PRODUCT NAME

TALVEY® (talquetamab) solution for injection.

DOSAGE FORMS AND STRENGTHS

TALVEY® (talquetamab) is a humanized immunoglobulin G4-proline, alanine, alanine (IgG4-PAA)-based bispecific antibody directed against G Protein-coupled receptor family C group 5 member D (GPRC5D) and the cluster of differentiation 3 (CD3) receptors, produced by cultivation of recombinant Chinese hamster ovary cells, followed by isolation, chromatographic purification, and formulation.

TALVEY® is a colorless to light yellow preservative-free solution for injection, with pH of 5.2 and osmolality of 287-290 mOsm/kg.

TALVEY® is available in the following presentations:

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

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

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

Dosage and Administration

TALVEY® is administered via subcutaneous injection.

Administer pretreatment medications prior to each dose of TALVEY® during the step-up phase (see *Dosage and Administration – Pretreatment medications).*

Dosage – Adults (≥18 years)

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

Table 1: Recommended Dose of TALVEY®

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.

[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.

Instruct patients to remain within proximity of a healthcare facility and monitor patients for 48 hours after administration of all doses within the TALVEY® step-up phase for signs and symptoms of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (see *Warnings and Precautions*).

Continue treatment until disease progression or unacceptable toxicity.

Pretreatment medications

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

- Corticosteroid (oral or intravenous dexamethasone, 16 mg or equivalent)
- Antihistamine (oral or intravenous diphenhydramine, 50 mg or equivalent)
- Antipyretics (oral or intravenous acetaminophen, 650 mg to 1000 mg or equivalent)

Administration of pretreatment medications may be required for subsequent doses of TALVEY® for patients who repeat doses within the TALVEY® step-up phase due to dose delays (Table 2) or for patients who experience CRS (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, restart therapy based on recommendations in Table 2 and resume weekly or biweekly (every 2 weeks) dosing accordingly (see *Dosage and Administration-Dosage – Adults (18 years of age and older)*). Administer pretreatment medications prior to

restarting TALVEY®, and monitor patients following administration of TALVEY® (see *Dosage and Administration – Pretreatment medications).*

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 medications prior to restarting TALVEY®. After restarting TALVEY®, resume weekly or biweekly (every 2 weeks) dosing accordingly (see *Dosage and Administration-Dosage – Adults (18 years of age and older)*).

Dose modifications for adverse reactions

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

See Table 3, Table 4 and Table 5 for recommended actions for the management of CRS, ICANS and neurologic toxicities. See Table 6 for recommended dose modifications for other adverse reactions.

Cytokine release syndrome (CRS)

Identify CRS based on clinical presentation (see *Warnings and Precautions – Cytokine release syndrome*). Evaluate and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, withhold TALVEY® until CRS resolves, and manage according to the recommendations in Table 3. Administer supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS. Consider laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

Table 3: Recommendations for Management of CRS

CRS Grade[a]	TALVEY® Actions	Tocilizumab[b]	Corticosteroids[c]

Grade 1 Temperature ≥100.4°F (38°C) [d]	Withhold TALVEY® until CRS resolves. Administer pretreatment medication prior to next dose of TALVEY®.	May be considered.	Not applicable
Grade 2 Temperature ≥100.4°F (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 pretreatment medications prior to next dose of TALVEY®. Monitor patient daily for 48 hours following the next dose of TALVEY®. Instruct patients to remain within proximity of a healthcare facility during daily 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 ≥100.4°F (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 ≥100.4°F (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 1000 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 anti-cytokine 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 toxicities, including Immune effector cell-associated neurotoxicity syndrome (ICANS)

At the first sign of neurologic toxicity, including ICANS, withhold TALVEY® and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for severe or life-threatening ICANS (see *Warnings and Precautions – ICANS*). Management recommendations for ICANS and neurologic toxicity are summarized in Table 4 and Table 5.

Table 4: Recommendations for Management of ICANS

ICANS Grade[a, b]	**Concurrent CRS**	**No Concurrent CRS**
Grade 1 ICE[c] score 7-9 or depressed level of consciousness[d]: awakens spontaneously.	Management of CRS per Table 3. Monitor neurologic symptoms.	Monitor neurologic symptoms.
	Withhold TALVEY® until ICANS resolves. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

<table>
<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.

Monitor patient daily for 48 hours following the next dose of TALVEY®. Instruct patients to remain within proximity of a healthcare facility during daily 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 generalized, that resolves rapidly, or
• non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention,

or raised intracranial pressure: focal/local edema on neuroimaging[d].</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.

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

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

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

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 edema[d], with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad.	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 1000 mg per day intravenously with first dose of tocilizumab, and continue methylprednisolone 1000 mg per day intravenously for 2 or more days.	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 1000 mg per day intravenously for 3 days; if improves, then manage as above.
	Permanently discontinue TALVEY®. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. In case of raised intracranial pressure/cerebral edema, refer to local institutional guidelines for management.	

[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	Actions
Neurologic Toxicity[a] (excluding ICANS)	Grade 1	• Withhold TALVEY® until neurologic toxicity symptoms resolve or stabilize.[b]
	Grade 2 Grade 3 (First occurrence)	• Withhold TALVEY® until neurologic toxicity symptoms improved to Grade 1 or less.[b] • Provide supportive therapy.
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue TALVEY®. • Provide supportive care, 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 *Warnings and Precautions*)	All Grades	• Withhold TALVEY® in the step-up phase until infection resolves.
	Grade 3-4	• Withhold TALVEY® during the treatment phase until infection improves to Grade 2 or better.
Cytopenias (see *Warnings and Precautions*)	Absolute neutrophil count less than 0.5×10^9/L	• Withhold TALVEY® until absolute neutrophil count is 0.5×10^9/L or higher.
	Febrile neutropenia	• Withhold TALVEY® until absolute neutrophil count is 1.0×10^9/L or higher and fever resolves.
	Hemoglobin less than 8 g/dL	• Withhold TALVEY® until hemoglobin is 8 g/dL or higher.
	Platelet count less than 25,000/µL Platelet count between 25,000/µL and 50,000/µL with bleeding	• Withhold TALVEY® until platelet count is 25,000/µL or higher and no evidence of bleeding.
Oral Toxicity (see *Warnings and Precautions*)	All grades	• Interrupt TALVEY® or consider less frequent dosing (biweekly [every 2 weeks] instead of weekly, monthly instead of biweekly) until improvement.
Skin Reactions (see *Warnings and Precautions*)	Grade 3-4	• Withhold TALVEY® until adverse reaction improves to Grade 1 or baseline.
Other Non-hematologic Adverse Reactions[a] (see *Adverse Reactions*)	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

Pediatrics (17 years of age and younger)

The safety and efficacy of TALVEY® have not been established in pediatric patients.

Elderly (65 years of age and older)

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

Renal impairment

No formal studies of TALVEY® in patients with renal impairment have been conducted.

Based on population pharmacokinetic analyses, no dose adjustment is recommended for patients with mild or moderate renal impairment (see *Pharmacokinetic Properties*).

Hepatic impairment

No formal studies of TALVEY® in patients with hepatic impairment have been conducted.

Based on population pharmacokinetic analyses, no dose adjustment is recommended for patients with mild hepatic impairment (see *Pharmacokinetic Properties*). Limited or no data are available in patients with moderate and severe hepatic impairment.

Administration

Administer TALVEY® via subcutaneous injection.

TALVEY® should be administered by a healthcare professional with adequate medical equipment and personnel to manage severe reactions, including cytokine release syndrome (see *Warnings and Precautions - Cytokine release syndrome*).

TALVEY® 2 mg/mL vial and 40 mg/mL vial are supplied as ready-to-use solution for injection that do not need dilution prior to administration.

Do not combine TALVEY® vials of different concentrations to achieve treatment dose.

Use aseptic technique to prepare and administer TALVEY®.

Preparation of TALVEY®

- Refer to the following reference tables for the preparation of TALVEY®.
    - Use Table 7 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 7: 0.01 mg/kg Dose: Injection Volumes using TALVEY® 2 mg/mL Vial

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

	136 to 145	1.4	0.7	1
	146 to 155	1.5	0.75	1
	156 to 160	1.6	0.8	1

- Use Table 8 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 8: 0.06 mg/kg Dose: Injection Volumes using TALVEY® 2 mg/mL Vial

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

- Use Table 9 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 9: 0.4 mg/kg Dose: Injection Volumes using TALVEY® 40 mg/mL Vial

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.0 mL)
	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
0.4 mg/kg Dose	76 to 85	32	0.8	1
	86 to 95	36	0.9	1
	96 to 105	40	1	1
	106 to 115	44	1.1	2
	116 to 125	48	1.2	2
	126 to 135	52	1.3	2
	136 to 145	56	1.4	2
	146 to 155	60	1.5	2
	156 to 160	64	1.6	2

- Use Table 10 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 10: 0.8 mg/kg Dose: Injection Volumes using TALVEY® 40 mg/mL Vial

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

- Check that the TALVEY® solution for injection is colorless to light yellow. Do not use if the solution is discolored, cloudy, or if foreign particles are present.
- Remove the appropriate strength TALVEY® vial(s) from refrigerated storage [2°C to 8°C (36°F to 46°F)] and equilibrate to ambient temperature [15°C to 30°C (59°F to 86°F)] for at least 15 minutes. Do not warm TALVEY® in any other way.
- Once equilibrated, gently swirl the vial for approximately 10 seconds to mix. Do not shake.
- Withdraw the required injection volume of TALVEY® from the vial(s) into an appropriately sized syringe using a transfer needle.
    - Each injection volume should not exceed 2.0 mL. Divide doses requiring greater than 2.0 mL equally into multiple syringes.
- TALVEY® is compatible with stainless steel injection needles and polypropylene or polycarbonate syringe material.
- Replace the transfer needle with an appropriately sized needle for injection.

Administration of TALVEY®

- Inject the required volume of TALVEY® into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, TALVEY® may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, TALVEY® injections should be at least 2 cm apart.

- Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.
- Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in *List of Excipients*.

Warnings and Precautions

Cytokine release syndrome (CRS)

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

Initiate TALVEY® therapy with step-up phase dosing and administer pre-treatment medications (corticosteroids, antihistamine, and antipyretics) prior to each dose of TALVEY® during the step-up phase to reduce the risk of CRS. Monitor patients following administration of TALVEY® accordingly. In patients who experience CRS, administer pre-treatment medications prior to the next TALVEY® dose (see *Dosage and Administration – Dosage – Adults (18 years and older), Pretreatment medications, Dose modifications for adverse reactions*).

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.

Counsel patients to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids, based on severity. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), should be avoided during CRS. Withhold TALVEY® until CRS resolves (see *Dosage and Administration – Dose modifications for adverse reactions*).

Neurologic toxicities, including Immune effector cell-associated neurotoxicity syndrome (ICANS)

Serious or life-threatening neurologic toxicities, including ICANS, have occurred following treatment with TALVEY®.

ICANS, including fatal reactions, have occurred following treatment with TALVEY® (see *Adverse Reactions)*. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

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

Due to the potential for ICANS, patients should be advised not to drive or operate heavy machinery during the TALVEY® step-up dosing phase and for 48 hours after completing the TALVEY® step-up dosing phase, and in the event of new onset of any neurological symptoms, until symptoms resolve (see *Effects on Ability to Drive and Use Machines*).

Oral toxicity

Oral toxicities, including dysgeusia, dry mouth, dysphagia, and stomatitis, may occur following treatment with TALVEY® (see *Adverse Reactions*). Seventy-eight percent (78%) of patients had Grade 1 or 2 events, with Grade 3 events occurring in 2% of patients.

Monitor patients for signs and symptoms of oral toxicity. Counsel patients to seek medical attention should signs or symptoms of oral toxicity occur and provide supportive care. Supportive care may include saliva stimulating agents, steroid mouth wash, or consultation with a nutritionist. Interrupt TALVEY® or consider less frequent dosing (see *Dosage and Administration – Dose modifications for adverse reactions*).

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

Serious infections

Serious infections, including life-threatening or fatal infections, have been reported in patients receiving TALVEY® (see *Adverse Reactions*). Monitor patients for signs and symptoms of infection prior to and during treatment with TALVEY® and treat appropriately. Administer prophylactic antimicrobials according to local guidelines. TALVEY® should not be administered in patients with active serious infection. Withhold TALVEY® as indicated (see *Dosage and Administration – Dose modifications for adverse reactions*).

Hypogammaglobulinaemia

Hypogammaglobulinaemia has been reported in patients receiving TALVEY® (see *Adverse Reactions*). 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 events occurred during the first 8 to 10 weeks. Monitor complete blood counts during treatment and withhold TALVEY® as warranted (see *Dosage and Administration – Dose modifications for adverse reactions*). Provide supportive care according to local institutional guidelines. Patients with neutropenia should be monitored for signs of infection.

Skin reactions

Skin reactions, including rash, maculo-papular rash, erythema, erythematous rash, as well as nail disorders, occurred in patients who received TALVEY® (see *Adverse Reactions*). Monitor skin reactions including rash progression for early intervention and treatment with corticosteroids. Rashes should be managed aggressively with topical steroids and early consideration of a short course of oral steroids to reduce the risk of rash progression. Withhold TALVEY® for skin reactions and nail disorders based on severity (see *Dosage and Administration – Dose modifications for adverse reactions*).

Vaccines

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

Liver enzyme elevations

TALVEY® can cause liver enzyme elevation. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TALVEY® or consider permanent discontinuation of TALVEY® based on severity (see table 3).

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.

Interactions

No drug interaction studies have been performed with TALVEY®.

Talquetamab causes release of cytokines (see *Pharmacodynamic Properties – Pharmacodynamic effects*) that may suppress activity of cytochrome P450 (CYP) enzymes, potentially resulting in increased exposure of CYP substrates. The highest risk of drug-drug interaction is expected to

occur from initiation of talquetamab step-up phase up to 9 days after the first treatment dose and during and after CRS (see *Warnings and Precautions – Cytokine release syndrome*). Monitor for toxicity or concentrations of drugs that are CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5) substrates where minimal concentration changes may lead to serious adverse reactions. Adjust the dose of the concomitant CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5) substrate drugs as needed.

Pregnancy, Breast-feeding and Fertility

Pregnancy

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

Breast-feeding

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

Females and males of reproductive potential

Pregnancy testing

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

Contraception

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of TALVEY®.

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

Fertility

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

Effects on Ability to Drive and Use Machines

Due to the potential for ICANS, patients receiving TALVEY® are at risk of depressed level of consciousness (see *Warnings and Precautions*). Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during the step-up phase and for 48 hours after completion of the step-up phase (see *Dosage and Administration – Dosage - Adults (18 years*

of age and older)) and in the event of new onset of any neurological symptoms, until symptoms resolve.

Adverse Reactions

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

The safety of TALVEY® was evaluated in 339 adult patients with relapsed or refractory multiple myeloma, including patients exposed to prior T cell redirection therapy, treated with TALVEY® at the recommended dosing regimen in MonumenTAL-1. The median duration of treatment was 7.4 (range: 0.0 to 32.9) months.

The most frequent adverse reactions (≥ 20%) were CRS, dysgeusia, hypogammaglobulinemia, nail disorder, musculoskeletal pain, anemia, fatigue, skin disorder, weight decreased, rash, dry mouth, neutropenia, pyrexia, xerosis, thrombocytopenia, upper respiratory tract infection, lymphopenia, diarrhea, dysphagia, pruritus, cough, decreased appetite, pain, and headache.

Serious adverse reactions reported in ≥ 2% of patients included CRS, pyrexia, ICANS, sepsis, COVID-19, bacterial infection, pneumonia, viral infection, neutropenia, and pain.

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

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

Table 11 summarizes adverse reactions reported in patients who received TALVEY®.

Table 11: 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			
Upper respiratory tract infection[1]	Very common	98 (28.9%)	7 (2.1%)
COVID-19[2]#	Very common	63 (18.6%)	10 (2.9%)
Bacterial infection[3]	Very common	40 (11.8%)	11 (3.2%)
Fungal infection[4]	Very common	39 (11.5%)	1 (0.3%)
Pneumonia[5]	Common	23 (6.8%)	11 (3.2%)
Viral infection[6]	Common	23 (6.8%)	6 (1.8%)
Sepsis[7]#	Common	15 (4.4%)	14 (4.1%)
Blood and lymphatic system disorders			
Anemia[8]	Very common	158 (46.6%)	99 (29.2%)

Neutropenia[9]	Very common	120 (35.4%)	104 (30.7%)
Thrombocytopenia	Very common	101 (29.8%)	71 (20.9%)
Lymphopenia	Very common	91 (26.8%)	83 (24.5%)
Leukopenia	Very common	62 (18.3%)	38 (11.2%)
Immune system disorders			
Cytokine release syndrome	Very common	260 (76.7%)	5 (1.5%)
Hypogammaglobulinaemia[10]	Very common	227 (67.0%)	0
Metabolism and nutrition disorders			
Decreased appetite	Very common	76 (22.4%)	4 (1.2%)
Hypokalaemia	Very common	55 (16.2%)	12 (3.5%)
Hypophosphataemia[11]	Very common	49 (14.5%)	21 (6.2%)
Nervous system disorders			
Headache[12]	Very common	69 (20.4%)	2 (0.6%)
Sensory neuropathy[13]	Very common	58 (17.1%)	0
Motor dysfunction[14]	Very common	43 (12.7%)	2 (0.6%)
Dizziness*	Very common	42 (12.4%)	8 (2.4%)
Encephalopathy[15]	Very common	36 (10.6%)	0
Immune effector cell-associated neurotoxicity syndrome	Common	26 (9.8%)	6 (2.3%)
Respiratory, thoracic and mediastinal disorders			
Cough[16]	Very common	78 (23.0%)	0
Oral Pain[17]	Very common	42 (12.4%)	0
Dyspnea*#	Very common	39 (11.5%)	5 (1.5%)
Gastrointestinal disorders			
Dysgeusia[18]	Very common	245 (72.3%)	0
Dry mouth	Very common	122 (36.0%)	0
Diarrhea	Very common	84 (24.8%)	4 (1.2%)
Dysphagia	Very common	82 (24.2%)	3 (0.9%)
Stomatitis[19]	Very common	67 (19.8%)	4 (1.2%)
Nausea	Very common	64 (18.9%)	0
Constipation	Very common	61 (18.0%)	0
Abdominal pain*	Very common	35 (10.3%)	1 (0.3%)
Vomiting	Very common	34 (10.0%)	2 (0.6%)
Skin and subcutaneous tissue disorders			
Nail disorder[20]	Very common	191 (56.3%)	0
Skin disorder[21]	Very common	145 (42.8%)	0
Rash[22]	Very common	132 (38.9%)	12 (3.5%)
Xerosis[23]	Very common	109 (32.2%)	0
Pruritus	Very common	79 (23.3%)	1 (0.3%)
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[24]	Very common	164 (48.4%)	12 (3.5%)
General disorders and administration site conditions			
Fatigue[25]	Very common	147 (43.4%)	12 (3.5%)
Pyrexia[26]	Very common	113 (33.3%)	6 (1.8%)
Pain[27]	Very common	76 (22.4%)	7 (2.1%)
Edema[28]	Very common	59 (17.4%)	0
Injection site reaction[29]	Very common	45 (13.3%)	0
Investigations			
Weight decreased	Very common	134 (39.5%)	11 (3.2%)
Transaminase elevation[30]	Very common	48 (14.2%)	12 (3.5%)

Adverse events are coded using MedDRA Version 25.0.

* Based on grouped term

\# Contains fatal outcome

Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.

Note: ICANS were only collected for Phase 2. Denominator is based on number of patients in Phase 2 (N=265).

[1] Upper respiratory tract infection: bronchiolitis, bronchitis, nasopharyngitis, pharyngitis, respiratory tract infection, respiratory tract infection bacterial, rhinitis, rhinovirus infection, sinusitis, tonsillitis, upper respiratory tract infection and viral upper respiratory tract infection.

[2] COVID-19: asymptomatic COVID-19, COVID-19, COVID-19 pneumonia, coronavirus infection and multisystem inflammatory syndrome.

[3] Bacterial infection: campylobacter infection, carbuncle, cellulitis, citrobacter infection, clostridium difficile colitis, clostridium difficile infection, cystitis escherichia, cystitis klebsiella, diverticulitis, escherichia pyelonephritis, folliculitis, gastroenteritis escherichia coli, helicobacter gastritis, human ehrlichiosis, impetigo, klebsiella sepsis, moraxella infection, otitis media acute, pitted keratolysis, pseudomonal bacteremia, pyuria, relapsing fever, renal abscess, skin infection, staphylococcal infection, tooth abscess, tooth infection, urinary tract infection enterococcal and urinary tract infection pseudomonal.

[4] Fungal infection: body tinea, candida infection, ear infection fungal, fungal foot infection, fungal infection, fungal skin infection, genital candidiasis, esophageal candidiasis, onychomycosis, oral candidiasis, oral fungal infection, oropharyngeal candidiasis, tinea pedis, vulvovaginal candidiasis and vulvovaginal mycotic infection.

[5] Pneumonia: pneumonia and pneumonia streptococcal.

[6] Viral infection: conjunctivitis viral, disseminated varicella zoster virus infection, gastroenteritis viral, HCoV-HKU1 infection, herpes ophthalmic, influenza, metapneumovirus infection, norovirus infection, parainfluenzae virus infection, respiratory syncytial virus bronchiolitis, respiratory syncytial virus infection, retinitis viral and viral infection.

[7] Sepsis: bacteremia, enterobacter bacteremia, escherichia sepsis, fungal sepsis, pneumococcal sepsis, salmonella sepsis, sepsis, septic shock, staphylococcal bacteremia, staphylococcal sepsis and streptococcal bacteremia.

[8] Anemia: anaemia, iron deficiency, blood iron decreased.

[9] Neutropenia: neutropenia and febrile neutropenia.

[10] Hypogammaglobulinemia: hypogammaglobulinemia and/or subjects with laboratory IgG levels below 500mg/dL following treatment with talquetamab.

[11] Hypophosphatemia: blood phosphorus decreased and hypophosphatemia.

[12] Headache: headache, migraine, procedural headache and tension headache.

[13] Sensory neuropathy: dysesthesia, hyperesthesia, hypoesthesia, hypoesthesia oral, immune-mediated neuropathy, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, polyneuropathy, sciatica and vestibular neuronitis.

[14] Motor dysfunction: dysarthria, dysgraphia, dysmetria, dysphonia, gait disturbance, muscle atrophy, muscle spasms, muscular weakness and tremor.

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

[16] Cough: cough, productive cough and upper-airway cough syndrome.

[17] Oral Pain: oropharyngeal pain.

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

[19] Stomatitis: cheilitis, glossitis, glossodynia, mouth ulceration, oral discomfort, oral mucosal erythema, oral pain, stomatitis, swollen tongue, tongue discomfort, tongue erythema, tongue edema and tongue ulceration.

[20] Nail disorder: koilonychia, nail bed disorder, nail cuticle fissure, nail discoloration, nail disorder, nail dystrophy, nail hypertrophy, nail pitting, nail ridging, nail toxicity, onychoclasis, onycholysis and onychomadesis.

[21] Skin disorder: palmar-plantar erythrodysesthesia syndrome, palmoplantar keratoderma, skin discoloration, skin exfoliation and skin fissures.

[22] Rash: dermatitis, dermatitis acneiform, dermatitis contact, dermatitis exfoliative, dermatitis exfoliative generalized, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular and stasis dermatitis.

[23] Xerosis: dry eye, dry skin and xerosis.

[24] Musculoskeletal pain: arthralgia, back pain, pain in extremity, bone pain, musculoskeletal chest pain, myalgia, neck pain, musculoskeletal stiffness, osteoarthritis, musculoskeletal pain, arthritis, sacral pain.

[25] Fatigue: asthenia, fatigue, malaise and muscle fatigue.

[26] Pyrexia: pyrexia and tumor associated fever.

[27] Pain: pain, toothache, pain in jaw, non-cardiac chest pain, pelvic pain, ear pain, flank pain, groin pain, procedural pain, sinus pain, cancer pain, eye pain, gingival pain, puncture site pain, tendon pain, testicular pain, burning feet syndrome, catheter site pain, coccydynia, gastrointestinal pain, lymph node pain, tumour pain, urinary tract pain.

[28] Edema: face edema, fluid retention, gingival swelling, hypervolemia, joint swelling, lip swelling, edema, edema peripheral, periorbital edema, peripheral swelling and swelling.

[29] Injection site reaction: injection site discomfort, injection site erythema, injection site hemorrhage, injection site inflammation, injection site irritation, injection site plaque, injection site pruritus, injection site rash and injection site reaction.

[30] Transaminase elevation: alanine aminotransferase increased and aspartate aminotransferase 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 and corticosteroids were used to treat 39% and 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, including Immune effector cell-associated neurotoxicity syndrome (ICANS)

In MonumenTAL-1 (N=339), neurologic toxicities were reported in 29% of patients receiving TALVEY®. Neurologic toxicity events were Grade 1 (17%), Grade 2 (10%), Grade 3 (2.4%) or Grade 4 (0.3%). The most frequently reported neurologic toxicity event was headache (9%).

In MonumenTAL-1 Phase 2 (N=265), ICANS occurred in 10% (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 (4.2%), disorientation (1.9%), and somnolence (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. 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 was 28 hours from the last dose, 68% of events started within 48 hours from the last dose, and the median duration was 9 hours.

In addition, one fatal ICANS event was reported in MonumenTAL-1.

Serious infections

In MonumenTAL-1 (N=339), Grade 3 or Grade 4 infections occurred in 19% of patients, and fatal infections occurred in 1.5% of patients.

Skin reactions

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

Oral toxicity

In MonumenTAL-1 (N=339), 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.

Overdose

Symptoms and signs

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

Treatment

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX29.

Mechanism of action

Talquetamab (also known as JNJ-64407564) is a humanized immunoglobulin G4 proline, alanine, alanine (IgG4 PAA) bispecific antibody that binds to the CD3 receptor expressed on the surface of T-cells and G protein-coupled receptor class C group 5 member D (GPRC5D) expressed on the surface of multiple myeloma cells and non-malignant plasma cells, as well as healthy tissues such as epithelial cells in keratinized tissues of the skin and tongue.

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.

Immunogenicity

In MonumenTAL-1, 260 patients treated with subcutaneous talquetamab monotherapy at 0.4 mg/kg weekly or 0.8 mg/kg biweekly (every 2 weeks) were evaluated for antibodies to talquetamab. Following treatment of 0.4 mg/kg weekly or 0.8 mg/kg biweekly (every 2 weeks), 64 of 260 patients (24.6%) developed anti-talquetamab antibodies. There was no identified clinically significant effect of anti-talquetamab antibodies on the pharmacokinetics, efficacy, or safety (e.g., CRS, systemic administration-related reaction, and injection site reaction).

Clinical studies

The efficacy of TALVEY® monotherapy was evaluated in patients with relapsed or refractory multiple myeloma in a single-arm, open-label, multicenter study, MMY1001 (MonumenTAL-1). The study included patients who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. The study included patients who received prior T cell redirection therapy (N=51). 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 allogeneic 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, POEMS syndrome, primary light chain amyloidosis, and active or documented history of autoimmune disease, with the exception of vitiligo, resolved childhood atopic dermatitis, 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 hospitalized 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 proteasome inhibitor, 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 overall response rate assessed by an Independent Review Committee using IMWG criteria.

Table 12: Efficacy Results for MMY1001 (MonumenTAL-1) in Patients Receiving 0.4 mg/kg Weekly TALVEY®

	0.4 mg/kg Weekly (N=143)
Overall response rate (ORR=sCR+CR+VGPR+PR)	106 (74.1%)
95% CI (%)	(66.1, 81.1)
Stringent complete response (sCR)	24%
Complete response (CR)	10%
Very good partial response (VGPR)	26%
Partial response (PR)	15%
Duration of Response (DOR)	
Number of responders	106
Median DOR (95% CI) (months)	9.5 (6.7, 13.3)
Patients with DOR ≥ 6 months	67%
Patients with DOR ≥ 12 months	44%
Time to First Response	
Number of responders	106
Median (range) (months)	1.2 (0.2; 10.9)
Progression-Free Survival (PFS)	
Median (95% CI) (months)	7.5 (5.7, 9.4)
6-month PFS rate % (95% CI)	57.9 (49.2, 65.6)
9-month PFS rate % (95% CI)	43.8 (35.3, 51.9)
Overall Survival (OS)	
Median (95% CI) (months)	NE (25.6, NE)
6-month OS rate % (95% CI)	88.5 (81.9, 92.8)
9-month OS rate % (95% CI)	81.0 (73.4, 86.7)

CI=confidence interval; NE=not estimable
Median duration of follow-up = 18.8 months.

Table 13: Efficacy Results for MMY1001 (MonumenTAL-1) in Patients Receiving 0.8 mg/kg Biweekly (Every 2 Weeks) TALVEY®

	0.8 mg/kg Biweekly (Every 2 Weeks) (N=145)
Overall response rate (ORR=sCR+CR+VGPR+PR)	104 (71.7%)
95% CI (%)	(63.7, 78.9)
Stringent complete response (sCR)	30%
Complete response (CR)	9%
Very good partial response (VGPR)	22%
Partial response (PR)	11%
Duration of Response (DOR)	
Number of responders	104
Median DOR (95% CI) (months)	NE (13.0, NE)
Patients with DOR ≥ 6 months	82%
Patients with DOR ≥ 9 months	76%
Time to First Response	
Number of responders	104

Median (range) (months)	1.3 (0.2;9.2)
Progression-Free Survival (PFS)	
Median (95% CI) (months)	14.2 (9.6, NE)
6-month PFS rate % (95% CI)	63.5 (54.9, 70.9)
9-month PFS rate % (95% CI)	58.9 (50.2, 66.6)
Overall Survival	
Median (95% CI) (months)	NE (20.1, NE)
6-month OS rate % (95% CI)	85.2 (78.2, 90.1)
9-month OS rate % (95% CI)	83.0 (75.8, 88.3)

CI=confidence interval; NE=not estimable
Median duration of follow-up = 12.7 months.

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

At approximately week 29, there were 54 patients who completed the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item) for the 0.4 mg/kg weekly group and 60 patients in the 0.8 mg/kg biweekly (every 2 weeks) group. Patients reported improvement from baseline in global health status, increased physical functioning and ability to participate in social roles and activities, decreased fatigue and reductions in pain with 0.4 mg/kg weekly of TALVEY®. With 0.8 mg/kg biweekly of TALVEY®, patients reported improvements in global health status, physical functioning, fatigue and pain and preserved ability to participate in social roles and activities. The results of the patient-reported outcomes should be interpreted with caution considering the open-label, single-arm design of the study.

MMY1001 also included 51 patients who were exposed to prior T cell redirection therapy and who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Patients received TALVEY® 0.4 mg/kg subcutaneously once a week, following 2 step-up doses (0.01 and 0.06 mg/kg), or 0.8 mg/kg Q2W, following 3 step-up doses (0.01, 0.06, and 0.3 mg/kg), until disease progression or unacceptable toxicity. The median age was 61 (range: 38 to 78) years, 61% were male, 92% were White, and 6% were Black or African American. Patients had received a median of 6 (range: 3 to 15) prior therapies. Prior T cell redirection therapy was CAR-T cell therapy for 75% of patients and bispecific antibody treatment for 31%. With a median duration of follow-up of 14.8 months, ORR per IRC assessment was 65%.

Pharmacokinetic Properties

0.4 mg/kg Weekly

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

Pharmacokinetic parameters of talquetamab following the 1st and 7th recommended weekly dose of 0.4 mg/kg are shown in Table 14.

Table 14: Pharmacokinetic Parameters of Talquetamab Following the First and Seventh Recommended 0.4 mg/kg Weekly Dose in Patients with Relapsed or Refractory Multiple Myeloma in MonumenTAL-1

Pharmacokinetic Parameters	1st dose of 0.4 mg/kg	7th dose of 0.4 mg/kg
T_{max} (days)	2.93 (0.98 - 7.75) (n=21)	2.01 (0.94 - 5.97) (n=13)
C_{max} (ng/mL)	1,568 ± 1,185 (n=21)	3,799 ± 2,411 (n=13)
C_{trough} (ng/mL)	178 ± 124 (n=19)	2,548 ± 1,308 (n=13)
AUC_{tau} (ng·h/mL)	178,101 ± 130,802 (n=17)	607,297 ± 371,399 (n=10)

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

0.8 mg/kg Biweekly (Every Two Weeks)

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

Pharmacokinetic parameters of talquetamab following the 1st and 5th recommended biweekly (every 2 weeks) dose of 0.8 mg/kg are shown in Table 15.

Table 15: Pharmacokinetic Parameters of Talquetamab Following the First and Fifth Recommended 0.8 mg/kg Biweekly (Every 2 Weeks) Dose in Patients with Relapsed or Refractory Multiple Myeloma in MonumenTAL-1

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

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

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

Special populations

Pediatrics (17 years of age and younger)

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

Elderly (65 years of age and older)

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

Renal impairment

No formal studies of talquetamab in patients with renal impairment have been conducted.

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

Hepatic impairment

No formal studies of talquetamab in patients with hepatic impairment have been conducted.

Results of population pharmacokinetic analyses indicate that mild hepatic impairment (total bilirubin >1 to 1.5 times upper limit of normal [ULN] and any aspartate aminotransferase [AST], or total bilirubin ≤ULN and AST>ULN) did not significantly influence the pharmacokinetics of talquetamab. Limited data (n=2) are available in patients with moderate hepatic impairment while no data is available in patients with severe hepatic impairment.

NON-CLINICAL INFORMATION

Carcinogenicity and Mutagenicity

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

Reproductive Toxicology

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

Fertility

No studies have been conducted to evaluate the effects of talquetamab on fertility.

PHARMACEUTICAL INFORMATION

List of Excipients

2 mg/mL vial and 40 mg/mL vial

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

Incompatibilities

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

Shelf Life

Unopened vial:

See expiry date on the outer pack.

Prepared syringe:

The prepared syringes should be administered immediately. If immediate administration is not possible, store the TALVEY® solution for up to 24 hours refrigerated at 2°C to 8°C (36°F to 46°F)

followed by up to 24 hours at ambient temperature of 15°C to 30°C (59°F to 86°F). Discard if stored for more than 24 hours refrigerated or more than 24 hours of being at ambient temperature. If stored in the refrigerator, allow the solution to come to ambient temperature before administration.

Storage Conditions

2 mg/mL vial and 40 mg/mL vial

Store refrigerated at 2°C to 8°C.

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

Do not freeze.

Keep out of the sight and reach of children.

Nature and Contents of Container

1.5 mL solution for injection in a Type 1 glass vial with an elastomeric stopper and a flip-off seal containing 3 mg of sterile talquetamab (2 mg/mL). Pack size of 1 vial.

1.0 mL solution for injection in a Type 1 glass vial with an elastomeric stopper and a flip-off seal containing 40 mg of sterile talquetamab (40 mg/mL). Pack size of 1 vial.

Instructions for Use and Handling [and Disposal]

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

LOCAL MARKETING AUTHORIZATION HOLDER

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