamethasone[e] 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td><td>Administer dexamethasone[e] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td></tr>
<tr><td colspan="2">Withhold TALVEY until ICANS resolves.

Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.

Monitor patient for 48 hours following the next dose of TALVEY. Instruct patients to remain within proximity of a healthcare facility during monitoring.</td></tr>
<tr><td rowspan="2">Grade 3

ICE[c] score 0-2
(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 generalised, that resolves rapidly, or
• non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention,

or raised intracranial pressure: focal/local oedema on neuroimaging[d].</td><td>Administer tocilizumab per Table 3 for management of CRS.

Administer dexamethasone[e] 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td><td>Administer dexamethasone[e] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.</td></tr>
<tr><td colspan="2">Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.

<u>First Occurrence:</u>
Withhold TALVEY until ICANS resolves.

Monitor patient for 48 hours following the next dose of TALVEY. Instruct patients to remain within proximity of a healthcare facility during monitoring.

<u>Recurrent:</u>
Permanently discontinue TALVEY.</td></tr>
</table>

<table>
<tr><td>Grade 4

ICE[c] score 0
(Patient is unarousable and unable to perform ICE assessment)

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 oedema[d], with signs/symptoms such as:
• diffuse cerebral oedema on neuroimaging, or
• decerebrate or decorticate posturing, or
• cranial nerve VI palsy, or
• papilledema, or
• Cushing’s triad.</td><td>Administer tocilizumab per Table 3 for management of CRS.

Administer dexamethasone[e] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.

Alternatively, consider administration of methylprednisolone 1 000 mg per day intravenously with first dose of tocilizumab, and continue methylprednisolone 1 000 mg per day intravenously for 2 or more days.</td><td>Administer dexamethasone[e] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.

Alternatively, consider administration of methylprednisolone 1 000 mg per day intravenously for 3 days; if improves, then manage as above.</td></tr>
<tr><td colspan="2">Permanently discontinue TALVEY.

Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.

In case of raised intracranial pressure/cerebral oedema, refer to local institutional guidelines for management.</td></tr>
</table>

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

[b] ASTCT 2019 grading for ICANS.

[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] All references to dexamethasone administration are dexamethasone or equivalent

Table 5: 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 stabilise.[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 2 for recommendations on restarting TALVEY after dose delays.

Other adverse reactions

The recommended dose modifications for other adverse reactions are provided in Table 6.

Table 6: Recommended dose modifications for other adverse reactions

Adverse reaction	Severity	Dose modification
Serious infections (see section 4.4)	All Grades	• Do not administer TALVEY step-up dosing schedule in patients with active infection. • 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 section 4.4)	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.
	Haemoglobin less than 8 g/dL	• Withhold TALVEY until haemoglobin 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, including weight loss (see section 4.4)	Toxicity not responding to supportive care	Interrupt TALVEY until stabilisation or improvement, and consider restarting on modified schedule as follows: • If current dose is 0.4 mg/kg every week, change to 0.4 mg/kg every two weeks • If current dose is 0.8 mg/kg every two weeks, change to 0.8 mg/kg every four weeks
Skin reactions, including nail disorders (see section 4.4)	Grade 3-4	• Withhold TALVEY until adverse reaction improves to Grade 1 or baseline.
Other non-haematologic adverse reactions[a] (see section 4.8)	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 populations

Paediatric population

There is no relevant use of TALVEY in the paediatric population in the treatment of multiple myeloma.

Elderly (65 years of age and older)
No dose adjustment is required (see section 5.2).

Renal impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment (see section 5.2). Limited or no data are available in patients with moderate and severe hepatic impairment.

Method of administration

TALVEY is for subcutaneous use.

The required volume of TALVEY should be injected 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.

TALVEY must not be injected into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Cytokine release syndrome (CRS)

CRS, including life-threatening or fatal reactions, may occur in patients receiving TALVEY (see section 4.8). Clinical signs and symptoms of CRS may include but are not limited to pyrexia, hypotension, chills, hypoxia, headache, tachycardia and elevated transaminases. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

TALVEY therapy should be initiated with step-up phase dosing and pre-treatment medicinal products (corticosteroids, antihistamine, and antipyretics) should be administered prior to each dose of TALVEY during the step-up phase to reduce the risk of CRS. Patients should be monitored following administration accordingly. In patients who experience CRS following their previous dose, pre-treatment medicinal products should be administered prior to the next TALVEY dose (see section 4.2).

Subjects who experienced Grade 3 or higher CRS with any previous T cell redirection therapy were excluded from clinical studies. It cannot be excluded that prior severe CRS with chimeric antigen receptor (CAR) T-cell therapy or other T-cell engagers might impact on the safety of TALVEY. The

potential benefits of treatment should be carefully weighed against the risk of neurologic events, and heightened caution should be exercised when administering TALVEY to these patients.

Patients should be counselled to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, patients should be immediately evaluated for hospitalisation and treatment with supportive care, tocilizumab and/or corticosteroids, should be instituted based on severity. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), should be avoided during CRS. TALVEY should be withheld until CRS resolves (see section 4.2).

Neurologic toxicity, including ICANS

Serious or life-threatening neurologic toxicities, including ICANS have occurred following treatment with TALVEY (see section 4.8).

ICANS, including fatal reactions, have occurred following treatment with TALVEY. 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.

Patients should be monitored for signs and symptoms of neurologic toxicities and treated promptly. Patients should be counselled to seek medical attention should signs or symptoms of neurologic toxicities including ICANS occur. At the first sign of neurologic toxicities including ICANS, the patient should be immediately evaluated and supportive care should be provided based on severity. Patients who experience Grade 2 or higher ICANS should be instructed to remain within proximity of a healthcare facility and monitored for signs and symptoms for 48 hours following the next dose of TALVEY.

For ICANS and other neurologic toxicities, TALVEY should be withheld or discontinued based on severity and management recommendations should be followed as indicated in Table 4 (see section 4.2).

There are no data on use of talquetamab in patients with CNS involvement of myeloma or other clinically relevant CNS pathologies as a result of their exclusion from the study due to the potential risk of ICANS.

Due to the potential for ICANS, patients should be instructed to avoid driving or operating machines during the step-up phase and for 48 hours after completion of the step-up phase, and in the event of new onset of any neurological symptoms, until symptoms resolve (see section 4.7).

Management of neurologic toxicities
At the first sign of neurologic toxicity, including ICANS, neurology evaluation should be considered. Other causes of neurologic symptoms should be ruled out. TALVEY should be withheld until adverse reaction resolves (see Table 4). Intensive care and supportive therapy should be provided for severe or life-threatening neurologic toxicities.

Oral toxicity

Oral toxicities, including dysgeusia, dry mouth, dysphagia, and stomatitis occur very commonly following treatment with TALVEY (see section 4.8).

Patients should be monitored for signs and symptoms of oral toxicity. Patients should be counselled to seek medical attention should signs or symptoms of oral toxicity occur, and supportive care should be provided. Supportive care may include saliva stimulating agents, steroid mouth wash, or consultation with a nutritionist. TALVEY should be interrupted or less frequent dosing should be considered (see section 4.2).

Over time, notable weight loss may occur (see section 4.8). Weight change should be monitored regularly during therapy. Clinically significant weight loss should be further evaluated. TALVEY should be interrupted or less frequent dosing should be considered (see section 4.2).

Serious infections

Serious infections, including life-threatening or fatal infections, have been reported in patients receiving TALVEY (see section 4.8). Patients should be monitored for signs and symptoms of infection prior to and during treatment with TALVEY and treated appropriately. Prophylactic antimicrobials should be administered according to local guidelines. TALVEY should not be administered in patients with active serious infection. TALVEY should be withheld as indicated (see section 4.2). Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur.

Hypogammaglobulinaemia

Hypogammaglobulinaemia has been reported in patients receiving TALVEY (see section 4.8). Immunoglobulin levels should be monitored during treatment with TALVEY. Intravenous or subcutaneous immunoglobulin therapy was used to treat hypogammaglobulinaemia patients. Patients should be treated according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement.

Cytopenias

Treatment-emergent Grade 3 or 4 neutropenia, febrile neutropenia and thrombocytopenia have been observed in patients who received TALVEY. A majority of cytopenias occurred during the first 8 to 10 weeks. Complete blood counts should be monitored at baseline and periodically during treatment. Supportive care should be provided per local institutional guidelines.
Patients with neutropenia should be monitored for signs of infection. TALVEY should be withheld as warranted (see section 4.2).

Skin reactions

TALVEY can cause skin reactions including rash, maculo-papular rash, erythema, erythematous rash, as well as nail disorders (see section 4.8). Skin reactions including rash progression should be monitored for early intervention and treatment with corticosteroids. For Grade 3 or higher, or worsening Grade 1 or 2 rashes, oral steroids should also be administered. For non-rash skin reactions dose modification may be considered (see Table 6).
For skin reactions and nail disorders, TALVEY should be withheld based on severity and institutional guidelines should be followed (see section 4.2).

Vaccines

Immune response to vaccines may be reduced when taking TALVEY. The safety of immunisation 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.
For unexpected exposure during pregnancy, see section 4.6.

Women of child-bearing potential/contraception

Pregnancy status of females of child-bearing potential should be verified prior to initiating treatment with TALVEY. Females of reproductive potential should use effective contraception during treatment and for 3 months after the last dose of TALVEY (see section 4.6).

Excipients

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Talquetamab causes release of cytokines (see section 5.1) 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 section 4.4). Monitor for toxicity or concentrations of medicinal products that are CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5, CYP2D6) substrates where minimal concentration changes may lead to serious adverse reactions. The dose of concomitant CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5, CYP2D6) substrate drugs should be adjusted as needed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Pregnancy status of females of child-bearing potential should be verified prior to initiating treatment with TALVEY.

Females of reproductive potential should use effective contraception during treatment and for 3 months after the last dose of TALVEY.

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 foetus. The effects of TALVEY on the developing foetus are unknown. TALVEY is not recommended for women who are pregnant or for women of childbearing potential not using contraception.

If TALVEY is taken during pregnancy, a reduced immune response to vaccines may be expected in newborns. Consequently, newborn vaccinations with live vaccines such as BCG vaccine should be postponed until 4 weeks.

Breast-feeding

It is not known whether talquetamab is excreted in human milk. Because the potential for serious adverse reactions in breast-fed infants is unknown for TALVEY, patients should not breast-feed during treatment with TALVEY and for at least 3 months after the last dose.

Fertility

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

4.7 Effects on ability to drive and use machines

TALVEY has major influence on the ability to drive and use machines.

Due to the potential for ICANS, patients receiving TALVEY are at risk of depressed level of consciousness (see section 4.4). Patients should be instructed to avoid driving or operating machines during the step-up phase and for 48 hours after completion of the step-up phase (see section 4.2), and in the event of new onset of any neurological symptoms, until symptoms resolve.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions were CRS (77%), dysgeusia (72%), hypogammaglobulinaemia (67%), nail disorder (56%), musculoskeletal pain (48%), anaemia (47%), skin disorder (43%), fatigue (43%), weight decreased (40%), rash (39%), dry mouth (36%), neutropenia (35%), pyrexia (33%), xerosis (32%), thrombocytopenia (30%), upper respiratory tract infection (29%), lymphopenia (27%), dysphagia (24%), diarrhoea (25%), pruritus (23%), cough (23%), pain (22%), decreased appetite (22%) and headache (20%).

Serious adverse reactions reported in patients included CRS (13%), pyrexia (5%), ICANS (3.8%), sepsis (3.8%), COVID-19 (3.2%), bacterial infection (2.4%), pneumonia (2.4%), viral infection (2.4%), neutropenia (2.1%) and pain (2.1%).

The most frequent adverse reactions leading to treatment discontinuation were ICANS (1.1%) and weight decreased (0.9%).

Tabulated list of adverse reactions

The safety of TALVEY was evaluated in 339 adult patients with relapsed or refractory multiple myeloma, including patients treated with TALVEY at the recommended dosing regimen with or without prior T cell redirection therapy in MonumenTAL-1. The median duration of treatment was 7.4 (range: 0.0 to 32.9) months.

Table 7 summarises adverse reactions reported in patients who received TALVEY. The safety data of TALVEY was also evaluated in the All Treated population (N=501) with no additional adverse reactions identified.

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 (≥ 1/1000 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 7: 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%)
Upper respiratory tract infection[*]	Very common	98 (29%)	7 (2.1%)
Sepsis[*#]	Common	15 (4.4%)	14 (4.1%)
Pneumonia[*]	Common	23 (7%)	11 (3.2%)
Viral infection[*]	Common	23 (7%)	6 (1.8%)
Blood and lymphatic system disorders			
Neutropenia[*]	Very common	119 (35%)	103 (30%)
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%)

Haemorrhage[1]	Common	27 (8%)	5 (1.5%)
Febrile neutropenia	Common	7 (2.1%)	7 (2.1%)
Immune system disorders			
Cytokine release syndrome	Very common	260 (77%)	5 (1.5%)
Hypogammaglobulinaemia[2]	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[*]	Very common	26 (10%)	6 (2.3%)
Encephalopathy[3]	Very common	36 (11%)	0
Headache[*]	Very common	69 (20%)	2 (0.6%)
Motor dysfunction[4]	Very common	38 (11%)	2 (0.6%)
Dizziness[*]	Very common	42 (12%)	8 (2.4%)
Sensory neuropathy[5]	Very common	34 (10%)	0
Respiratory, thoracic and mediastinal disorders			
Cough[*]	Very common	78 (23%)	0
Dyspnea[6#]	Very common	39 (12%)	5 (1.5%)
Oral Pain[*]	Very common	42 (12%)	0
Gastrointestinal disorders			
Dysgeusia[‡7]	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[8]	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[9]	Very common	109 (32%)	0
Pruritus	Very common	79 (23%)	1 (0.3%)
Nail disorder[*]	Very common	191 (56%)	0
Alopecia	Common	30 (9%)	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[10]	Very common	59 (17%)	0
Injection site reaction[11]	Very common	45 (13%)	0
Chills	Very common	39 (12%)	1 (0.3%)
Investigations			
Fibrinogen decreased	Very common	52 (15%)	12 (3.5%)
aPTT prolonged	Very common	49 (15%)	0
Transaminase elevation[12]	Very common	48 (14%)	12 (3.5%)
INR increased	Very common	47 (14%)	1 (0.3%)
Gamma-glutamyltransferase increased	Very common	36 (11%)	16 (4.7%)

Adverse reactions 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] Haemorrhage includes: Conjunctival haemorrhage, Epistaxis, Haematoma, Haematuria, Lower gastrointestinal haemorrhage, Periorbital haemorrhage, Petechiae, Rectal haemorrhage, Subdural haematoma and Vaginal haemorrhage.

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

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

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

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

[6] Dyspnoea includes: acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure and tachypnoea.

[7] Dysgeusia includes: ageusia, dysgeusia, hypogeusia and taste disorder.

[8] 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.

[9] Xerosis includes: dry eye, dry skin and xerosis.

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

[11] 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.

[12] Transaminase elevation includes: alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased.

Description of selected adverse reactions

Cytokine release syndrome

In MonumenTAL-1 (N=339), CRS occurred in 77% of patients. Most events were Grade 1 or 2, with Grade 3 events occurring in 1.5% of patients. Thirty one percent (31%) of patients experienced more than one CRS event. Most events occurred during the step-up phase following the 0.01 mg/kg dose (29%), the 0.06 mg/kg dose (44%), the 0.3 mg/kg dose (for patients who received biweekly [every 2 weeks] dosing; 33%), or the initial treatment dose (0.4 mg/kg [30%] or 0.8 mg/kg [12%]). Less than 4% of CRS events occurred from week 5 onward; all events were Grade 1. The median time to onset of CRS was 27 hours from the last dose, 91% of events occurred within 48 hours from the last dose, and the median duration was 17 hours. Tocilizumab, corticosteroids and tocilizumab in combination with corticosteroids were used to treat CRS in 39%, 5% and 3.5% of CRS events, respectively. Clinical signs and symptoms of CRS may include but are not limited to pyrexia (76%), hypotension (15%), chills (12%), hypoxia (7%), headache (4.7%), tachycardia (5%) and elevated transaminases (aspartate aminotransferase [1.5%] and alanine aminotransferase [0.9%]).

Neurologic toxicities

In MonumenTAL-1 (N=339), neurologic toxicity events were reported in 29% of patients receiving TALVEY. Neurologic toxicity events were Grade 1 (17%), Grade 2 (11%), Grade 3 (2.3%) or Grade 4 (0.3%). The most frequently reported neurologic toxicity event was headache (9%).

ICANS were only collected for Phase 2 in MonumenTAL-1. Of the 265 patients in Phase 2, ICANS occurred in 9.8% (n=26) of patients. Most events were Grade 1 or 2, with Grade 3 and 4 events occurring in 2.3% of patients. The most frequent clinical manifestation of ICANS reported were confusional state (3.8%), disorientation (1.9%), somnolence (1.9%) and depressed level of consciousness (1.9%). Sixty-eight percent (68%) were concurrent with CRS (during or within 7 days of CRS resolution). Three percent (3%) of patients experienced more than one ICANS event. In addition, one fatal ICANS event was reported in MonumenTAL-1. Most patients experienced ICANS during the step-up phase following the 0.01 mg/kg dose, the 0.06 mg/kg dose, or the initial treatment dose (0.4 mg/kg and 0.8 mg/kg) (3% each). The median time to onset of ICANS was 28 hours from the last dose, 68% of events started within 48 hours from the last dose, 32% of events occurred after 48 hours, and the median duration of ICANS was 9 hours.

Oral toxicity

In MonumenTAL-1 (N=339), seventy-eight percent (78%) of patients had Grade 1 or 2 events, with Grade 3 events occurring in 2% of patients. Oral toxicity events included dysgeusia, dry mouth, dysphagia, and stomatitis were reported.

Serious infections
In MonumenTAL-1 (N=339), Grade 3 or Grade 4 infections occurred in 19% of patients; fatal infections occurred in 1.5% of patients - COVID-19 pneumonia, fungal sepsis, infection and septic shock. The most frequently reported (≥ 2%) Grade 3 or 4 infection was pneumonia. Febrile neutropenia was observed in 1% of patients with 1.2% experiencing serious febrile neutropenia. See section 4.4 for monitoring and management guidance.

Hypogammaglobulinaemia
Post baseline IgG values of less than 500 mg/dl consistent with hypogammaglobulinaemia have been reported in 64% of patients treated with talquetamab at the 0.4 mg/kg weekly dose schedule, 66% of patients at the 0.8 mg/kg biweekly dose schedule and in 71% of patients with prior T cell redirection therapy (see section 4.4).

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 from the first treatment dose for rash was 22 days. The majority of non-rash skin toxicities were Grade 1 or 2, with Grade 3 pruritus occurring in 0.3% of patients. Nail disorders occurred in 56% of patients and were Grade 1 or 2. See section 4.4 for management guidance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs

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

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Monoclonal antibodies and antibody drug conjugates, ATC code: not yet assigned

Mechanism of action

Talquetamab is a immunoglobulin G4 proline, alanine, alanine (IgG4 PAA) bispecific antibody directed against GPRC5D 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 on plasma cells with

minimal to no expression detected on B cells and B cell precursors, talquetamab targets multiple myeloma cells particularly.

Pharmacodynamic effects

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

Clinical efficacy and safety

The efficacy of TALVEY monotherapy was evaluated in patients with relapsed or refractory multiple myeloma in a single-arm, open-label, multicentre study, 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 excluded patients who received T cell redirection therapy within 3 months, prior Grade 3 or higher CRS related to any T cell redirection therapy, an allogenic stem cell transplant within the past 6 months, autologous stem cell transplant within 3 months, stroke or seizure within the past 6 months, CNS involvement or clinical signs of meningeal involvement of multiple myeloma, plasma cell leukaemia, active or documented history of autoimmune disease, with the exception of vitiligo, resolved childhood atopic dermatitis, POEMS syndrome, primary light chain amyloidosis and prior Grave's disease that was euthyroid based on clinical symptoms and laboratory testing.
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 hospitalised for monitoring for at least 48 hours after each TALVEY dose during the step-up phase.

Of 143 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: 46 to 86) years, 55% were male, 90% were White, and 8% were Black or African American. Patients had received a median of 5 (range: 2 to 13) prior therapies, and 78% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-four percent (94%) of patients were refractory to their last therapy, and 74% were refractory to a PI, immunomodulatory agent, and anti-CD38 antibody. Of the 132 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 31% of patients. Twenty-three percent (23%) of patients had extramedullary plasmacytomas.

Of 145 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 84) years, 57% were male, 86% were White, and 6% were Black or African American. Patients had received a median of 5 (range: 2 to 17) prior therapies, and 79% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-four percent (94%) of patients were refractory to their last therapy, and 69% were refractory to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody. Of the 128 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 29% of patients. Twenty-six percent (26%) of patients had extramedullary plasmacytomas.

Efficacy results were based on an overall response rate as determined by the Independent Review Committee assessment using IMWG criteria. The median duration of follow-up among patients receiving TALVEY 0.4 mg/kg weekly was 18.8 months; an estimated 51.5% of responders maintained response for at least 9 months.

Table 8: Efficacy results for MMY1001 (MonumenTAL-1) in patients receiving TALVEY 0.4 mg/kg weekly

	0.4 mg/kg weekly[a] (N=143)
Overall response rate (ORR=sCR+CR+VGPR+PR)	106 (74.1%)
95% CI (%)	(66.1, 81.1)
Stringent complete response (sCR)	23.8%
Complete response (CR)	9.8%
Very good partial response (VGPR)	25.9%
Partial response (PR)	14.7%
Duration of response (DOR)	
Number of responders	106
Median DOR (95% CI) (months)	9.5 (6.7, 13.3)
Time to first response	
Number of responders	106
Median (range) (months)	1.2 (0.2, 10.9)
MRD negativity rate[a]	
MRD negativity rate in all treated patients, n (%)	44 (30.8%)
95% CI (%)	(23.3, 39.0)
MRD negativity rate[b] in patients achieving CR or sCR	
Number of patients with CR or better	N=48
MRD negativity rate, n (%)	26 (54.2%)
95% CI (%)	(39.2, 68.6)

CI=confidence interval; MRD=minimal residual disease;

[a] MRD-negativity rate is defined as the proportion of participants who achieved MRD negative status (at 10^{-5}) at any timepoint after initial dose and prior to progressive disease (PD) or subsequent anti-myeloma therapy.

[b] Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death/progression/subsequent therapy (exclusive) are considered.

The median duration of follow-up among patients receiving TALVEY 0.8 mg/kg biweekly was 12.7 months; an estimated 76.3% of responders maintained response for at least 9 months.

Table 9: Efficacy results for MMY1001 (MonumenTAL-1) in patients receiving TALVEY 0.8 mg/kg biweekly (every 2 weeks)

	0.8 mg/kg biweekly (every 2 weeks)[a] (N=145)
Overall response rate (ORR=sCR+CR+VGPR+PR)	104 (71.7%)
95% CI (%)	(63.7, 78.9)
Stringent complete response (sCR)	29.7%
Complete response (CR)	9.0%
Very good partial response (VGPR)	22.1%
Partial response (PR)	11.0%
Duration of response (DOR)	
Number of responders	104
Median DOR (95% CI) (months)	NE (13.0, NE)
Time to first response	
Number of responders	104
Median (range) (months)	1.3 (0.2, 9.2)
MRD negativity rate[a]	
MRD negativity rate in all treated patients, n (%)	43 (29.7%)
95% CI (%)	(22.4, 37.8)
MRD negativity rate[b] in patients achieving CR or sCR	
Number of patients with CR or better	N=56
MRD negativity rate, n (%)	24 (42.9%)
95% CI (%)	(29.7, 56.8)

CI=confidence interval; MRD=minimal residual disease; NE=not estimable

[a] MRD-negativity rate is defined as the proportion of participants who achieved MRD negative status (at 10^{-5}) at any timepoint after initial dose and prior to progressive disease (PD) or subsequent anti-myeloma therapy.

[b] Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death/progression/subsequent therapy (exclusive) are considered.

ORR results were consistent across pre-specified subgroups, including number of prior lines of therapy, refractoriness to prior therapy, and cytogenetic risk at baseline.

Immunogenicity

In MonumenTAL-1, 328 patients treated with subcutaneous talquetamab monotherapy at 0.4 mg/kg weekly or 0.8 mg/kg biweekly (every 2 weeks), with or without prior T cell redirection therapy, were evaluated for antibodies to talquetamab. Following treatment 0.4 mg/kg weekly or 0.8 mg/kg biweekly (every 2 weeks), 106 of 328 patients (32.3%) developed anti-talquetamab antibodies.
The limited number of anti-talquetamab antibody (ADA) positive subjects and the lack of information of the neutralising ADA, preclude drawing a definite conclusion regarding the effect of the neutralising ADAs on clinical parameters.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with TALVEY in all subsets of the paediatric population in the treatment of multiple myeloma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

0.4 mg/kg weekly dose

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 10.

Table 10: Pharmacokinetic parameters of talquetamab following the first and seventh recommended weekly dose (0.4 mg/kg) 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 dose

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_{tau}, respectively.

Pharmacokinetic parameters of talquetamab following the 1st and 5th recommended biweekly maintenance dose of 0.8 mg/kg are shown in Table 11.

Table 11: Pharmacokinetic parameters of talquetamab following the first and fifth recommended biweekly (every 2 weeks) dose (0.8 mg/kg) 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).

Absorption

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.

Elimination

Talquetamab exhibited both linear time-independent and time-dependent clearance. Based on the population pharmacokinetic model and the post hoc parameters of participants receiving SC doses (N=392), the median total clearance is 1.64 L/day at initial treatment and 0.80 L/day at steady state. 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 was 7.56 days at initial treatment, and 12.2 days at steady state.

Special populations

The pharmacokinetic analysis includes 86 % White (n=424), 9% Black (n=43), 2.2% Asian (n=11), and 2.8% Others (n=14). Based on population PK analysis, the race or ethnicity, sex and body weight (range: 40 to 143 kg) did not have clinically meaningful effects on the pharmacokinetics of talquetamab.

Paediatric population

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

Elderly

Results of population pharmacokinetic analyses indicate that age (33 to 86 years) did not influence the pharmacokinetics of talquetamab. Only limited data for patients ≥ 85 years was available (see Table 12).

Table 12: Proportion of elderly subjects in the pharmacokinetic (PK) studies of talquetamab

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Studies	181/492	73/492	1/492

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 ≤ absolute glomerular filtration rate (GFR) < 90 mL/min) or moderate (30 mL/min ≤ absolute GFR < 60 mL/min) renal impairment did not significantly influence the pharmacokinetics of talquetamab. No data is available in patients with severe renal impairment.

Hepatic impairment

No formal studies of talquetamab in patients with hepatic impairment have been conducted.
Using the NCI classification, 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) did not significantly influence the pharmacokinetics of talquetamab. Limited data (n=2) are available in participants with moderate hepatic impairment while no data are available in participants with severe hepatic impairment.

5.3 Preclinical safety data

A tool molecule was well tolerated in general toxicity studies in cynomolgus monkeys, but the results of these studies conducted with normal healthy monkeys have limited translatability to multiple myeloma patients.

Carcinogenicity and mutagenicity

No animal studies have been performed to assess the carcinogenic or genotoxic potential of talquetamab.

Reproductive toxicology and fertility

No animal studies have been conducted to evaluate the effects of talquetamab on reproduction and foetal development. No studies have been conducted to evaluate the effects of talquetamab on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

15 months

Prepared syringe

Chemical and physical in-use stability has been demonstrated up to 24 hours at 2 to 8°C followed by up to 24 hours at temperature of 15°C to 30°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless preparation has taken place in controlled and validated aseptic conditions. Discard if stored for more than 24 hours refrigerated or more than 24 hours of being at ambient temperature.

The prepared syringe should be stored protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

TALVEY 2 mg/mL solution for injection
1.5 mL solution for injection in a Type 1 glass vial with an elastomeric stopper and an aluminium seal with a light green flip-off cap containing 3 mg of talquetamab.

Pack size of 1 vial.

TALVEY 40 mg/mL solution for injection
1 mL solution for injection in a Type 1 glass vial with an elastomeric stopper and an aluminium seal with a violet flip-off cap containing 40 mg of talquetamab.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

The TALVEY vials are supplied as ready-to-use solution for injection that do not need dilution prior to administration.

TALVEY vials of different concentrations should not be combined to achieve treatment dose.

Aseptic technique should be used to prepare and administer TALVEY.

Preparation of TALVEY

- Refer to the following reference tables for the preparation of TALVEY
  - Use Table 13 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 13: 0.01 mg/kg dose: injection volumes using TALVEY 2 mg/mL vial

	Body weight (kg)	Total dose[a] (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

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL)

  - Use Table 14 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 14: 0.06 mg/kg dose: injection volumes using TALVEY 2 mg/mL vial

	Body weight (kg)	Total dose[a] (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

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL)

  - Use Table 15 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 15: 0.4 mg/kg dose: injection volumes using TALVEY 40 mg/mL vial

	Body weight (kg)	Total dose[a] (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

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL)

- Use Table 16 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 16: 0.8 mg/kg dose: injection volumes using TALVEY 40 mg/mL vial

	Body weight (kg)	Total dose[a] (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

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL)

- Check that the TALVEY solution for injection is colourless to light yellow. Do not use if the solution is discoloured, cloudy, or if foreign particles are present.
- Remove the appropriate strength TALVEY vial 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 vial 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.
- If the prepared syringe is stored in the refrigerator, allow the solution to come to ambient temperature before administration.
- Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1748/001 (2 mg/ml)
EU/1/23/1748/002 (40 mg/ml)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Janssen Sciences Ireland UC
Barnahely,
Ringaskiddy, Co. Cork
Ireland

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where TALVEY is marketed, all patients/carers who are expected to use talquetamab have access to/are provided with the Patient Card which will inform and explain to patients the risks of CRS and neurologic toxicity including ICANS. The Patient Card

also includes a warning message for healthcare professionals treating the patient that the patient is receiving talquetamab.

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

HCP educational program

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

The MAH shall ensure that in each Member State where talquetamab is marketed, all HCPs who are expected to prescribe or administer talquetamab shall be provided with medical education material to:
- ensure awareness of the risk of neurologic toxicity including ICANS and recommendations to help minimise the risk, including information on frequency, severity, and time to onset observed in patients who received treatment with talquetamab
- facilitate identification of neurologic toxicity including ICANS
- facilitate management of neurologic toxicity including ICANS
- facilitate monitoring of neurologic toxicity including ICANS
- ensure that adverse reactions are adequately and appropriately reported

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of talquetamab indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on or after the last therapy, the MAH shall submit the results of study 64407564MMY3002, a Phase 3 randomised study comparing talquetamab SC in combination with daratumumab SC and pomalidomide (Tal-DP) or talquetamab SC in combination with daratumumab SC (Tal-D) versus daratumumab SC, pomalidomide and dexamethasone (DPd), in participants with relapsed or refractory multiple myeloma.	April 2027
In order to further characterise the long-term safety in subjects with multiple myeloma who have been previously treated with ≥3 prior lines of therapy, including an immunomodulatory agent, a PI and anti-CD38 antibody, and have demonstrated disease progression on or after the last therapy, the MAH shall submit an updated safety report of 64407564MMY1001, a Phase 1/2, first-in-human, open-label, dose escalation study of talquetamab, a humanised GPRC5D x CD3 bispecific antibody, in subjects with relapsed or refractory multiple myeloma	September 2024

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (2 mg/mL)

1. NAME OF THE MEDICINAL PRODUCT

TALVEY 2 mg/mL solution for injection
talquetamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 1.5 mL vial contains 3 mg of talquetamab (2 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: EDTA disodium salt dihydrate, glacial acetic acid, polysorbate 20, sodium acetate trihydrate, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
3 mg/1.5 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1748/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL (2 mg/mL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TALVEY 2 mg/mL injection
talquetamab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mg/1.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (40 mg/mL)

1. NAME OF THE MEDICINAL PRODUCT

TALVEY 40 mg/mL solution for injection
talquetamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 1 mL vial contains 40 mg of talquetamab (40 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: EDTA disodium salt dihydrate, glacial acetic acid, polysorbate 20, sodium acetate trihydrate, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
40 mg/1 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1748/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL (40 mg/mL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

TALVEY 40 mg/mL injection
talquetamab
talquetamabum
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Talvey 2 mg/mL solution for injection
Talvey 40 mg/mL solution for injection
talquetamab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Talvey is and what it is used for

Talvey is a cancer medicine that contains the active substance talquetamab. Talquetamab is an antibody, a type of protein that recognises and attaches to specific targets in your body. It has been designed to attach to the protien GPRC5D (G Protein-coupled receptor family C group 5 member D), which is found on multiple myeloma cancer cells, and to CD3, a protein on T cells (a type of white blood cell). T cells are a part of the body's natural defences and help protect the body from infection. They can also destroy cancer cells. When this medicine attaches to these cells, it brings the cancer cells and T cells together. This encourages the T cells to destroy the multiple myeloma cancer cells.

Talvey is used to treat adults with multiple myeloma, a cancer of the bone marrow.
It is used when patients have had at least three other types of treatment that have not worked or have stopped working.

2. What you need to know before you are given Talvey

You must not be given Talvey
- if you are allergic to talquetamab or any of the other ingredients of this medicine (listed in section 6).

Do not use Talvey if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given Talvey.

Warnings and precautions

Talk to your doctor or nurse before you are given Talvey.

Serious side effects
There are serious side effects that may occur after you start taking Talvey. You need to tell your doctor or nurse straight away if these occur, as they may require that you get immediate medical attention.

Tell your doctor or nurse right away if you experience any of the following:
- signs of a condition known as 'cytokine release syndrome' (CRS). CRS is a serious immune reaction with symptoms such as fever, low blood pressure, chills, difficulty breathing, fatigue, headache, fast heart beat and increased level of liver enzymes in the blood.
- effects on your nervous system. Symptoms include feeling confused, feeling disoriented, feeling sleepy, feeling less alert, slow or difficulty thinking, altered thinking or decreased conciousness, confusion, difficulty speaking and understanding speech. Some of these may be signs of a serious immune reaction called 'immune effector cell-associated neurotoxicity syndrome' (ICANS).
- problems with the mouth, such as a loss of taste, dry mouth, difficulty swallowing and inflammation of the lining of the mouth.
- skin problems such as rash, redness and nail problems.
- feeling warm, fever, chills or shivering, sore throat or mouth ulcers may be signs of an infection.

Talvey and vaccines
Talk to your doctor or nurse before you are given Talvey if you have had a recent vaccination or are going to have a vaccination. Your immune system (the body's natural defences) may not respond as well to vaccination when you are taking this medicine.

You should not receive live vaccines, a specific type of vaccine, from at least 4 weeks before starting your treatment with Talvey until at least 4 weeks after you have taken your last dose.

Tests and checks
Before you are given Talvey your doctor will check your blood to look at the levels of different blood cells and to test for signs of infection. Infections will be treated before you start taking this medicine.
After you have Talvey your doctor will monitor you for side effects. They will also regularly check your blood counts, as the number of blood cells and other blood components may decrease when you use this medicine.

Children and adolescents
Talvey should not be used in children or young people below 18 years of age, because the medicine has not been studied in this age group and it is not known how this medicine will affect them.

Other medicines and Talvey
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines you can get without a prescription and herbal medicines.

Pregnancy, contraception and breast-feeding

Pregnancy and contraception
Talvey has the potential to be transmitted from the mother to the developing foetus. The effects of Talvey on the developing foetus are unknown and a risk to newborns/infants cannot be excluded.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before you are given this medicine.
If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away.

If you could become pregnant, you must use effective contraception during treatment and for 3 months after stopping treatment with Talvey. Your doctor will check if you are pregnant before starting treatment.

If your partner becomes pregnant while you are taking this medicine, tell your doctor straight away.

If you have taken this medicine during pregnancy, your newborn baby should not be given any live vaccines until he or she is at least four weeks old.

Breast-feeding
It is not known if Talvey passes into breast milk. There may be a risk to breastfed newborns/infants. Ask your doctor for advice before starting this medicine. You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby. If you and your doctor decide to stop taking this medicine, you should not breast-feed for 3 months after stopping treatment.

Driving and using machines
Some people may feel tired, dizzy, or confused while taking Talvey. Do not drive, use tools or machines from recieving your first dose until at least 48 hours after receiving your first treatment dose of Talvey or as instructed by your doctor.

Talvey contains sodium
Talvey contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Talvey is given

How much is given
Talvey will be given to you under supervision by a doctor experienced in treating patients with multiple myeloma. Your doctor will decide how much Talvey you are given. The dose of Talvey will depend on your body weight.

Talvey is given either once a week or once every 2 weeks, depending on the dose, as follows:

0.4 mg/kg once a week:
- For your first dose, you will receive 0.01 mg per kilogram of bodyweight.
- For your second dose, which will be given 2-4 days later, you will receive 0.06 mg per kilogram of bodyweight.
- For your third dose, you will receive a 'Treatment dose' of 0.4 mg per kilogram of bodyweight 2-4 days after your second dose.
- After your third dose, you will then receive a 'Treatment dose' once a week thereafter.
- Treatment will continue for as long as you benefit from having Talvey.

Your doctor will monitor you for side effects after each of your first three doses. They will do this for 2 days after each dose. You should stay close to a healthcare facility after each of the first three doses in case you have side effects.

If you experience side effects after any of your first two doses, your doctor may decide to wait up to 7 days before giving you your next dose.

0.8 mg/kg once every 2 weeks:
- For your first dose, you will receive 0.01 mg for each kilogram of bodyweight.
- For your second dose, which will be given 2-4 days later, you will receive 0.06 mg per kilogram of bodyweight.
- For your third dose, which will be given 2-4 days later, you will receive 0.4 mg per kilogram of bodyweight
- For your fourth dose, you will then receive a 'Treatment dose' of 0.8 mg per kilogram of bodyweight 2-4 days after your third dose.
- After your fourth dose, you will then receive a 'Treatment dose' once every 2 weeks thereafter.
- Treatment will continue for as long as you benefit from having Talvey.

Your doctor will monitor you for side effects after each of your first four doses. They will do this for 2 days after each dose. You should stay close to a healthcare facility after each of the first four doses in case you have side effects.

If you experience side effects after any of your first three doses, your doctor may decide to wait up to 7 days before giving you your next dose.

The decision to use either the 0.4 mg/kg once weekly or 0.8 mg/kg every two weeks should be made in consultation with your doctor.

How the medicine is given
Talvey will be given to you by a doctor or nurse as an injection under your skin ('subcutaneous' injection). It is given in the stomach area (abdomen) or thigh.

Medicines given during treatment with Talvey
Before the first three doses (if you are given 0.4 mg/kg bodyweight) or the first four doses (if you are given 0.8 mg/kg bodyweight) of Talvey, you will be given medicines which help to lower the chance of side effects. These may include:
- medicines to reduce an allergic reaction (antihistamines)
- medicines to reduce inflammation (corticosteroids)
- medicines to reduce fever (such as paracetamol)

You may also be given these medicines for when you take later doses of Talvey based on any symptoms you have.

You may also be given additional medicines based on any symptoms you experience or your medical history.

If you are given more Talvey than you should
This medicine will be given by your doctor or nurse. In the event that you are given too much (an overdose) your doctor will check you for side effects.

If you forget your appointment to have Talvey
It is very important to go to all your appointments to make sure your treatment works. If you miss an appointment, make another one as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

<u>Serious side effects</u>
Get medical help straight away if you get any of the following serious side effects which may be severe and can be fatal.

Very Common (may affect more than 1 in 10 people):
- Immune effector cell-associated neurotoxicity syndrome (ICANS), a serious immune reaction that may affect your nervous system. Some of the symptoms are:
  - feeling confused
  - being less alert or aware
  - feeling disoriented
  - feeling sleepy
  - low energy
  - slow and difficulty thinking.

- Cytokine release syndrome (CRS), a serious immune reaction. CRS may cause symptoms such as:
  - fever
  - low blood pressure
  - chills
  - low level of oxygen in the blood
  - headache
  - fast heart beat
  - increased level of liver enzymes in the blood
- low levels of neutrophils (neutropenia), a type of white blood cell that helps fight infection
- low number of blood platelets (thrombocytopenia), which help blood to clot

Tell your doctor right away if you notice any of the above listed serious side effects.

Other side effects
Other side effects are listed below. Tell your doctor or nurse if you get any of these side effects.

Very common (may affect more than 1 in 10 people):
- nail problems
- pain in the muscles and bones (musculoskeletal pain)
- low number of red blood cells (anaemia)
- feeling tired
- chills
- weight loss
- abnormally dry skin or membranes such as the mouth and eyes (xerosis)
- low number of lymphocytes (lymphopenia), a type of white blood cell
- problem being able to produce or control movement (motor dysfunction)
- feeling dizzy
- nerve damage that may cause tingling, numbness, pain or loss of pain sensation (sensory neuropathy)
- damage or disease affecting brain function (encephalopathy)
- diarrhoea
- nausea
- constipation
- stomach pain
- vomiting
- infected nose, sinuses or throat (upper respiratory tract infection)
- itching (pruritus)
- decreased appetite
- pain
- low number of white blood cells (leukopenia)
- low levels of potassium in the blood (hypokalaemia)
- low levels of phosphate in the blood (hypophosphataemia)
- low levels of magnesium in the blood (hypomagnesaemia)
- low level of immunoglobulins, a type of antibody in the blood (hypogammaglobulinaemia), which may make infections more likely
- swelling caused by fluid build up in the body (oedema)
- irritation or pain where the injection is given
- increased level of liver enzymes in the blood
- COVID-19 infection
- blood tests may show it takes longer for blood to clot (fibrinogen decreased, INR increased and PTT prolongation)
- bacterial infection
- mouth pain
- fungal infection

- fever (pyrexia)
- headache
- shortness of breath (dyspnea)
- cough
- problems with the mouth and swallowing, such as change in sense of taste (dysgeusia), dry mouth, difficulty swallowing (dysphagia), and inflammation of the lining of the mouth (stomatitis)
- skin problems, including skin rash

Common (may affect up to 1 in 10 people)
- hair loss
- bleeding, which can be severe (haemorrhage)
- infection of the lungs (pneumonia)
- viral infection
- blood poisoning (sepsis)
- low number of a type of white blood cell (neutrophils), with a fever

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Talvey

Talvey will be stored at the hospital or clinic by your doctor. The following information is therefore mainly intended for healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Store in the original carton in order to protect from light.

Before using the medicine, check the solution for particles or discolouration. The solution should be colourless to light yellow. Do not use this medicine if it is cloudy, discoloured, or contains visible particles.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What Talvey contains
- The active substance is talquetamab. Talvey comes in two different strengths:
  - 2 mg/mL – one 1.5 mL vial contains 3 mg talquetamab
  - 40 mg/mL – one 1 mL vial contains 40 mg talquetamab

- The other ingredients are EDTA disodium salt dihydrate, glacial acetic acid, polysorbate 20, sodium acetate trihydrate, sucrose, water for injection (see “Talvey contains sodium” in section 2).

What Talvey looks like and contents of the pack
Talvey is a solution for injection (injection) and is a colourless to light yellow liquid.
Talvey is supplied as a carton pack containing 1 glass vial.

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Manufacturer
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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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The following information is intended for healthcare professionals only:

The Talvey vials are supplied as ready-to-use solution for injection that do not need dilution prior to administration.

Talvey vials of different concentrations should not be combined to achieve treatment dose.

Aseptic technique should be used to prepare and administer Talvey.

Preparation of Talvey

- Refer to the following reference tables for the preparation of Talvey
    - Use Table 1 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 1: 0.01 mg/kg dose: injection volumes using Talvey 2 mg/mL vial

	Body weight (kg)	Total dose[a] (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

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL)

    - Use Table 2 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 2: 0.06 mg/kg Dose: injection volumes using Talvey 2 mg/mL vial

	Body weight (kg)	Total dose[a] (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 to 135	7.8	3.9	3
	136 to 145	8.4	4.2	3
	146 to 155	9	4.5	3
	156 to 160	9.6	4.8	4

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL)

- Use Table 3 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 3: 0.4 mg/kg dose: injection volumes using Talvey 40 mg/mL vial

	Body weight (kg)	Total dose[a] (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

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL)

- Use Table 4 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 4: 0.8 mg/kg dose: injection volumes using Talvey 40 mg/mL vial

	Body weight (kg)	Total dose[a] (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

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL)

- Check that the Talvey solution for injection is colourless to light yellow. Do not use if the solution is discoloured, cloudy, or if foreign particles are present.
- Remove the appropriate strength Talvey vial 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 vial 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

- Talvey should be administered via subcutaneous injection.
- Talvey should be administered by a healthcare professional with adequate medical equipment and personnel to manage severe reactions, including CRS.
- 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.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.