3 History of the development of TALVEY™

Summary statement

TALVEY™ is a novel GPRC5D-directed T-cell–redirecting bispecific antibody and is the first approved therapy to target GPRC5D. TALVEY™ has two antigen binding sites: CD3, expressed by all CD8+ and CD4+ T cells, and the novel myeloma target GPRC5D. TALVEY™ induces T-cell–mediated cytotoxicity of myeloma cells via recruitment of CD3-expressing T cells into close proximity with GPRC5D-expressing cells (primarily tumor cells), leading to T-cell activation and subsequent target cell lysis.[75,76]

GPRC5D is an orphan G protein-coupled receptor with no known ligand, signaling mechanism, or function in normal tissues.[77] Outside the immune cell compartment, GPRC5D expression is largely restricted to subsets of cells in epithelial tissues. In cells of the immune system, expression levels are low or nonexistent on normal B cells, T cells, natural killer cells, monocytes, granulocytes, and bone marrow progenitors; however, GPRC5D is highly expressed on myeloma cells and is abundant in the bone marrow from patients with MM to smoldering MM.[77]

US Food and Drug Administration's (FDA) approval of TALVEY™ was based on MonumenTAL-1, a phase 1/2, open-label, multicenter study of TALVEY™ monotherapy in patients with RRMM. Patients in MonumenTAL-1 were heavily pretreated individuals with historically poor outcomes, including a cohort of patients who received prior T-cell–redirecting therapy. MonumenTAL-1 investigated two doses of TALVEY™ (0.4 mg/kg weekly [QW] or 0.8 mg/kg every other week [Q2W]).[78] TALVEY™ demonstrated high ORRs of 74.1% in the QW cohort, 69.5% in the Q2W cohort, and 66.7% in patients with prior exposure to novel T-cell–redirecting therapy.[79] TALVEY™ had a clinically manageable safety profile. Adverse events associated with GPRC5D targeting, such as changes in taste and issues affecting the skin and nails were clinically manageable and did not lead to high rates of treatment discontinuation. TALVEY™ also demonstrated sustained, clinically meaningful improvements in quality of life, including general health, physical and role function, fatigue, and pain symptoms.

3.1 Rationale for the development of TALVEY™

TALVEY™ is a novel GPRC5D-directed T-cell–redirecting bispecific antibody that has demonstrated deep and durable efficacy in patients with heavily pretreated RRMM,[80] and it is the first therapy to be approved that targets GPRC5D.[81,82] Based on research suggesting high expression of GPRC5D in myeloma cells and limited off-target expression elsewhere, TALVEY™ was developed as a bispecific antibody to redirect a patient's T cells to this novel myeloma target.[75] Bispecific antibodies have 2 binding sites and can simultaneously bind to an antigen on a tumor cell and CD3 on CD8+ and CD4+ T cells. In this way, bispecific antibodies engage the patients' own T cells in tumor surveillance and elimination.[75,76,83,84] Off-the-shelf bispecific antibodies have some advantages in availability over CAR-T therapies, which are limited by manufacturing complexity and patient eligibility requirements.[85,86] TALVEY™ was developed as a novel T-cell–redirecting bispecific antibody designed to bind CD3 on T cells and GPRC5D on plasma cells to induce T-cell–mediated killing of GPRC5D-expressing myeloma cells.[75,76,78]

Characterization of TALVEY™ showed that it activated T cells to induce cytotoxicity of GPRC5D-expressing cells using in vitro MM models.[75] The humanized, full-size immunoglobulin G4-based bispecific antibody also showed favorable pharmacokinetics, with sustained effective concentrations over weeks with subcutaneous (SC) dosing.[78] Subsequent phase 1 efficacy data would provide the first validation of GPRC5D as a novel target in MM.[78]

3.1.1 GPRC5D is a novel target in myeloma that is highly expressed in myeloma cells with limited expression in normal tissues

GPRC5D is an orphan G protein-coupled receptor with no recognized ligand, signaling mechanism, or function in normal tissues.[77] Overall, studies show that GPRC5D expression is limited in normal cells.[75,76,87,88] In the immune cell compartment, GPRC5D protein is predominantly expressed in cells with a plasma cell phenotype and, unlike other MM targets, has little to no expression in normal B cells, T cells, natural killer cells, monocytes, granulocytes, and bone marrow progenitors.[75,76,88-90] Outside the immune cell compartment, GPRC5D expression is largely restricted to subsets of cells in epithelial tissues, including hair, skin cells associated with hair follicle-specific keratin, eccrine glands, and filiform papillae on the tongue.[76,87,91,92] In contrast to its limited expression in normal cells, GPRC5D is highly expressed on myeloma cells, and it is abundant in the bone marrow from patients with MM to smoldering MM.[77]

3.1.2 TALVEY™ incorporates the novel GPRC5D target into the class of T-cell–redirecting bispecific antibodies

TALVEY™ is a bispecific antibody with 2 antigen binding sites: (1) CD3, that is expressed by all CD8+ and CD4+ T cells, and (2) the novel myeloma target GPRC5D **(Figure 1)**.[75,76] TALVEY™ induces T-cell–mediated cytotoxicity of myeloma cells via recruitment of CD3-expressing T cells into close proximity with GPRC5D-expressing cells (primarily tumor cells), leading to T-cell activation and subsequent target cell lysis.[75,76] To minimize off-target effects and allow for sustained effective concentrations with SC dosing, the structure of TALVEY™ is designed to be equivalent to a full-size antibody built on a modified immunoglobulin G4 scaffold.[75,76]

The first bispecific antibody, blinatumomab, was a fusion of 2 single-chain variable antibody fragments (scFvs) into a bispecific T-cell engager (BiTE®) that was approved for the treatment of acute lymphoblastic leukemia in 2014.[93] This introduced bispecific antibodies as an effective therapy for cancer treatment.[94] Bispecific antibodies can activate T cells without the requirement of major histocompatibility complex molecules, which are often downregulated in malignant cells, allowing the tumor to escape immune surveillance.[95] However, BiTEs had a short serum half-life due to the lack of an Fc antibody domain, and required portable pumps for continuous infusion.[93] New strategies like CAR-T cell production similarly had delivery issues, requiring time-consuming and costly manufacturing logistics for patients at risk of disease progression during their wait for treatment.[96-98] Full-size bispecific antibodies, such as TALVEY™, have a longer serum half-life than scFv-based BiTEs®, with less potential for nonspecific binding due to modification of the Fc domain, and they are available for same-day administration in patients with severe disease who cannot afford to wait for CAR-T cell production.[64,96,99]

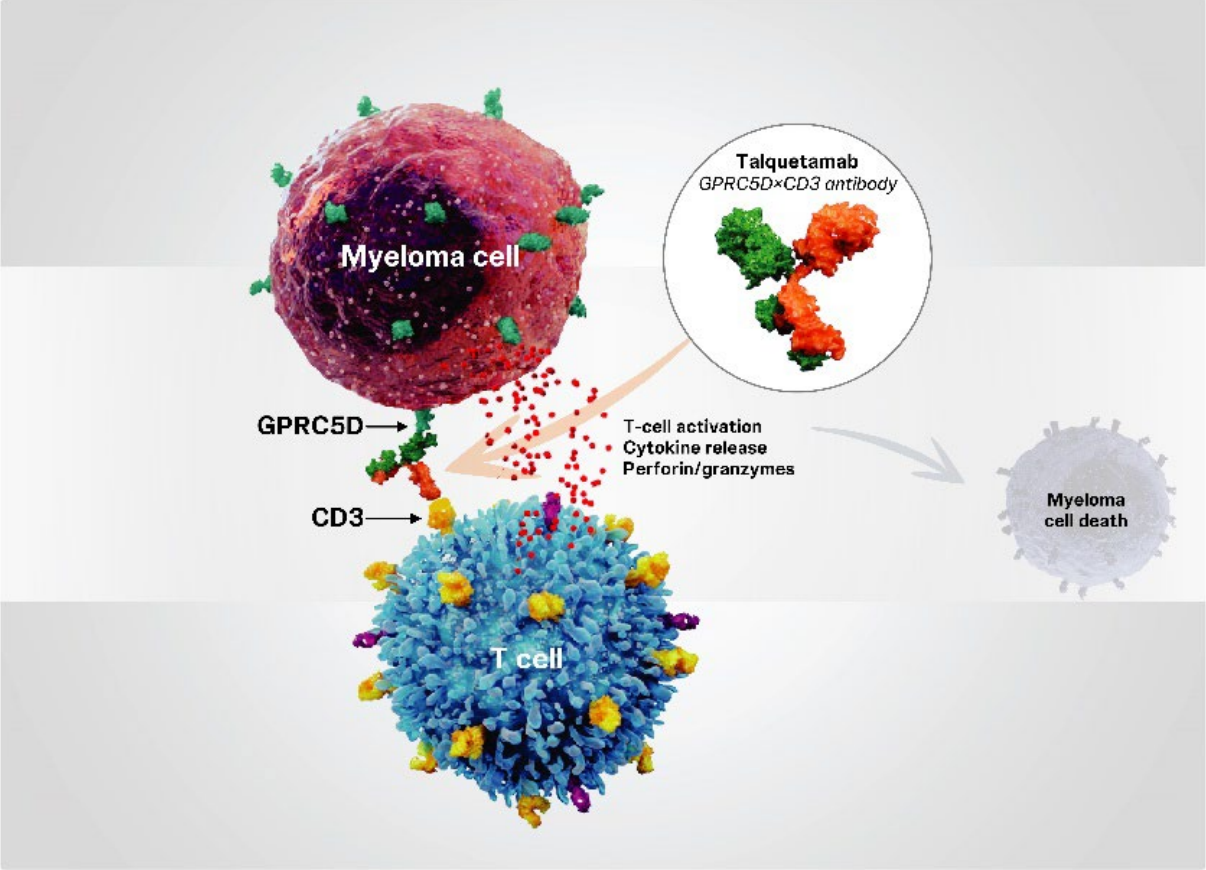

Figure 1. *Method of action of TALVEY™. Binding to the CD3 receptor on T cells and GPRC5D on MM cells causes the release of proinflammatory cytokines and the lysis of MM cells.[81,100] GPRC5D, G protein-coupled receptor class C group 5 member D; MM, multiple myeloma.*

3.2 TALVEY™ clinical development

3.2.1 TALVEY™ registrational trial data

US FDA approval of TALVEY™ was based on MonumenTAL-1, a phase 1/2, open-label, multicenter study of TALVEY™ monotherapy in patients with RRMM who were triple-class exposed (had received a PI, an IMiD, and an anti-CD38 antibody in prior lines of therapy), which showed high ORRs that were durable with a clinically manageable safety profile, including relatively low rates of severe infections.[100,101] Patients in MonumenTAL-1 were heavily-pretreated individuals with historically poor outcomes, including a cohort of patients who received prior T-cell–redirecting therapy (CAR-T or bispecific antibody), which is a recent unmet need as patients relapse on these therapies and become more difficult to treat.[100] The pivotal cohort included 143 patients who received the 0.4 mg/kg SC dose schedule (QW) and 145 patients who received the 0.8 mg/kg SC dose schedule (Q2W).[100] The 51 patients who had prior T-cell–redirecting therapy received either dose schedule.[100] Median number of prior lines of

therapy was 5 or 6 for each cohort, and >69% of patients in each cohort were triple-class refractory (ie, refractory to a PI, IMiD, and anti-CD38 antibody).[100]

High ORRs (74.1%, 69.5%, and 66.7% across the QW, Q2W, and prior T-cell–redirecting therapy cohorts, respectively; **Figure 2**) were durable (median duration of response [DOR]: 9.5 and 16.9 for the QW and Q2W cohort, with 12-month DOR rate 56% in the prior T-cell–redirecting therapy cohort) over 25.6, 19.4, and 16.8 months of follow-up, respectively.[79] Median PFS was 7.5, 11.2, and 7.7 months, respectively, in the registrational data, and in the long-term follow-up the median OS was 34 months, not reached at 3 years, and 28 months, respectively, with 36-month OS rates of 49.3%, 60.8%, and 44.6%, respectively.[79,102] Consistently high ORRs (≥60%) were observed in patients with high-risk characteristics, including International Staging System stage III disease, cytogenetics associated with poor outcomes, ≥4 prior lines of therapy, triple-class refractory status, and exposure to the BCMA-targeted ADC belantamab mafodotin **(Table 1)**.[79,103]

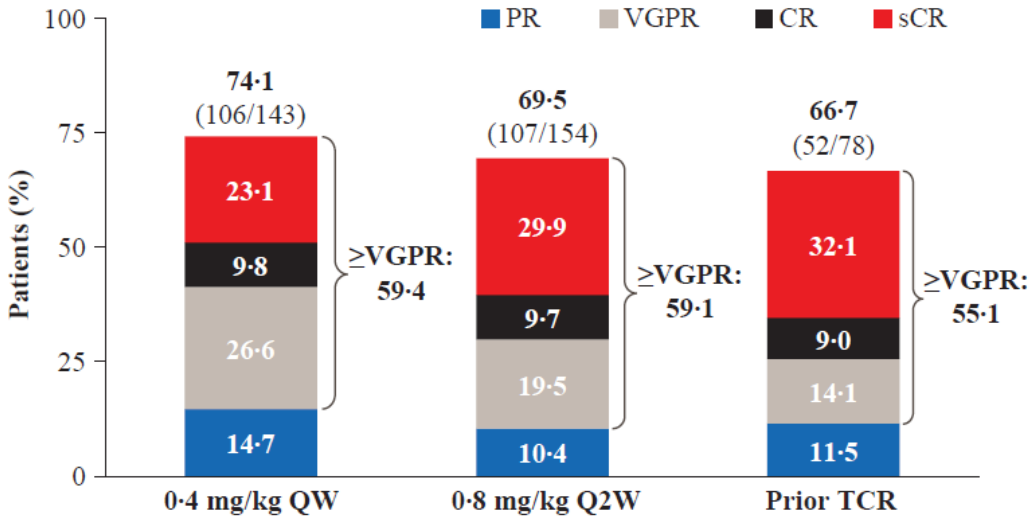

Figure 2. *ORR assessed by independent review committee using International Myeloma Working Group (IMWG) criteria. Due to rounding, individual response rates may not sum to the ORR. CR, complete response; ORR, overall response rate; PR, partial response; Q2W, every 2 weeks; QW, weekly; SC, subcutaneous; sCR, stringent complete response; TCR, T-cell–redirecting; VGPR, very good partial response.*

ORR in subgroups, % (95% CI)	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)
High-risk cytogenetics,[a]	70.7 (54.5–83.9)	75.0 (58.8–87.3)
ISS stage		
I	82.3 (70.5–90.8)	76.5 (64.6–85.9)
II	69.8 (55.7–81.7)	66.7 (51.6–79.6)
III	64.3 (44.1–81.4)	59.5 (42.1–76.1)
Prior lines of therapy ≥4	71.8 (62.7–79.7)	69.0 (59.6–75.2)
Prior ADC	68.2 (45.1–86.1)	64.7 (38.3–85.8)
Refractory status		
Triple-class	72.9 (63.4–81.0)	67.3 (57.7–75.9)
Penta-drug	71.1 (55.7–83.6)	69.2 (52.4–83.0)
To last line of therapy	73.9 (65.6–81.1)	69.0 (60.8–76.4)
Extramedullary plasmacytomas		
0	81.8 (73.3–88.5)	79.6 (71.0–86.6)
≥1	48.5 (30.8–66.5)	41.5 (26.3–57.9)

Table 1. *ORR in select high-risk subgroups.*[79] *ISS, International Staging System; ORR, overall response rate; Q2W, every 2 weeks; QW, weekly.*

TALVEY™ demonstrated a distinct and clinically manageable safety profile.[80] Cytokine release syndrome (CRS), a known adverse event (AE) with CD3-targeting bispecific antibodies, occurred in 79.0%, 74.5%, and 76.5% of patients in the QW cohort, Q2W cohort, and the prior T-cell–redirecting therapy cohort, respectively, and were mostly grade 1/2.[100] Immune effector cell–associated neurotoxicity syndrome occurred in 10.7%, 11.0%, and 2.9% of patients, respectively.[100] Anemia occurred in 45–49% of patients across all cohorts, neutropenia in >28% and thrombocytopenia in >27%.[100] All-grade infections occurred in 58.7%, 66.2%, and 72.5% of patients, respectively. Relatively low rates of severe (grade 3/4) infections were observed across cohorts including in patients with prior T-cell–redirecting therapy (19.6%, 14.5%, and 27.5% of patients, respectively). This is distinct from BCMA-targeting bispecific antibodies, which induce persistent depletion of the normal B cells and plasma cells that underlie the adaptive immune response, resulting in an increased risk of serious infection.[37,90,100,104] Rates of opportunistic infections were also relatively low (<6%) with talquetamab, with fewer than 2.0% leading to discontinuation.[100]

Several of the more common AEs observed with TALVEY™ may be related to the novel GPRC5D target, including dysgeusia (72.0%, 71.0%, 76.5%), skin-related AEs (55.9%, 73.1%, 68.6%), nail-related AEs (54.5%, 53.8%, 62.7%), rash-related AEs (39.9%, 29.7%, 35.3%), and dry mouth (26.6%, 40.0%, 51.0%).[100] However only 5 patients discontinued treatment due to

skin-related AEs or dysgeusia.[100] The low rates of treatment discontinuation suggest these AEs were clinically manageable. An ongoing phase 2 study, TALISMAN (NCT06500884), aims to better understand the oral-related AEs and investigate prophylactic interventions for oral AEs using objective and subjective assessment tools.[105]

Patients receiving TALVEY™ reported sustained, clinically meaningful improvements in health-related quality of life that were consistent with the clinical outcomes in MonumenTAL-1.[106] Following an initial decline, potentially related to disease factors, symptoms of treatment initiation, and/or the onset of AEs in early treatment, improvements over baseline were reported for general health status (GHS), physical function, and role function after 2–3 months, as assessed by the EORTC QLQ-C30.[106] Patient-reported fatigue and pain symptoms also improved **(Figure 3)**.[106]

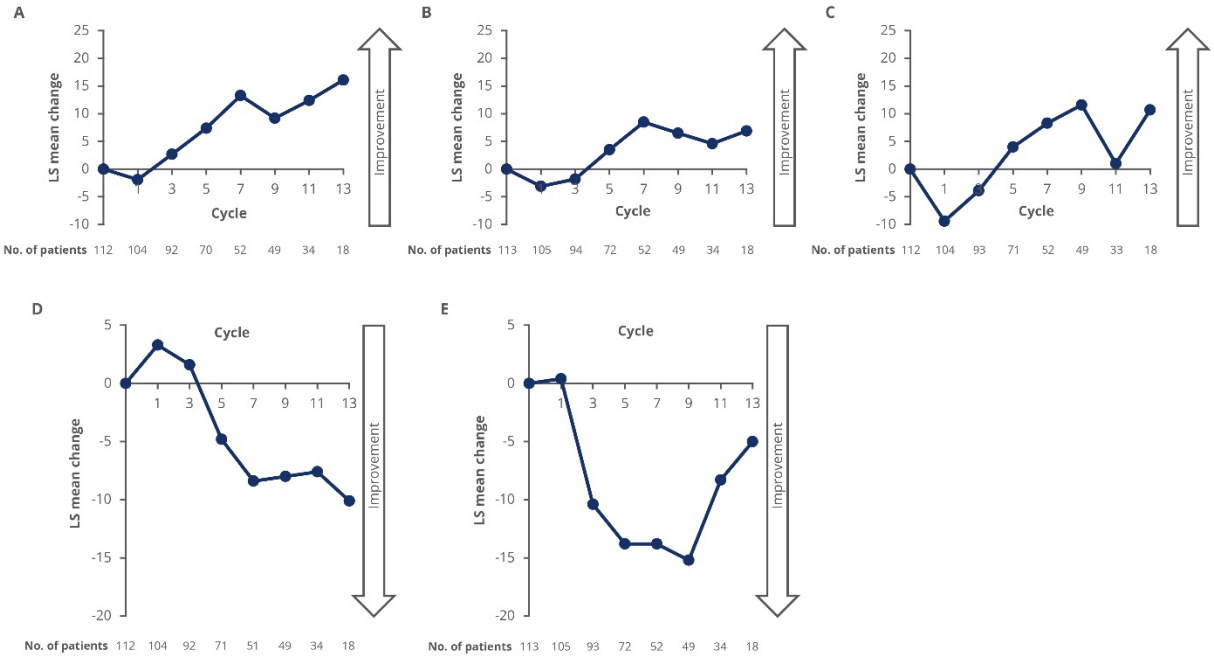

Figure 3. *Quality of life improvements with TALVEY™ assessed by LS mean change from baseline in (A) GHS, (B) physical functioning, (C) role functioning, (D) fatigue, and (E) pain.[106] GHS, Global Health Status; LS, least squares.*