

METHODS FOR TREATING MULTIPLE MYELOMA

SEQUENCE LISTING

5 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 3, 2021, is named "Sequence Listing 065768_89US4txt" and is 26.8 kilobytes in size.

FIELD OF THE INVENTION

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Methods of treating a hematological malignancy, particularly relapsed or refractory multiple myeloma, using a GPRC5DxCD3 bispecific antibody are disclosed.

BACKGROUND OF THE INVENTION

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G-protein coupled receptor, class C, group 5, member D (GPRC5D) is an orphan, atypical, class C GPCR first identified in 2001 (Bräuner-Osborne *et al.*, *Biochim Biophys Acta.*, 1518(3):237-248, 2001). GPRC5D and other group 5 GPCRs have unusually short amino-terminal domains for class C receptors, and are therefore, predicted to be conformationally similar to class A receptors. In this regard they are unique, with

20 sequence homology to class C GPCRs and predicted structural topology comparable to class A receptors. Functional consequence of GPRC5D activation has not been described and the ligand remains unknown. The gene has three exons and is located on chromosome 12p13.3 in humans. GPRC5D receptor is highly conserved among various species and shares 92% identity with cynomolgus monkey GPRC5D.

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GPRC5D mRNA is predominantly expressed in all malignant plasma cells from MM patients (Atamaniuk J A *et al.*, *Eur J Clin Invest*, 42(9) 953-960; 2012; Frigyesi-blood and Cohen, *et al.*, *Hematology* 18(6): 348-35; 2013). GPRC5D expression is variable among the patients and correlates well with plasma cell burden and genetic aberrations such as Rb-1 deletion (Atamaniuk J A *et al.*, *Eur J Clin Invest*, 42(9) 953-

30 960; 2012).

Multiple myeloma (MM) is the second most common hematological malignancy and constitutes 2% of all cancer deaths. MM is a heterogeneous disease and caused mostly by chromosome translocations inter alia t(11;14),t(4; 14),t(8;14),del(13),del(17) (Drach *et al.*, *Blood*. 1998;92(3):802-809, Gertz *et al.*, *Blood*. 2005;106(8):2837-2840;

Facon *et al.*, Blood. 2001;97(6): 1566-1571). MM-affected patients can experience a variety of disease-related symptoms due to, bone marrow infiltration, bone destruction, renal failure, immunodeficiency, and the psychosocial burden of a cancer diagnosis.

Based on people diagnosed with MM between 2009 and 2015, the 5-year relative survival rate for MM was approximately 51%. This highlights that MM is a difficult-to-treat disease where there are currently insufficient curative options.

Relapsed and refractory MM constitutes a specific unmet medical need. Patients with relapsed and refractory disease are defined as those who achieve minor response or better then progress while on therapy or who experience progression within 60 days of their last therapy. Patients who progress after receiving both an immunomodulatory drug and proteasome inhibitor have limited options. Heavily pretreated patients often present with a compromised immune system, which can result in other disease conditions such as opportunistic infections and toxicities (e.g., myelosuppression, peripheral neuropathy, deep vein thrombosis) that persist from prior treatment. Furthermore, patients with advanced MM are often elderly and are susceptible to serious treatment-emergent adverse events (TEAEs) with continued exposure to these therapies. After standard available therapies (such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies) have been exhausted, there is no standard therapy. Selinexor, BLENREP (belantamab mafodotin-blmf), recently approved Melfufen (melphalan flufenamide) administered in combination with dexamethasone, as well as recently approved Ide-cel (idecabtagene vicleucel, formerly termed bb2121) are licensed in the United States for this highly refractory disease setting. The remaining options for these patients are either entry into a clinical trial, or they can be offered retreatment with a prior treatment regimen (if the toxicity profile for retreatment permits). But often, if no other treatment options remain, they are provided with palliative care to ameliorate disease-related symptoms only. In elderly population, for whom stem cell transplantation is often not a viable option, and in patients with refractory disease who have exhausted all available therapies, the median overall survival is only 8 to 9 months (Kumar *et al.*, *Leukemia*, 2012, 26:149-157; Usmani *et al.*, *Oncologist*, 2016, 21:1355-1361). For patients with disease that is refractory to commonly administered proteasome inhibitors and immunomodulatory drugs, the medium overall survival decreases to only 5 months (Usmani *et al.*, 2016).

Thus, there remains an unmet medical need to develop treatment options for MM patients, particularly those who are relapsed or refractory to treatment with a prior anti-cancer therapeutic.

5 SUMMARY OF THE INVENTION

In one general aspect, provided herein is a method of treating a hematological malignancy, such as multiple myeloma, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof, wherein the subject is relapsed
10 or refractory to treatment with a prior anti-cancer therapy.

In one embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof comprises a GPRC5D binding domain comprising the HCDR1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, the HCDR3 of SEQ ID NO: 6, the LCDR1 of SEQ ID NO: 7, the LCDR2 of SEQ ID NO: 8 and the
15 LCDR3 of SEQ ID NO: 9, and a CD3 binding domain comprising the HCDR1 of SEQ ID NO: 14, the HCDR2 of SEQ ID NO: 15, the HCDR3 of SEQ ID NO: 16, the LCDR1 of SEQ ID NO: 17, the LCDR2 of SEQ ID NO: 18 and the LCDR3 of SEQ ID NO: 19.

In a further embodiment of a method of the application, the GPRC5D binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of
20 SEQ ID NO: 10 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 11, and the CD3 binding domain comprises a VH having the amino acid sequence of SEQ ID NO: 20 and a VL having the amino acid sequence of SEQ ID NO: 21.

In a yet further embodiment of a method of the application, the GPRC5DxCD3
25 bispecific antibody is of IgG4 isotype and comprises phenylalanine at position 405 and arginine at position 409 in a first heavy chain (HC1) and leucine at position 405 and lysine at position 409 in a second heavy chain (HC2).

In a yet further embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody further comprises proline at position 228, alanine at position 234 and
30 alanine at position 235 in both the HC1 and the HC2.

In a yet further embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody comprises the HC1 having the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having the amino acid sequence of SEQ ID NO: 13, the HC2

having the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having the amino acid sequence of SEQ ID NO: 23.

In a yet further embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody is talquetamab.

5 In a yet further embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody is administered intravenously or subcutaneously at a dose of about 0.2 µg/kg to about 1200 µg/kg.

In a yet further embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody is administered intravenously at a dose of about 0.2 µg/kg to about
10 500 µg/kg, preferably about 1 µg/kg to about 300 µg/kg, most preferably about 10 µg/kg to about 200 µg/kg, such as about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200 µg/kg, or any value in between. The dose can be administered monthly, tri-weekly (i.e., one dose every three weeks), bi-weekly (i.e., one dose every other week), weekly, twice weekly (i.e., two doses every week).

15 In a yet further embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody is administered subcutaneously at a dose of about 0.5 µg/kg to about 2400 µg/kg, about 0.5 µg/kg to about 1200 µg/kg, or about 1 µg/kg to about 100 µg/kg, or about 10 µg/kg to about 800 µg/kg, such as about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 135, 150, 200, 250, 300, 350, 400, 405, 450, 500, 550, 600, 650, 700, 750, 800, 900,
20 950, 1000, 1050, 1100, 1150, 1200 µg/kg, or any value in between. The dose can be administered monthly, tri-weekly, bi-weekly, weekly, or twice weekly. In certain embodiments, the GPRC5DxCD3 bispecific antibody is administered subcutaneously at a dose of about 10 µg/kg to about 1000 µg/kg weekly, such as 1 at a dose of about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 135, 150, 200, 250, 300, 350, 400, 405, 450, 500, 550,
25 600, 650, 700, 750, 800, 900, 950, 1000 µg/kg weekly. In certain other embodiments, the GPRC5DxCD3 bispecific antibody is administered subcutaneously at a dose of about 100 µg/kg to about 2400 µg/kg biweekly, such as 1 at a dose of about 100, 135, 150, 200, 250, 300, 350, 400, 405, 450, 500, 550, 600, 650, 700, 750, 800, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300 or 2400 µg/kg,
30 or any dose in between biweekly.

In a yet further embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody is administered for a time sufficient to achieve complete response, stringent complete response, very good partial response, partial response, minimal

response or stable disease status, and can be continued until disease progression or lack of patient benefit.

In a yet further embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody is administered to achieve negative minimal residual disease (MRD) status, preferably negative MRD status defined as fewer than one tumor cell in 10^6 bone marrow cells, as determined by next generation sequencing (NGS), or an overall response rate of at least 20%, such as at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or any value in between.

In a yet further embodiment of a method of the application, the GPRC5DxCD3 bispecific antibody is administered to a subject in need thereof to result in an exposure of GPRC5DxCD3 bispecific antibody at a steady state mean C_{max} of 10 to 25,000 ng/ml, such as 100 to 20,000 ng/ml or 1000-10,000 ng/ml, and a steady state mean AUC_{0-14d} of 1000 to 1,500,000 ng h/ml, such as 5000 to 1,000,000 ng h/ml or 10,000 to 1,000,000 ng h/mL.

In a yet further embodiment of a method of the application, the prior anti-cancer therapy is selected from the group consisting of thalidomide, lenalidomide, pomalidomide, bortezomib, ixazomib, carfilzomib, panobinostat, pamidronate, zoledronic acid, daratumumab, elotuzumab, melphalan, selinexor, belantamab mafodotin-blmf, Venetoclax, CC-92480 (CELMoD (cereblon E3 ligase modulator) agent), CAR-T therapies, other BCMA-directed therapies, other CD38-directed therapies, and combinations of two or more thereof. In some embodiment, the subject is relapsed or refractory to treatment with more than one prior anti-cancer therapies. For example, the subject can be relapsed or refractory to 2-20 prior anti-cancer therapies, such as at least two, three, four, five, six, seven, eight, nine, ten or more prior anti-cancer therapies.

In a yet further embodiment of a method of the application, the subject is a human. In certain embodiments, the subject has relapsed or refractory multiple myeloma or is intolerant to standard therapies. The subject can be previously treated with a B-cell maturation antigen (BCMA)-directed therapy. In a yet further embodiment of a method of the application, the method further comprises administering to the subject one or more additional anti-cancer therapies.

In a yet further embodiment of a method of the application, the one or more additional anti-cancer therapies are selected from the group consisting of autologous stem cell transplants (ASCT), radiation, surgery, chemotherapeutic agents, CAR-T

therapies, cellular therapies, immunomodulatory agents, targeted cancer therapies, and combinations of two or more thereof.

In a yet further embodiment of any of the methods above, the one or more additional anti-cancer therapies are selected from the group consisting of selinexor,
 5 belantamab mafodotin-blmf, isatuximab, venetoclax, lenalidomide, thalidomide, pomalidomide, bortezomib, carfilzomib, elotuzumab, ixazomib, melphalan, dexamethasone, vincristine, cyclophosphamide, hydroxydaunorubicin, prednisone, rituximab, imatinib, dasatinib, nilotinib, bosutinib, ponatinib, bafetinib, saracatinib, tozasertib, danusertib, cytarabine, daunorubicin, idarubicin, mitoxantrone, hydroxyurea,
 10 decitabine, cladribine, fludarabine, topotecan, etoposide 6-thioguanine, corticosteroid, methotrexate, 6-mercaptopurine, azacitidine, arsenic trioxide and all-trans retinoic acid, and combinations of two or more thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

15 The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings. It should be understood that the invention is not limited to the precise embodiments shown in the drawings.

Figure 1A shows a schematic example of potential escalation steps.

20 **Figure 1B** shows the study design of a phase 1 study with 184 patients in total, which includes an escalation study with weekly (QW) subcutaneous administration (SC) of 5-800 µg/kg of talquetamab, or with intravenous administration (IV) of 0.3 – 180 µg/kg of talquetamab, with or without step-up dosing, wherein the step-up dosing contained 1-3 step-up doses administered to the patients within 1 week before a full dose, e.g., the SC
 25 of 405 µg/kg talquetamab was administered with step-up doses of 10 and 60 µg/kg within 1 week before the administration of the full dose.

Figure 2A is a graph showing mean PK profile following first treatment with IV dose of 60 µg/kg (n = 5) and SC dose of 405 µg/kg (n = 8), and **Figure 2B** is a graph showing mean PK profile following first SC dose of 405 µg/kg with increased number of patients
 30 tested (n = 18), wherein, EC₉₀ values were from *ex vivo* cytotoxicity assay using bone marrow mononuclear cells from patients with multiple myeloma (n=6) (EC₉₀, concentration of talquetamab at 90% of maximum effect; max, maximum; min, minimum).

Figure 3A is a graph showing induction of interleukin-2 receptor subunit alpha (IL2R α) with SC dosing with the cut-off date for the analysis of 24 Oct 2020, and **Figure 3B** is a graph showing induction of programmed cell death protein 1 (PD-1)+ T cells with SC dosing with the cut-off date for the analysis of April 18, 2021.

- 5 **Figure 4** is a bar chart showing the overall response rate for SC doses, (CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response).

Figure 5A is a graph showing duration of response for IV doses with the cut-off date for the analysis of 24 Oct 2020, **Figure 5B** is a graph showing duration of response for SC
 10 doses ranging from 45 to 800 μ g/kg with the cut-off date for the analysis of April 18, 2021, **Figure 5C** is a graph showing duration of response for SC at 405 μ g/kg weekly, and **Figure 5D** is a graph showing duration of response for SC at 800 μ g/kg biweekly (MR=minimal response; SD=stable disease; PD=progressive disease).

Figures 6A and 6B are graphs showing GPRC5D cell surface expression profile.

- 15 Abbreviations: HD, healthy donor; NDMM, newly diagnosed MM; RRMM, relapsed/refractory MM; DARA-R MM, daratumumab-refractory MM. Bone marrow mononuclear cells (BM-MNCs) were analyzed using flow cytometry (HD n=11, MM n=74, *P < 0.05; ***P < 0.001; ****P < 0.0001; ns = not significant).

Figure 7 is a graph showing talquetamab-mediated MM cell lysis. Incubation of HD
 20 peripheral blood MNCs + luciferase-transduced cell line (ratio 10:1) with serial dilutions of talquetamab, Bioluminescence Imaging read out after 48 hours.

Figure 8 is a graph showing lysis of primary MM cells. Incubation of freshly isolated BM-MNCs with serial dilutions of talquetamab or control antibodies, FACS read out after 48 hours (EC₅₀= concentration of talquetamab at 50% of maximum effect).

- 25 **Figures 9A-9D** are graphs showing impacts of pre-treatment and cytogenetic abnormalities on talquetamab-mediated lysis. Incubation of freshly isolated BM-MNCs with serial dilutions of talquetamab (n=45), FACS read out after 48 hours. RRMM: prior lines =3, 88% lenalidomide-refractory, 24% bortezomib-refractory. DARA-R MM: prior lines =6, 100% lenalidomide-refractory, 60% bortezomib-refractory, 100%
 30 daratumumab-refractory. Standard risk cytogenetics n=28, high risk n=10.

Figures 10A-10C are graphs showing impact of tumor and immune characteristics by talquetamab. Samples were divided in groups based on the median group-value of the indicated variable.

Figures 11A-11D are graphs showing impact of Treg on talquetamab efficacy. (A) Tregs and CD4+CD25- effector T-cells were isolated from healthy donor-derived buffy coats using an immune-magnetic cell isolation kit, and baseline immune cell frequencies and purity of isolated fractions were determined by flow cytometry, representative density plots are depicted; (B) Violet tracer labeled T-cells were incubated with or without Tregs for 5 days in the presence of anti-CD3/CD28 beads, proliferation was read out using flow cytometry (n=3). (C) Luciferase transduced RPMI-8226 cell line was incubated for 48 hours with 4 µg/mL of talquetamab in different conditions (n=3). (D) Cytokines and granzyme B were measured in supernatants using flow cytometry and ELISA, respectively (*P < 0.05; **P < 0.01, ***P < 0.001; ****P < 0.0001).

Figures 12A and 12B are graphs showing the impact of bone marrow stromal cells (BMSC) on talquetamab efficacy. (A) Luciferase-transduced MM cell lines were incubated with patient derived stromal cells (ratio 1:2) + HD PBMCs (PBMC:MM ratio 10:1) and serial dilutions of talquetamab for 48 hours. (B) Stromal cells were placed directly in the well containing MM cells and PBMCs (direct) or in a transwell insert (indirect).

Figures 13A-13C are graphs showing that patient-specific factors can determine response to T-cell redirectors targeting different agents. Single agent activity of both talquetamab and the BCMA-targeting bispecific antibody teclistamab (only differing in tumor-binding domain) was determined in 41 MM-patient derived BM samples (*P < 0.05; **P < 0.01, ns = not significant).

Figure 14 is a graph showing the maximum Cytokine Release Syndrome (CRS) Grade in patients treated with weekly (QW) subcutaneous (SC) administration of talquetamab during the study. RP2D stands for recommended Phase 2 dose, which was administered at 405 µg/kg, with step-up doses of 10 and 60 µg/kg; CRS was graded according to Lee et al. *Blood*. 2014.124:188.

DETAILED DESCRIPTION OF THE INVENTION

The disclosed methods can be understood more readily by reference to the following detailed description taken in connection with the accompanying figures, which form a part of this disclosure. It is to be understood that the disclosed methods are not limited to the specific methods described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed methods. All patents, published

patent applications and publications cited herein are incorporated by reference as if set forth fully herein.

As used herein, the singular forms “a,” “an,” and “the” include the plural.

Various terms relating to aspects of the description are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

The term “about” as used herein refers to numerical ranges, cutoffs, or specific values means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. Unless explicitly stated otherwise within the Examples or elsewhere in the Specification in the context of an assay, result or embodiment, “about” means within one standard deviation per the practice in the art, or a range of up to 5%, whichever is larger.

The term “antibodies” as used herein is meant in a broad sense and includes immunoglobulin molecules including monoclonal antibodies including murine, human, humanized and chimeric monoclonal antibodies, antigen binding fragments, multispecific antibodies, such as bispecific, trispecific, tetraspecific etc., dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the immunoglobulin molecule that comprises an antigen binding site of the required specificity. “Full length antibodies” are comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds as well as multimers thereof (e.g. IgM). Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region (comprised of domains CH1, hinge, CH2 and CH3). Each light chain is comprised of a light chain variable region (VL) and a light chain constant region (CL). The VH and the VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-to-carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. Immunoglobulins can be assigned to five major classes, IgA, IgD, IgE, IgG and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4. Antibody light chains of any vertebrate species

can be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

The terms “antigen binding fragment” or “antigen binding domain” as used herein refer to a portion of an immunoglobulin molecule that binds an antigen. Antigen binding fragments can be synthetic, enzymatically obtainable or genetically engineered polypeptides and include the VH, the VL, the VH and the VL, Fab, F(ab')₂, Fd and Fv fragments, domain antibodies (dAb) consisting of one VH domain or one VL domain, shark variable IgNAR domains, camelized VH domains, minimal recognition units consisting of the amino acid residues that mimic the CDRs of an antibody, such as FR3-CDR3-FR4 portions, the HCDR1, the HCDR2 and/or the HCDR3 and the LCDR1, the LCDR2 and/or the LCDR3. VH and VL domains can be linked together via a synthetic linker to form various types of single chain antibody designs where the VH/VL domains can pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chain antibody constructs, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody; described for example in Int. Patent Publ. Nos. WO1998/44001; WO1988/01649; WO1994/13804; and WO1992/01047.

The term “bispecific” as used herein refers to an antibody that specifically binds two distinct antigens or two distinct epitopes within the same antigen. The bispecific antibody can have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca cynomolgus* (cynomolgus, cyno) or *Pan troglodytes*, or can bind an epitope that is shared between two or more distinct antigens.

Specifically binds” or “binds specifically” or derivatives thereof when used in the context of antibodies, or antibody fragments, represents binding via domains encoded by immunoglobulin genes or fragments of immunoglobulin genes to one or more epitopes of a protein of interest, without preferentially binding other molecules in a sample containing a mixed population of molecules. Typically, an antibody binds to a cognate antigen with a K_d of less than about 1×10^{-6} M, as measured by a surface plasmon resonance assay or a cell-binding assay. Phrases such as “[antigen]-specific” antibody (e.g., GPRC5D-specific antibody) are meant to convey that the recited antibody specifically binds the recited antigen.

The term “CH3 region” or “CH3 domain” as used herein refers to the CH3 region of an immunoglobulin. The CH3 region of human IgG1 antibody corresponds to amino

acid residues 341-446. However, the CH3 region can also be any of the other antibody isotypes as described herein.

As used herein, a “GPRC5D×CD3 antibody” is a multispecific antibody, optionally a bispecific antibody, which comprises two different antigen-binding regions, one of which binds specifically to the antigen GPRC5D and one of which binds specifically to CD3. A multispecific antibody can be a bispecific antibody, diabody, or similar molecule (see for instance PNAS USA 90(14), 6444-8 (1993) for a description of diabodies). The bispecific antibodies, diabodies, and the like, provided herein can bind any suitable target in addition to a portion of GPRC5D. The term “bispecific antibody” is to be understood as an antibody having two different antigen-binding regions defined by different antibody sequences. This can be understood as different target binding but includes as well binding to different epitopes in one target.

As used herein, the terms “G-protein coupled receptor family C group 5 member D” and “GPRC5D” specifically include the human GPRC5D protein, for example as described in SEQ ID NO: 1 or GenBank Accession No. BC069341, NCBI Reference Sequence: NP_061124.1 and UniProtKB/Swiss-Prot Accession No. Q9NZD1 (see also Brauner-Osborne, H. et al. 2001, Biochim. Biophys. Acta 1518, 237-248).

SEQ ID NO: 1

MYKDCIESTGDYFLLCDAEGPWGHIIESLAILGIVVTILLLLAFLFLMRKIQDCSQ
 WNVLPQTLLFLLSVLGLFGLAFAFIIELNQQTAPVRYFLFGVLFALCFSCLLAHAS
 NLVKLVRGCVSFSWTTILCIAIGCSLLQIIIATEYVTLIMTRGMMFVNMTPCQLNV
 DFVVLLVYVLFMLALTFFVSKATFCGPCENWKQHGRILFITVLFSIIWVWISML
 LRGNPQFQRQPQWDDPVVCIALVTNAWVFLLLYIVPELCILYRSCRQECPLQGN
 ACPVTAYQHSFQVENQELSRARDSGDGAEDVALTSYGTPIQPQTVDPTQECFIPQ
 AKLSPQQDAGGV

The term “CD3” refers to the human CD3 protein multi-subunit complex. The CD3 protein multi-subunit complex is composed to 6 distinctive polypeptide chains. These include a CD3γ chain (SwissProt P09693), a CD3δ chain (SwissProt P04234), two CD3ε chains (SwissProt P07766), and one CD3 ζ chain homodimer (SwissProt 20963), and which is associated with the T cell receptor α and β chain. The term “CD3” includes any CD3 variant, isoform and species homolog which is naturally expressed by cells (including T cells) or can be expressed on cells transfected with genes or cDNA encoding those polypeptides, unless noted. For example, human CD3 epsilon can

comprise the amino acid sequence of SEQ ID NO: 2. SEQ ID NO: 3 shows the extracellular domain of a human CD3 epsilon.

SEQ ID NO: 2

MQSGTHWRVLGLCLLSVGWVGQDGNEEMGGITQTPYKVSISGTTVILTCPQYP
 5 GSEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSGYYVCYPRGSKPED
 ANFYLYLRARVCENCMEMDVMSVATIVIVDICTGGLLLLVEYYWSKNRKAKAK
 PVTRGAGAGGRQGRGQNKERPPVPNPDIPIRKQGRDLYSGLNQRR

SEQ ID NO: 3

DGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGS
 10 DEDHLSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVCENCMEMD

The term “cancer” as used herein refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and can also metastasize to distant parts of the body through the lymphatic system
 15 or bloodstream. A “cancer” or “cancer tissue” can include a tumor.

The term “combination” as used herein means that two or more therapeutics are administered to a subject together in a mixture, concurrently as single agents or sequentially as single agents in any order.

The term “complementarity determining regions” (CDR) as used herein refers to
 20 antibody regions that bind an antigen. CDRs can be defined using various delineations such as Kabat (Wu *et al. J Exp Med* 132: 211-50, 1970) (Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991), Chothia (Chothia *et al. J Mol Biol* 196: 901-17, 1987), IMGT (Lefranc *et al. Dev Comp Immunol* 27: 55-77, 2003) and AbM (Martin and
 25 Thornton *J Biol Biol* 263: 800-15, 1996). The correspondence between the various delineations and variable region numbering are described in, e.g., Lefranc *et al. Dev Comp Immunol* 27: 55-77, 2003; Honegger and Pluckthun, *J Mol Biol* 309:657-70, 2001; International ImMunoGeneTics (IMGT) database; and Web resources:
<http://www.imgt.org>. Available programs such as abYsis by UCL Business PLC can be
 30 used to delineate CDRs. The term “CDR”, “HCDR1”, “HCDR2”, “HCDR3”, “LCDR1”, “LCDR2” and “LCDR3” as used herein includes CDRs defined by any of the methods described supra, Kabat, Chothia, IMGT or AbM, unless otherwise explicitly stated in the specification.

The term “comprising” as used herein is intended to include examples encompassed by the terms “consisting essentially of” and “consisting of”; similarly, the term “consisting essentially of” as used herein is intended to include examples encompassed by the term “consisting of.” Unless the context clearly requires otherwise, throughout the description and the claims, the terms “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

The term “enhance” or “enhanced” as used herein refers to enhancement in one or more functions of a test molecule when compared to a control molecule or a combination of test molecules when compared to one or more control molecules. Exemplary functions that can be measured are tumor cell killing, T cell activation, relative or absolute T cell number, Fc-mediated effector function (e.g. ADCC, CDC and/or ADCP) or binding to an Fc γ receptor (Fc γ R) or FcRn. “Enhanced” can be an enhancement of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% or more, or a statistically significant enhancement.

The term “Fc gamma receptor” (Fc γ R) as used herein refers to well-known Fc γ RI, Fc γ RIIa, Fc γ RIIb or Fc γ RIII. Activating Fc γ R includes Fc γ RI, Fc γ RIIa and Fc γ RIII.

The term “human antibody” as used herein refers to an antibody that is optimized to have minimal immune response when administered to a human subject. Variable regions of human antibody are derived from human immunoglobulin sequences. If human antibody contains a constant region or a portion of the constant region, the constant region is also derived from human immunoglobulin sequences. Human antibody comprises heavy and light chain variable regions that are “derived from” sequences of human origin if the variable regions of the human antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Such exemplary systems are human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice or rats carrying human immunoglobulin loci. “Human antibody” typically contains amino acid differences when compared to the immunoglobulins expressed in humans due to differences between the systems used to obtain the human antibody and human immunoglobulin loci, introduction of somatic mutations or intentional introduction of substitutions into the frameworks or CDRs, or both. Typically, “human antibody” is at least about 80%, 81%,

82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical in amino acid sequence to an amino acid sequence encoded by human germline immunoglobulin or rearranged immunoglobulin genes. In some cases, “human antibody” can contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik et al., (2000) *J Mol Biol* 296:57-86, or synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example as described in Shi et al., (2010) *J Mol Biol* 397:385-96, and in Int. Patent Publ. No. WO2009/085462. Antibodies in which at least one CDR is derived from a non-human species are not included in the definition of “human antibody”.

The term “humanized antibody” as used herein refers to an antibody in which at least one CDR is derived from non-human species and at least one framework is derived from human immunoglobulin sequences. Humanized antibody can include substitutions in the frameworks so that the frameworks cannot be exact copies of expressed human immunoglobulin or human immunoglobulin germline gene sequences.

The term “isolated” as used herein refers to a homogenous population of molecules (such as synthetic polynucleotides or a protein such as an antibody) which have been substantially separated and/or purified away from other components of the system the molecules are produced in, such as a recombinant cell, as well as a protein that has been subjected to at least one purification or isolation step. The term “isolated antibody” as used herein refers to an antibody that is substantially free of other cellular material and/or chemicals and encompasses antibodies that are isolated to a higher purity, such as to 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% purity.

The term “monoclonal antibody” as used herein refers to an antibody obtained from a substantially homogenous population of antibody molecules, i.e., the individual antibodies comprising the population are identical except for possible well-known alterations such as removal of C-terminal lysine from the antibody heavy chain or post-translational modifications such as amino acid isomerization or deamidation, methionine oxidation or asparagine or glutamine deamidation. Monoclonal antibodies typically bind one antigenic epitope. A bispecific monoclonal antibody binds two distinct antigenic epitopes. Monoclonal antibodies can have heterogeneous glycosylation within the antibody population. Monoclonal antibody can be monospecific or multispecific such as bispecific, monovalent, bivalent or multivalent.

The term “mutation” as used herein refers to an engineered or naturally occurring alteration in a polypeptide or polynucleotide sequence when compared to a reference sequence. The alteration can be a substitution, insertion or deletion of one or more amino acids or polynucleotides.

5 The term “multispecific” as used herein refers to an antibody that specifically binds at least two distinct antigens or at least two distinct epitopes within the same antigen. Multispecific antibody can bind for example two, three, four or five distinct antigens or distinct epitopes within the same antigen.

 Current IMWG guidelines define “negative minimal residual disease status” or
10 “negative MRD status” or “MRD negative” as fewer than one tumor cell in 100000 bone marrow cells (10^{-5}) in a patient who fulfills the criteria for complete response (CR). Negative minimal residual disease status was determined using next generation sequencing (NGS).

 The term “pharmaceutical composition” as used herein refers to composition that
15 comprises an active ingredient and a pharmaceutically acceptable carrier.

The term “pharmaceutically acceptable carrier” or “excipient” as used herein refers to an ingredient in a pharmaceutical composition, other than the active ingredient, which is nontoxic to a subject.

 The term “recombinant” as used herein refers to DNA, antibodies and other
20 proteins that are prepared, expressed, created or isolated by recombinant means when segments from different sources are joined to produce recombinant DNA, antibodies or proteins.

 The term “reduce” or “reduced” as used herein refers to a reduction in one or more functions of a test molecule when compared to a control molecule or a combination
25 of test molecules when compared to one or more control molecules. Exemplary functions that can be measured are tumor cell killing, T cell activation, relative or absolute T cell number, Fc-mediated effector function (e.g. ADCC, CDC and/or ADCP) or binding to an Fcγ receptor (FcγR) or FcRn. “Reduced” can be a reduction of about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% or more, or a statistically
30 significant enhancement.

 The term “refractory” as used herein refers to a cancer that is unresponsive to an anti-cancer therapy.

The term “relapsed” as used herein refers to a cancer that responded to a treatment but then returns after the treatment.

The term “subject” as used herein includes any human or nonhuman animal. “Nonhuman animal” includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, *etc.* Except when noted, the terms “patient” or “subject” are used interchangeably.

The term “T cell redirecting therapeutic” as used herein refers to a molecule containing two or more binding regions, wherein one of the binding regions specifically binds a cell surface antigen on a target cell or tissue and wherein a second binding region of the molecule specifically binds a T cell antigen. Examples of cell surface antigen include a tumor associated antigen, such as GPRC5D. Examples of T cell antigens include, e.g., CD3. This dual/multi-target binding ability of a T cell redirecting therapeutic recruits T cells to a target cell or tissue, such as that having a tumor associated antigen, leading to the eradication of the target cell or tissue.

The term “therapeutically effective amount” as used herein refers to an amount effective, at doses and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount can vary depending on factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Exemplary indicators of an effective therapeutic or combination of therapeutics that include, for example, improved well-being of the patient.

The term “treat” or “treatment” as used herein refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder. Beneficial or desired clinical results include alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. “Treatment” can also mean prolonging survival as compared to expected survival if a subject was not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

The term “tumor cell” or a “cancer cell” as used herein refers to a cancerous, pre-cancerous or transformed cell, either *in vivo*, *ex vivo*, or in tissue culture, that has

- spontaneous or induced phenotypic changes. These changes do not necessarily involve the uptake of new genetic material. Although transformation can arise from infection with a transforming virus and incorporation of new genomic nucleic acid, uptake of exogenous nucleic acid or it can also arise spontaneously or following exposure to a carcinogen, thereby mutating an endogenous gene. Transformation/cancer is exemplified by morphological changes, immortalization of cells, aberrant growth control, foci formation, proliferation, malignancy, modulation of tumor specific marker levels, invasiveness, tumor growth in suitable animal hosts such as nude mice, and the like, *in vitro*, *in vivo*, and *ex vivo*.
- The numbering of amino acid residues in the antibody constant region throughout the specification is according to the EU index as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991), unless otherwise explicitly stated. Antibody constant chain numbering can be found for example at ImMunoGeneTics website, at IMGT Web resources at IMGT Scientific charts.

Conventional one and three-letter amino acid codes are used herein as shown in Table 1.

Table 1

Amino acid	Three-letter code	One-letter code
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartate	Asp	D
Cysteine	Cys	C
Glutamate	Gln	E
Glutamine	Glu	Q
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

In an attempt to help the reader of the application, the description has been separated in various paragraphs or sections, or is directed to various embodiments of the application. These separations should not be considered as disconnecting the substance of a paragraph or section or embodiments from the substance of another paragraph or section or embodiments. To the contrary, one skilled in the art will understand that the description has broad application and encompasses all the combinations of the various sections, paragraphs and sentences that can be contemplated. The discussion of any embodiment is meant only to be exemplary and is not intended to suggest that the scope of the disclosure, including the claims, is limited to these examples. The application contemplates use of any of the applicable components and/or steps in any combination that can be used the application, whether or not a particular combination is expressly described.

GPRC5DxCD3 bispecific antibodies and uses thereof

Overexpression of GPRC5D in the bone marrow is associated with poor prognosis in patients with multiple myeloma (see e.g., Atamaniuk *et al.*, *Eur. J. Clin. Invest.* 42:953-960(2012)). This exclusive expression of GPRC5D on the plasma-cell lineage designates it as an ideal target for antimyeloma antibodies. Anti-GPRC5D antibodies and bispecific antibodies against GPRC5D and CD3 are described, e.g., in U.S. Patent No. 10,562,968, the content of which is incorporated herein by reference in its entirety.

The invention is based, at least in part, on the finding that a GPRC5DxCD3 bispecific antibody, such as talquetamab, can be used to treat a hematological malignancy, such as multiple myeloma in subjects in need thereof, preferably subjects that are relapsed or refractory to treatment with a prior anti-cancer therapy. Accordingly, in one general aspect, the invention relates to a method of treating a hematological malignancy, such as multiple myeloma, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody to treat the hematological malignancy, wherein the subject is relapsed or refractory to treatment with a prior anti-cancer therapy.

Antibodies

Any suitable GPRC5DxCD3 bispecific antibody known to those skilled in the art in view of the present disclosure can be used in the invention.

Various bispecific antibody formats include formats described herein and recombinant IgG-like dual targeting molecules, wherein the two sides of the molecule each

- contain the Fab fragment or part of the Fab fragment of at least two different antibodies; IgG fusion molecules, wherein full length IgG antibodies are fused to an extra Fab fragment or parts of Fab fragment; Fc fusion molecules, wherein single chain Fv molecules or stabilized diabodies are fused to heavy-chain constant-domains, Fc-regions or parts thereof;
- 5 Fab fusion molecules, wherein different Fab-fragments are fused together; ScFv- and diabody-based and heavy chain antibodies (e.g., domain antibodies, nanobodies) wherein different single chain Fv molecules or different diabodies or different heavy-chain antibodies (e.g. domain antibodies, nanobodies) are fused to each other or to another protein or carrier molecule, or bispecific antibodies generated by arm exchange. Exemplary
- 10 bispecific formats include dual targeting molecules include Dual Targeting (DT)-Ig (GSK/Domantis), Two-in-one Antibody (Genentech) and mAb2 (F-Star), Dual Variable Domain (DVD)-Ig (Abbott), DuoBody (Genmab), Ts2Ab (MedImmune/AZ) and BsAb (Zymogenetics), HERCULES (Biogen Idec) and TvAb (Roche), ScFv/Fc Fusions (Academic Institution), SCORPION (Emergent BioSolutions/Trubion, Zymogenetics/BMS)
- 15 and Dual Affinity Retargeting Technology (Fc-DART) (MacroGenics), F(ab)2 (Medarex/AMGEN), Dual-Action or Bis-Fab (Genentech), Dock-and-Lock (DNL) (ImmunoMedics), Bivalent Bispecific (Biotecnol) and Fab-Fv (UCB-Celltech), Bispecific T Cell Engager (BITE) (Micromet), Tandem Diabody (Tandab) (Affimed), Dual Affinity Retargeting Technology (DART) (MacroGenics), Single-chain Diabody (Academic), TCR-
- 20 like Antibodies (AIT, ReceptorLogics), Human Serum Albumin ScFv Fusion (Merrimack) and COMBODY (Epigen Biotech), dual targeting nanobodies (Ablynx), dual targeting heavy chain only domain antibodies. Various formats of bispecific antibodies have been described, for example in Chames and Baty (2009) Curr Opin Drug Disc Dev 12: 276 and in Nunez-Prado et al., (2015) Drug Discovery Today 20(5):588-594.
- 25 In some embodiment, a GPRC5DxCD3 bispecific antibody useful for the invention comprises a GPRC5D binding domain comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 4, a HCDR2 of SEQ ID NO: 5, a HCDR3 of SEQ ID NO: 6, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 7, a LCDR2 of SEQ ID NO: 8 and a LCDR3 of SEQ
- 30 ID NO: 9.
- In other embodiment, a GPRC5DxCD3 bispecific antibody further comprises a CD3 binding domain comprising a HCDR1 of SEQ ID NO: 14, a HCDR2 of SEQ ID NO: 15, a HCDR3 of SEQ ID NO: 16, a LCDR1 of SEQ ID NO: 17, a LCDR2 of SEQ ID NO: 18, and a LCDR3 of SEQ ID NO: 19.

Unless stated otherwise herein, references to residue numbers in the variable domain of antibodies means residue numbering by the Kabat numbering system. Unless stated otherwise herein, references to residue numbers in the constant domain of antibodies means residue numbering by the EU numbering system.

5 In one embodiment, a GPRC5DxCD3 bispecific antibody useful for the invention comprises a GPRC5D binding domain having a heavy chain variable region (VH) of SEQ ID NO: 10 and a light chain variable region (VL) of SEQ ID NO: 11, and a CD3 binding domain having a VH of SEQ ID NO: 20 and a VL of SEQ ID NO: 21. In a yet further embodiment, a GPRC5DxCD3 bispecific antibody useful for the invention is of IgG1, IgG2, IgG3 or IgG4 isotype. In preferred embodiments, the bispecific antibody is of IgG4 isotype. An exemplary wild-type IgG4 Fc region comprises the amino acid sequence of SEQ ID NO: 24.

SEQ ID NO: 24:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
15 VLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPSCP
APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK
AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLG
20 K

A GPRC5DxCD3 bispecific antibody useful for the invention can be of any allotype. It is expected that allotype has no influence on properties of the bispecific antibodies, such as binding or Fc-mediated effector functions. Immunogenicity of therapeutic antibodies is associated with increased risk of infusion reactions and decreased duration of therapeutic response (Baert *et al.*, (2003) *N Engl J Med* 348:602-08). The extent to which therapeutic antibodies induce an immune response in the host can be determined in part by the allotype of the antibody (Stickler *et al.*, (2011) *Genes and Immunity* 12:213-21). Antibody allotype is related to amino acid sequence variations at specific locations in the constant region sequences of the antibody. Table 2 shows exemplary IgG1, IgG2 and IgG4 allotypes.

Table 2

Allotype	Amino acid residue at position of diversity (residue numbering: EU Index)		
	IgG2	IgG4	IgG1

	189	282	309	422	214	356	358	431
G2m(n)	T	M						
G2m(n-)	P	V						
G2m(n)/(n-	T	V						
nG4m(a)			L	R				
G1m(17)					K	E	M	A
G1m(17,1)					K	D	L	A

In a yet further embodiment, a GPRC5DxCD3 bispecific antibody useful for the invention comprises one or more Fc substitutions that reduces binding of the bispecific antibody to a Fcγ receptor (FcγR) and/or reduces Fc effector functions such as C1q binding, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) or phagocytosis (ADCP). The specific substitutions can be made in comparison to the wild-type IgG4 Fc region of SEQ ID NO: 24.

Fc positions that can be substituted to reduce binding of the Fc to the activating FcγR and subsequently to reduce effector function include, but are not limited to, substitutions L234A/L235A on IgG1, V234A/G237A/P238S/H268A/V309L/A330S/P331S on IgG2, F234A/L235A on IgG4, S228P/F234A/L235A on IgG4, N297A on all Ig isotypes, V234A/G237A on IgG2, K214T/E233P/L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M on IgG1, H268Q/V309L/A330S/P331S on IgG2, S267E/L328F on IgG1, L234F/L235E/D265A on IgG1, L234A/L235A/G237A/P238S/H268A/A330S/P331S on IgG1, S228P/F234A/L235A/G237A/P238S on IgG4, and S228P/F234A/L235A/G236-deleted/G237A/P238S on IgG4, wherein residue numbering is according to the EU index.

Fc substitutions that can be used to reduce CDC include, but are not limited to a K322A substitution. Substitutions, such as S228P substitution, can further be made in IgG4 antibodies to enhance IgG4 stability.

In a yet further embodiment, the GPRC5DxCD3 bispecific antibody can comprise one or more asymmetric substitutions in a first CH3 domain or in a second CH3 domain, or in both the first CH3 domain and the second CH3 domain.

In a yet further embodiment, the one or more asymmetric substitutions can include, but are not limited to, those selected from the group consisting of F405L/K409R, wild-type/F405L_R409K, T366Y/F405A, T366W/F405W, F405W/Y407A, T394W/Y407T, T394S/Y407A, T366W/T394S, F405W/T394S and T366W/T366S_L368A_Y407V, L351Y_F405A_Y407V/T394W, T366I_K392M_T394W/F405A_Y407V, T366L_K392M_T394W/F405A_Y407V,

L351Y_Y407A/T366A_K409F, L351Y_Y407A/T366V_K409F, Y407A/T366A_K409F and T350V_L351Y_F405A_Y407V/T350V_T366L_K392L_T394W.

In a yet further embodiment, a GPRC5DxCD3 bispecific antibody useful for the invention is of IgG4 isotype and comprises phenylalanine at position 405 and arginine at position 409 in a first heavy chain (HC1) and leucine at position 405 and lysine at position 409 in a second heavy chain (HC2).

In a yet further embodiment, a GPRC5DxCD3 bispecific antibody useful for the invention further comprises proline at position 228, alanine at position 234 and alanine at position 235 in both the HC1 and the HC2.

In a yet further embodiment, a GPRC5DxCD3 bispecific antibody useful for the invention comprises the HC1 of SEQ ID NO: 12, a first light chain (LC1) of SEQ ID NO: 13, the HC2 of SEQ ID NO: 22, and a second light chain (LC2) of SEQ ID NO: 23, wherein the LC1 binds to the HC1, the LC2 binds to the HC2, and the HC1 is linked to the HC2.

In a yet further embodiment, a GPRC5DxCD3 bispecific antibody useful for the invention is talquetamab, having the HC1 of SEQ ID NO: 12, LC1 of SEQ ID NO: 13, HC2 of SEQ ID NO: 22 and LC2 of SEQ ID NO: 23.

Cancers

Methods of the application can be used to treat a cancer, preferably, a hematological malignancy, more preferably a relapsed or refractory hematological malignancy.

Examples of hematological malignancy can be selected from multiple myeloma, smoldering multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma (BL), follicular lymphoma (FL), mantle-cell lymphoma (MCL), Waldenstrom's macroglobulinemia, plasma cell leukemia, light chain amyloidosis (AL), precursor B-cell lymphoblastic leukemia, precursor B-cell lymphoblastic leukemia, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic lymphocytic leukemia (CLL), B cell malignancy, chronic myeloid leukemia (CML), hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm, Hodgkin's lymphoma, non-Hodgkin's lymphoma, marginal zone B-cell lymphoma (MZL), mucosa-associated lymphatic tissue lymphoma (MALT), plasma cell leukemia, anaplastic large-cell lymphoma (ALCL), leukemia or lymphoma.

In one embodiment, the hematological malignancy is multiple myeloma.

In a further embodiment, the subject has a newly diagnosed multiple myeloma. In a yet further embodiment, the subject is relapsed or refractory to treatment with a prior anti-cancer therapeutic, such as a therapeutic used to treat multiple myeloma or other hematological malignancies.

5 In a yet further embodiment, the subject is refractory or relapsed to one or more prior anti-cancer treatments or therapies. Exemplary prior anti-cancer treatments or therapies, include, without limitation, THALOMID[®] (thalidomide), REVLIMID[®] (lenalidomide), POMALYST[®] (pomalidomide), VELCADE[®] (bortezomib), NINLARO (ixazomib), KYPROLIS[®] (carfilzomib), FARADYK[®] (panobinostat), AREDIA[®] (pamidronate), ZOMETA[®] (zoledronic acid), DARZALEX[®] (daratumumab),
10 EMPLICITI[®] (elotuzumab), melphalan, Xpovio[®] (Selinexor), BLENREP (belantamab mafodotin-blmf), Venclexta[®] (Venetoclax), CAR-T therapies, other BCMA-directed therapies, other CD38-directed therapies, or any combinations thereof.

Various qualitative and/or quantitative methods can be used to determine relapse
15 or refractory nature of the disease. According to NCCN Guidelines, “clinical relapse” are defined as having one of more of the following occurred: there are direct signs of cancer growth, signs of organ damage, an increase in the number of size (at least 50% larger) of plasmacytomas or bone lesions, increased calcium levels, an increase in creatinine levels in blood, or a decrease in the number of red blood cells, and “relapse
20 from complete response” is defined as having one or more of the following occurred in a patient who had a complete response: a return of M-proteins in blood or urine, or other signs of myeloma but not meeting the criteria for a clinical relapse progressive disease. (“Progressive disease” is defined as having one or more of the following occurred: at least 25% increase in the amount of M-proteins in the blood or urine, a 25% increase in
25 the number of plasma cells in the bone marrow, an increase in the size or number of bone lesions, or an increase in calcium levels not explained by other conditions.)

In a yet further embodiment, the multiple myeloma is a high-risk multiple myeloma. Subjects with high-risk multiple myeloma are known to relapse early and have poor prognosis and outcome. Subjects can be classified as having high-risk multiple myeloma
30 if they have one or more of the following cytogenetic abnormalities: t(4;14)(p16;q32), t(14;16)(q32;q23), del17p, 1qAmp, t(4;14)(p16;q32) and t(14;16)(q32;q23), t(4;14)(p16;q32) and del17p, t(14;16)(q32;q23) and del17p, or t(4;14)(p16;q32), t(14;16)(q32;q23) and del17p. In some embodiments, the subject having the high-risk multiple myeloma can have one or more chromosomal abnormalities comprising:

t(4;14)(p16;q32), t(14;16)(q32;q23), del17p, 1qAmp, t(4;14)(p16;q32) and t(14;16)(q32;q23), t(4;14)(p16;q32) and del17p, t(14;16)(q32;q23) and del17p; or t(4;14)(p16;q32), t(14;16)(q32;q23) and del17p, or any combination thereof.

The cytogenetic abnormalities can be detected for example by fluorescent *in situ* hybridization (FISH). In chromosomal translocations, an oncogene is translocated to the IgH region on chromosome 14q32, resulting in dysregulation of these genes. t(4;14)(p16;q32) involves translocation of fibroblast growth factor receptor 3 (FGFR3) and multiple myeloma SET domain containing protein (MMSET) (also called WHSC1/NSD2), and t(14;16)(q32;q23) involves translocation of the MAF transcription factor C-MAF. Deletion of 17p (del17p) involves loss of the p53 gene locus. Chromosomal rearrangements can be identified using well known methods, for example fluorescent in situ hybridization, karyotyping, pulsed field gel electrophoresis, or sequencing.

Compositions

A GPRC5DxCD3 bispecific antibody useful for the invention can be formulated as a pharmaceutical composition comprising about 1 mg/mL to about 200 mg/mL antibody.

In one embodiment, the pharmaceutical composition further comprises one or more excipients. In some embodiments, the one or more excipients include, but are not limited to, a buffering agent, a sugar, a surfactant, a chelator, metal ion scavenger, or any combination thereof.

In a further embodiment, the pharmaceutical composition comprises: about 1 mg/mL to about 200 mg/mL of a GPRC5DxCD3 bispecific antibody, such as about 1 mg/mL, about 5 mg/mL, about 10 mg/mL, about 15 mg/mL, about 20 mg/mL, about 25 mg/mL, about 30 mg/mL, about 35 mg/mL, about 40 mg/mL, about 45 mg/mL, about 50 mg/mL, about 60 mg/mL, about 70 mg/mL, about 80 mg/mL, about 90 mg/mL, about 100 mg/mL, about 110 mg/mL, about 120 mg/mL, or any value in between, of the GPRC5DxCD3 bispecific antibody; about 5 mM to about 20 mM buffering agent, such as about 5 mM, about 10 mM, about 15 mM, about 20 mM, or any value in between, sodium phosphate, KH_2PO_4 , sodium acetate, histidine, or sodium citrate; about 1% w/v to about 20% w/v sugar, such as about 1% w/v, about 2% w/v, about 3% w/v, about 4% w/v, about 5% w/v, about 6% w/v, about 7% w/v, about 8% w/v, about

9% w/v, about 10% w/v, about 15% w/v, about 20% w/v, or any value in between, glucose, sucrose or cellobiose;
about 0.01% w/v to about 2% w/v surfactant, such as about 0.01% w/v, about 0.02% w/v, about 0.03% w/v, about 0.04% w/v, about 0.05% w/v, about 0.06% w/v, about
5 0.07% w/v, about 0.08% w/v, about 0.09% w/v, about 0.1% w/v, about 0.5% w/v, about 1% w/v, about 1.5% w/v, about 2% w/v, or any value in between, polysorbate 80 (PS-80) or PS-20; and
about 5 mM to about 40 mM ethylenediaminetetraacetic acid (EDTA), such as about 5 mM, about 10 mM, about 15 mM, about 20 mM, about 25 mM, about 30 mM, about 35
10 mM, about 40 mM, or any value in between, EDTA or an edetate salt, at a pH of about 5-6, such as about 5, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6, or any value in between.

The pharmaceutical composition disclosed herein may further comprise about 0.1 mg/mL to about 5 mg/mL amino acid, such as about 0.1 mg/mL, about 0.2 mg/mL, about
15 0.3 mg/mL, about 0.4 mg/mL, about 0.5 mg/mL, about 0.6 mg/mL, about 0.7 mg/mL, about 0.8 mg/mL, about 0.9 mg/mL, about 1 mg/mL, about 2 mg/mL, about 3 mg/mL, about 4 mg/mL, about 5 mg/mL, or any value in between, methionine or arginine.

In one embodiment, a pharmaceutical composition useful for the invention comprises 5 mg/ml to 20 mg/ml, such as 5, 10, 15, 20 mg/ml, or any value in between, of
20 a GPRC5DxCD3 bispecific antibody, such as talquetamab, 20 mM sodium phosphate, 10% weight/volume (w/v) sucrose, 0.06% (w/v) PS80, and 25 µg/mL EDTA at pH 5.4.

In a further embodiment, the pharmaceutical composition disclosed herein comprises 5 mg/ml to 20 mg/ml, such as 5, 10, 15, 20 mg/ml, or any value in between, of
a GPRC5DxCD3 bispecific antibody, such as talquetamab, 10 to 15 mM sodium acetate,
25 8% (w/v) sucrose, 0.04% (w/v) PS20, and 20 µg/mL EDTA at pH 5.2.

In a yet further embodiment, the pharmaceutical composition disclosed herein comprises 5 mg/ml to 20 mg/ml, such as 5, 10, 15, 20 mg/ml, or any value in between, of
a GPRC5DxCD3 bispecific antibody, such as talquetamab, 15 mM KH₂PO₄, 10% (w/v) cellobiose, 0.05% (w/v) PS20, and 25 µg/mL EDTA at pH 5.1.

30 In a yet further embodiment, the pharmaceutical composition disclosed herein comprises 2 mg/ml to 40 mg/ml, such as 5, 10, 15, 20, 30, 40 mg/ml, or any value in between, of a GPRC5DxCD3 bispecific antibody, such as talquetamab, 15 mM Histidine, 8% (w/v) sucrose, 0.04% (w/v) PS20, and 20 µg/mL EDTA at pH 5.2.

Administration

In accordance with the present invention, the GPRC5DxCD3 bispecific antibody can be administered to the subject by intravenous infusion or subcutaneous injection.

The dose of a GPRC5DxCD3 bispecific antibody given to a subject having a hematological malignancy, such as multiple myeloma, is sufficient to alleviate or at least

5 partially arrest the disease being treated. Examples of the dosages useful for the invention include from about 0.2 µg/kg to about 1200 µg/kg, e.g. about 0.5 µg/kg to 100 µg/kg, about 1 µg/kg to about 800 µg/kg, about 1 µg/kg to about 500 µg/kg of the antibody. Suitable doses include, e.g., about 0.2 µg/kg, about 0.6 µg/kg, about 1.2 µg/kg, about 2.4 µg/kg, about 4.8 µg/kg, about 9.6 µg/kg, about 19.2 µg/kg, about 20
10 µg/kg, about 38.4 µg/kg, about 40 µg/kg, about 57.6 µg/kg, about 60 µg/kg, about 80 µg/kg, about 120 µg/kg, about 180 µg/kg, about 240 µg/kg, about 270 µg/kg, about 300 µg/kg, about 460, about 720 µg/kg, about 800 µg/kg, about 1000 µg/kg, about 1200 µg/kg, about 1600 µg/kg, about 2000 µg/kg, about 2400 µg/kg, or any dose in between.

In one embodiment, a GPRC5DxCD3 bispecific antibody is administered to a
15 subject intravenously at a dose of about 0.2 µg/kg to about 200 µg/kg, or about 0.5 µg/kg to about 180 µg/kg, or about 1 µg/kg to about 150 µg/kg, or about 5 µg/kg to about 100 µg/kg, or about 10 µg/kg to about 70 µg/kg. Examples of the dose for intravenous administration include, e.g., about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200 µg/kg, or any value in between. The dose can be
20 intravenously administered monthly, tri-weekly, bi-weekly, weekly, twice weekly, or any frequency in between.

In a further embodiment, the GPRC5DxCD3 bispecific antibody is administered to a subject subcutaneously at a dose of about 0.5 µg/kg to about 2400 µg/kg, about 0.5 µg/kg to about 1200 µg/kg, or about 1 µg/kg to about 800 µg/kg, or about 10 µg/kg to
25 about 500 µg/kg. Examples of the dose for subcutaneous administration include, e.g., about 10, 50, 100, 135, 150, 200, 250, 300, 350, 400, 405, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150 µg/kg, 1200 µg/kg, 1600 µg/kg, 2000 µg/kg, 2400 µg/kg, or any value in between. The dose can be subcutaneously administered monthly, tri-weekly, bi-weekly, weekly, twice weekly, or any frequency in
30 between.

A fixed unit dose of a GPRC5DxCD3 bispecific antibody can also be given, for example, at 50, 100, 200, 500, or 1000 mg, or any value in between, per administration. The dose can also be based on the patient's surface area, e.g., 500, 400, 300, 250, 200, or 100 mg/m², or any value in between. Multiple doses can be administered to treat a

hematological malignancy, such as a multiple myeloma, such as 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more doses can be given.

The administration of a GPRC5DxCD3 bispecific antibody can be repeated after one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, two months, three months, four months, five months, six months, or longer. Repeated courses of treatment are also possible, as is chronic administration. The repeated administration can be at the same dose or at a different dose. For example, a GPRC5DxCD3 bispecific antibody can be administered at a first dose for a first time period, followed by administration at a second dose for a second time period. In one embodiment, the GPRC5DxCD3 bispecific antibody is administered every two weeks (i.e., bi-weekly) for a certain number of weeks, followed by administration at a second dose every week (i.e., weekly) for an additional certain number of weeks, followed by administration at a third dose every week for an additional certain number of weeks.

A GPRC5DxCD3 bispecific antibody can be administered, such as, once a week for a period needed. For example, the GPRC5DxCD3 bispecific antibody can be provided every 2 to 4 days (e.g., for the step up doses) and then weekly, biweekly, triweekly or monthly (e.g., for the full dose) in an amount of about 0.2 µg/kg to about 2400 µg/kg, 0.2 µg/kg to about 1000 µg/kg, e.g. about 0.3 µg/kg to about 1000 µg/kg, about 0.6 µg/kg to about 600 µg/kg, about 1.2 µg/kg to about 500 µg/kg, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 after initiation of treatment, or any combination thereof, using single or divided doses of every 24, 12, 8, 6, 4, or 2 hours, or any combination thereof.

In one embodiment, a GPRC5DxCD3 bispecific antibody is administered intravenously twice a week, once a week, once every two weeks, once every three weeks, monthly or any frequency in between in an amount of about 0.3 µg/kg, about 0.5 µg/kg, about 1.0 µg/kg, about 1.5 µg/kg, about 2.25 µg/kg, about 2.5 µg/kg, about 2.75 µg/kg, about 3 µg/kg, about 3.25 µg/kg, about 3.38 µg/kg, about 3.5 µg/kg, about 3.75 µg/kg, about 4 µg/kg, about 4.25 µg/kg, about 4.5 µg/kg, about 4.75 µg/kg, about 5 µg/kg, about 7.5 µg/kg, about 10 µg/kg, about 11.25 µg/kg, about 20 µg/kg, about 30 µg/kg, about 40 µg/kg, about 50 µg/kg, about 60 µg/kg, about 80 µg/kg, about 120 µg/kg, about 180 µg/kg, about 200 µg/kg, or any dose in between.

In a further embodiment, a GPRC5DxCD3 bispecific antibody is administered subcutaneously twice a week, once a week, once every two weeks, once every three weeks, monthly or any frequency in between in an amount of about 0.3 µg/kg, about 0.6 µg/kg, about 1.2 µg/kg, about 1.5 µg/kg, about 2.5 µg/kg, about 5 µg/kg, about 10 µg/kg, about 15 µg/kg, about 20 µg/kg, about 25 µg/kg, about 30 µg/kg, about 40 µg/kg, about 45 µg/kg, about 50 µg/kg, about 55 µg/kg, about 60 µg/kg, about 80 µg/kg, about 120 µg/kg, about 135 µg/kg, about 180 µg/kg, about 240 µg/kg, about 270 µg/kg, about 300 µg/kg, about 350 µg/kg, about 400 µg/kg, about 405 µg/kg, about 720 µg/kg, about 800 µg/kg, about 1000 µg/kg, about 1200 µg/kg, about 1600 µg/kg, about 2000 µg/kg, about 2400 µg/kg, or any dose in between.

In some embodiments, a GPRC5DxCD3 bispecific antibody is administered in one or more priming administrations that gradually increase the dose levels. The priming dose strategies can be utilized effectively for bispecific T cell engager antibodies such as a GPRC5DxCD3 bispecific antibody, due to the potential for these antibodies to cause more pronounced acute toxicities with the initial dose. One or more priming doses, can be used to ensure safety, obtain the desired T cell adaptation effect, decrease cytokine levels, and decrease the incidence of symptomatic cytokine release syndrome (CRS) in a majority of treated subjects. Priming dose(s) is administered prior to Day 1 of the bi-weekly, weekly, triweekly or monthly dose schedules with higher dose.

Accordingly, in one embodiment, a GPRC5DxCD3 bispecific antibody is administered intravenously at a step-up (or “priming”) dose, followed by weekly, biweekly, triweekly, or monthly administration at a higher dose intravenously or subcutaneously. For example, the GPRC5DxCD3 bispecific antibody can be administered intravenously at a priming dose of about 0.3 µg/kg, about 0.5 µg/kg, about 0.6 µg/kg, about 1.0 µg/kg, about 1.5 µg/kg, about 2.25 µg/kg, about 2.4 µg/kg, about 3.0 µg/kg, about 3.38 µg/kg, about 3.5 µg/kg, about 3.75 µg/kg, about 4 µg/kg, about 4.25 µg/kg, about 4.5 µg/kg, about 4.75 µg/kg, about 5 µg/kg, or any dose in between. After the priming administration, the GPRC5DxCD3 bispecific antibody can be administered weekly, biweekly, triweekly or monthly intravenously at a higher dose, such as about 1.0 µg/kg, about 1.5 µg/kg, about 2.25 µg/kg, about 2.5 µg/kg, about 2.75 µg/kg, about 3 µg/kg, about 3.25 µg/kg, about 3.38 µg/kg, about 3.5 µg/kg, about 3.75 µg/kg, about 4 µg/kg, about 4.25 µg/kg, about 4.5 µg/kg, about 4.75 µg/kg, about 5 µg/kg, about 7.5 µg/kg, about 10 µg/kg, about 11.25 µg/kg, about 20 µg/kg, about 30

μg/kg, about 40 μg/kg, about 50 μg/kg, about 60 μg/kg, about 80 μg/kg, about 120 μg/kg, about 180 μg/kg, about 200 μg/kg, or any dose in between.

In another embodiment, after the priming administration, the GPRC5DxCD3 bispecific antibody is administered weekly, biweekly, triweekly or monthly subcutaneously at a higher dose, such as about 1.2 μg/kg, about 1.5 μg/kg, about 2.5 μg/kg, about 5 μg/kg, about 10 μg/kg, about 15 μg/kg, about 20 μg/kg, about 25 μg/kg, about 30 μg/kg, about 40 μg/kg, about 45 μg/kg, about 50 μg/kg, about 55 μg/kg, about 60 μg/kg, about 80 μg/kg, about 120 μg/kg, about 135 μg/kg, about 180 μg/kg, about 240 μg/kg, about 270 μg/kg, about 300 μg/kg, about 350 μg/kg, about 400 μg/kg, about 405 μg/kg, about 720 μg/kg, about 800 μg/kg, about 1000 μg/kg, about 1200 μg/kg, about 1600 μg/kg, about 2000 μg/kg, about 2400 μg/kg, or any dose in between.

In a yet further embodiment, a GPRC5DxCD3 bispecific antibody is administered intravenously at a first step-up dose, followed by administration at a second higher step-up dose, followed by weekly, biweekly, triweekly or monthly administration at a third, higher dose. For example, the GPRC5DxCD3 bispecific antibody can be administered intravenously at a step-up dose of about 0.5 μg/kg, about 1.0 μg/kg, about 1.5 μg/kg, about 2.25 μg/kg, about 2.5 μg/kg, about 2.75 μg/kg, about 3.0 μg/kg, about 3.25 μg/kg, about 3.5 μg/kg, or any dose in between, followed by intravenous administration at a second step-up dose of about 5 μg/kg, about 7.5 μg/kg, about 10 μg/kg, about 12.5 μg/kg, about 15 μg/kg, or any dose in between, followed by weekly intravenous administration at a dose of about 15 μg/kg, about 20 μg/kg, about 30 μg/kg, about 40 μg/kg, about 50 μg/kg, about 60 μg/kg, about 80 μg/kg, about 120 μg/kg, about 180 μg/kg, or any dose in between.

In a yet further embodiment, the GPRC5DxCD3 bispecific antibody is administered intravenously at a first step-up dose, followed by administration at a second higher step-up dose, followed by administration at a third higher step-up dose, followed by weekly, biweekly, triweekly or monthly administration at a fourth, higher dose. For example, the GPRC5DxCD3 bispecific antibody can be administered intravenously at a first step-up dose of about 0.3 μg/kg, about 0.6 μg/kg, about 1.2 μg/kg, about 1.5 μg/kg, about 1.75 μg/kg, about 2.0 μg/kg, about 2.25 μg/kg, about 2.5 μg/kg, about 2.75 μg/kg, about 3 μg/kg, or any dose in between, followed by intravenous administration at a second step-up dose of about 5 μg/kg, about 7.5 μg/kg, about 10 μg/kg, about 12.5 μg/kg, about 15 μg/kg, or any dose in between, followed by intravenous administration at a step-up dose of about 40 μg/kg, about 50 μg/kg, about 60 μg/kg, about 70 μg/kg,

about 80 µg/kg, or any dose in between, followed by weekly, biweekly, triweekly or monthly intravenous administration at a dose of about 150 µg/kg, about 180 µg/kg, about 200 µg/kg, or any dose in between.

In a yet further embodiment, the GPRC5DxCD3 bispecific antibody is
5 administered subcutaneously at a step-up dose, followed by weekly, biweekly, triweekly or monthly administration at a higher dose. For example, the GPRC5DxCD3 bispecific antibody can be administered subcutaneously at a step-up dose of about 1.5 µg/kg, about 5 µg/kg, about 10 µg/kg, about 20 µg/kg, about 40 µg/kg, about 45 µg/kg, about 60 µg/kg, or any dose in between, followed by weekly subcutaneously administration at a
10 dose of about 5 µg/kg, about 10 µg/kg, about 15 µg/kg, about 20 µg/kg, about 25 µg/kg, about 30 µg/kg, about 40 µg/kg, about 45 µg/kg, about 50 µg/kg, about 55 µg/kg, about 60 µg/kg, about 80 µg/kg, 120 µg/kg, about 135 µg/kg, about 180 µg/kg, about 240 µg/kg, about 300 µg/kg, about 270 µg/kg, about 360 µg/kg, about 400 µg/kg, about 405 µg/kg, about 420 µg/kg, about 480 µg/kg, about 540 µg/kg, about 600 µg/kg, about 760 µg/kg, about 920 µg/kg, about 1000 µg/kg, about 1200 µg/kg, about 1600 µg/kg, about
15 2000 µg/kg, about 2400 µg/kg, or any dose in between.

In a yet further embodiment, a GPRC5DxCD3 bispecific antibody is administered subcutaneously at a first step-up dose, followed by administration at a second higher step-up dose, followed by weekly, biweekly, triweekly or monthly
20 administration at a third, higher dose. For example, the GPRC5DxCD3 bispecific antibody can be administered subcutaneously at a step-up dose of about 1.5 µg/kg, about 5 µg/kg, about 10 µg/kg, about 15 µg/kg, or any dose in between, followed by subcutaneously administration at a higher step-up dose of about 30 µg/kg, about 40 µg/kg, about 45 µg/kg, about 60 µg/kg or any dose in between, followed by weekly
25 subcutaneously administration at a dose of about 100 µg/kg, about 135 µg/kg, about 240 µg/kg, about 300 µg/kg, about 400 µg/kg, about 405 µg/kg, about 800 µg/kg, about 1000 µg/kg, about 1200 µg/kg, about 1600 µg/kg, about 2000 µg/kg, about 2400 µg/kg or any dose in between.

In a yet further embodiment, a GPRC5DxCD3 bispecific antibody is
30 administered subcutaneously at a first step-up dose, followed by administration at a second higher step-up dose, followed by administration at a third, higher step-up dose, followed by weekly, biweekly, triweekly or monthly administration at a fourth, higher dose. For example, the GPRC5DxCD3 bispecific antibody can be administered subcutaneously at a first step-up dose of about 1.5 µg/kg, about 4 µg/kg, about 6 µg/kg,

about 8 µg/kg, about 10 µg/kg, about 12 µg/kg, about 14 µg/kg, about 16 µg/kg, about 18 µg/kg, about 20 µg/kg, or any dose in between, followed by subcutaneously administration at a second step-up dose of about 30 µg/kg, about 45 µg/kg, about 60 µg/kg, about 75 µg/kg, about 100 µg/kg, or any dose in between, followed by
5 subcutaneously administration at a third step-up dose of about 150 µg/kg, about 200 µg/kg, about 250 µg/kg, about 300 µg/kg, about 350 µg/kg, about 400 µg/kg, or any dose in between, followed by weekly subcutaneous administration at a dose of about 500 µg/kg, 600 µg/kg, about 700 µg/kg, about 800 µg/kg, about 900 µg/kg, about 1000 µg/kg, about 1200 µg/kg, about 1600 µg/kg, about 2000 µg/kg, about 2400 µg/kg, or any
10 dose in between.

In a yet further embodiment, a GPRC5DxCD3 bispecific antibody is administered for a time sufficient to achieve complete response, stringent complete response, very good partial response, partial response, minimal response or stable disease status, and can be continued until disease progression or lack of patient benefit. The
15 disease status can be determined by any suitable method known to those skilled in the art in view of the present disclosure, including, e.g., analysis of serum and urine monoclonal protein concentrations, M-protein levels, GPRC5D levels.

In certain embodiments, a GPRC5DxCD3 bispecific antibody is administered for a time sufficient to achieve complete response that is characterized by negative minimal
20 residual disease (MRD) status. Negative MRD status can be determined by any method suitable method known to those skilled in the art in view of the present disclosure. In some embodiments, negative MRD status is determined using next generation sequencing (NGS). In other embodiments, negative MRD status is determined using EuroFlow, a sensitive flow cytometric test. In some embodiments, negative MRD
25 status is determined at 10^{-4} cells, 10^{-5} cells, or 10^{-6} cells. In some embodiment, the administration of GPRC5DxCD3 can be continued after the negative MRD status is achieved as a maintenance therapy. In another embodiment, the administration of GPRC5DxCD3 is discontinued after the negative MRD status is achieved.

A GPRC5DxCD3 bispecific antibody can also be administered prophylactically
30 in order to reduce the risk of developing cancer, such as smoldering multiple myeloma (SMM), delay the onset of the occurrence of an event in cancer progression, and/or reduce the risk of recurrence when the cancer is in remission.

Combinations

In certain embodiments, a method of the application further comprises administering to the subject one or more other anti-cancer therapies.

The one or more other anti-cancer therapies can include, without limitation, autologous stem cell transplants (ASCT), radiation, surgery, chemotherapeutic agents, CAR-T
5 therapies, cellular therapies, immunomodulatory agents, targeted cancer therapies, and any combination thereof. In certain embodiments, a method of the application further comprises administering to the subject a therapy that reduces or depletes Treg, such as low-dose cyclophosphamide.

The one or more other anti-cancer therapies can also include, without limitation,
10 selinexor, belantamab mafodotin-blmf, isatuximab, venetoclax, lenalidomide, thalidomide, pomalidomide, bortezomib, carfilzomib, elotozumab, ixazomib, melphalan, CC-92480, dexamethasone, vincristine, cyclophosphamide, hydroxydaunorubicin, prednisone, rituximab, imatinib, dasatinib, nilotinib, bosutinib, ponatinib, bafetinib, saracatinib, tozasertib, danusertib, cytarabine, daunorubicin, idarubicin, mitoxantrone,
15 hydroxyurea, decitabine, cladribine, fludarabine, topotecan, etoposide 6-thioguanine, corticosteroid, methotrexate, 6-mercaptopurine, azacitidine, arsenic trioxide and all-trans retinoic acid, and any combination thereof.

Thus, provided herein is a combination of an effective amount of a GPRC5D $\times$ CD3 bispecific antibody, and an effective amount of other anti-cancer
20 therapies for use in treating a hematological malignancy, such as MM, preferably a MM that is relapsed or refractory to a prior anti-cancer therapy.

As used herein, the terms and phrases “in combination,” “in combination with,” “co-delivery,” and “administered together with” in the context of the administration of two or more therapies or components to a subject refers to simultaneous administration,
25 overlapping administration or subsequent administration of two or more therapies or components. “Simultaneous administration” or “simultaneously administered” refers to administration of the two or more therapies or components within the same treatment period. When two components are administered “within the same treatment period,” they can be administered in separate compositions according to their own administration
30 schedules, as long as the periods of administration for the two components end around the same day or within a short time period, such as within 1 day, 1 week, or 1 month. “Overlapping administration” refers to administration of the two or more therapies or components not within the same overall treatment period, but with at least one overlapping treatment period. “Subsequent administration” refers to administration of

the two or more therapies or components during different treatment periods, one after the other. The use of the term “in combination with” does not restrict the order in which therapies or components are administered to a subject. For example, a first therapy or component can be administered prior to, concomitantly with or simultaneously with, or
 5 subsequent to the administration of a second therapy or component.

The term “BLRM model” refers to the Bayesian logistic regression model as described in Neuenschwander et al. *Stat Med.* 2008. 27(13): 2420-39. In Part 1 (dose escalation), the probability of dose-limiting toxicities (DLTs) from a BLRM with the EWOC (Escalation with overdose control) principle guides the dose escalation. The
 10 BLRM with the EWOC principle will also be implemented in Part 2 (dose expansion). The following two-parameter BLRM is central to the calculation of the probability of DLTs when a subject’s planned maximum dose during the first cycle is d :

$$\text{logit} () = \alpha + \beta \log(d/d^*) ; \alpha \in \mathbb{R}, \beta > 0$$

where, π is the probability that a DLT occurs during the DLT evaluation period when talquetamab is given as a single agent with planned maximum dose= d during the first
 15 cycle, $\text{logit} () = \log(\frac{\pi}{1-\pi})$, and d^* is a reference planned maximum dose during the first cycle.

While having described the invention in general terms, the embodiments of the invention will be further disclosed in the following examples that should not be
 20 construed as limiting the scope of the claims.

EXAMPLES

The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the
 25 disclosed embodiments.

Antibodies and reagents

A fully humanized IgG4 anti-GPRC5D/anti-CD3 bispecific antibody talquetamab (described in U.S. Patent No. 10,562,968, the content of which is incorporated herein by reference in its entirety) was made by Janssen Pharmaceuticals. It was produced by
 30 cultivation of recombinant Chinese Hamster Ovary cells followed by isolation, chromatographic purification, and formulation. Talquetamab comprises a GPRC5D binding arm GC5B596 and a CD3 binding arm CD3B219, the amino acid sequences of which are shown in Table 3 and Table 4, respectively.

Table 3. Sequences of GPRC5D binding arm of Talquetamab

	Region	Sequence	SEQ ID NO:
GC5B59 6	HCDR1	GYTMN	4
	HCDR2	LINPYNSDTNYAQKLQG	5
	HCDR3	VALRVALDY	6
	LCDR1	KASQNVATHVG	7
	LCDR2	SASYRYS	8
	LCDR3	QQYNRYPYT	9
	VH	QVQLVQSGAEVKKPGASVKVSCKASGYSF TGYTMNWVRQAPGQGLEWMGLINPYNSD TNYAQKLQGRVTMTTDTSTSTAYMELRSL RSDDTAVYYCARVALRVALDYWGQGT LVTVSS	10
	VL	DIQMTQSPSSLSASVGDRVTITCKASQNV A THVGWYQQKPGKAPKRLIYSASYRYS GVP SRFSGSGSGTEFTLTISNLQPEDF ATYYCQQYNRYPYTFGQGTKLEIK	11
	HC	QVQLVQSGAEVKKPGASVKVSCKASGYSF TGYTMNWVRQAPGQGLEWMGLINPYNSD TNYAQKLQGRVTMTTDTSTSTAYMELRSL RSDDTAVYYCARVALRVALDYWGQGT LVTVSSASTKGPSVFPLAPCSRSTSE STAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVP SSSLGKTKYTCNVDHKPSNTKVKDR VESKYGPPCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVDV SQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTTPVLDSDGSF FLYSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLSLGK	12
	LC	DIQMTQSPSSLSASVGDRVTITCKASQNV A THVGWYQQKPGKAPKRLIYSASYRYS GVP SRFSGSGSGTEFTLTISNLQPEDF ATYYCQQYNRYPYTFGQGTKLEIK KAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKGDS SPVKAGVETTTTPSKQSNNKYA ASSYLSLTP EQWKSHRSYSCQV THEGSTVEKTVAPTECS	13

Table 4. Sequences of CD3 binding arm of talquetamab

	Region	Sequence	SEQ ID NO:
CD3B21 9	HCDR1	TYAMN	14
	HCDR2	RIRSKYNNYATYYAASVKG	15

	HCDR3	HGNFGNSYVSWFAY	16
	LCDR1	RSSTGAVTTSNYAN	17
	LCDR2	GTNKRAP	18
	LCDR3	ALWYSNLWV	19
	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNT YAMNWVRQAPGKGLEWVARIRSKYNNYAT YYAASVKGRFTISRDDSKNSLYLQMNSLKTE DTAVYYCARHGNFGNSYVSWFAYWGQGT LTVSS	20
	VL	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTT SNYANWVQQKPGQAPRGLIGGTNKRAPGTP ARFSGSLLGGKAALTLGSGVQPEDEAEYYCAL WYSNLWVFGGGTKLTVLGQP	21
	HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFNT YAMNWVRQAPGKGLEWVARIRSKYNNYAT YYAASVKGRFTISRDDSKNSLYLQMNSLKTE DTAVYYCARHGNFGNSYVSWFAYWGQGT LTVSSASTKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGKTYTCNVDHK PSNTKVDKRVESKYGPPCPPCAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFLLYSKLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLGLK	22
	LC	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTT SNYANWVQQKPGQAPRGLIGGTNKRAPGTP ARFSGSLLGGKAALTLGSGVQPEDEAEYYCAL WYSNLWVFGGGTKLTVLGQPKAAPSVTLFP PSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTTPSKQSNNKYAASSYLSLT PEQWKSHRYSYSCQVTHEGSTVEKTVAPTECS	23

Example 1: Mechanisms of Resistance and Determinants of Response of Talquetamab in Multiple Myeloma

In this study, it is demonstrated that GPRC5D cell surface expression, measured by flow cytometry, is significantly higher on malignant plasma cells in different stages of the disease (newly diagnosed (ND), relapsed/refractory (RR), and daratumumab-refractory (DARA-R)) than on normal plasma cells from healthy donors (Figure 6A). GPRC5D expression is also higher on MM cells than on other immune cells (Figure 6B). This selective expression renders it an attractive target for immunotherapy. In addition, talquetamab showed substantial activity in GPRC5D+ cell lines (Figure 7).

Next, bone marrow mononuclear cells (BM-MNCs) from 45 MM patients (containing MM cells, effector cells and immunosuppressive cells) were isolated and analyzed tumor- and immune cell characteristics by flow cytometry. Subsequently, cells were incubated with serial dilutions of talquetamab for 48 hours, after which lysis of CD138+ MM cells was determined by flow cytometry. Mean lysis at the highest dose was 61% (Figure 8), but ranged from -5 to 97%. Mechanisms of resistance and determinants of response of talquetamab were then further investigated.

It was further found that pre-treatment and cytogenetic abnormalities have no impact on talquetamab-mediated lysis (Figures 9A-9D). Specifically, no difference was found in dose-response curves between ND- dara naive RR- and DARA-R MM patients. Although talquetamab-mediated T-cell activation (defined by CD25+) in samples derived from ND patients was slightly higher than in dara naive RR patients, there was no difference in T-cell degranulation (as defined by CD107+) between groups. Importantly, the presence of high-risk cytogenetic abnormalities did not impair talquetamab-mediated MM cell lysis. This indicates that heavily pretreated and/or high-risk patients may benefit from GPRC5D-targeting bispecific antibody therapy.

Figures 10A-10C shows the impact of tumor and immune characteristics. The level of target expression was an important determinant of response, as evidenced by superior MM cell lysis in samples with higher than median GPRC5D expression (in darker dots), when compared to lower GPRC5D expression (in lighter dots). Inferior MM cell lysis was observed in samples with low T-cell counts or low effector:target (E:T) ratios, and in those with a high frequency of Tregs, PD-1+ T-cells, HLA-DR+ activated T-cells, and in older patients. These determinants of response also affected talquetamab mediated T-cell activation and degranulation. The variability of GPR5D expression and Treg count most affected talquetamab-efficacy.

As shown in Figures 11A-11D, additional cell line experiments were performed and the impact of Tregs on talquetamab efficacy was further investigated. Tregs and CD4+CD25- effector T cells were purified from a buffy coat. Tregs impaired T-cell proliferation, confirming their suppressive function. Tregs were significantly less potent to kill MM cells when redirected by talquetamab, compared to CD4+CD25- T-cells (Figure 11C). This was accompanied by reduced secretion of IFN- γ , TNF- α , IL-2 and granzyme B. Patients with high Treg counts may benefit from Treg depletion strategies, such as low-dose cyclophosphamide.

To evaluate the impact of BM stromal cells (BMSCs) on talquetamab activity, MM cell lines were co-incubated with PBMCs and patient-derived BMSCs. Direct cell-cell contact hampered MM cell lysis, while indirect contact (transwell) did not affect talquetamab activity (Figures 12A and 12B). This indicates that cell-cell contact is required to reduce talquetamab-mediated MM cell lysis, whereas BMSC-derived soluble factors alone do not impair the activity of talquetamab. The protection conferred by BMSCs against talquetamab-mediated lysis may be due to acquired resistance of MM cells (e.g., altered target expression following adhesive interactions) and/or T-cell suppression. Additional experiments showed that contact with BMSCs resulted in reduced expression of GPRC5D on RPMI-8226 and MM.1S cells, but not on UM9 cells, correlating with BMSC-mediated talquetamab resistance of RPMI-8226 and MM.1S, but not of UM9. However, talquetamab-mediated lysis was inhibited by BMSCs without a reduction in T-cell activation and degranulation, indicating the induction of cell intrinsic resistance mechanisms against the cytotoxic machinery of T cells by BMSCs. Similar results were obtained when CD4 and CD8 T cells were analyzed separately. While not wishing to be bound by theories, direct contact of MM cells with BMSCs contributed to the induction of talquetamab resistance, at least in part through reducing GPRC5D expression on MM cells. Combination strategies with established anti-MM agents could improve the efficacy of GPRC5D-targeting bispecific.

Since more T-cell redirecting bispecific antibodies targeting different tumor-associated antigens are being investigated in the field, a question was if there were shared determinants of response between bispecifics. A simultaneous evaluation of the single agent activity in 41 BM samples of both talquetamab and the BCMA-targeting bispecific antibody teclistamab (only differing in tumor-binding domain) was performed (Figures 13A-13C). MM cell lysis induced by both agents was strongly correlated. In 7 samples, both agents exhibited poor activity (<50% lysis), whereas in 9 samples very good activity was observed (>80% lysis). Comparison of characteristics between these groups showed that a low E:T ratio and high frequency of Tregs significantly impaired efficacy of both BsAbs (Figure 13B). It was also shown that LDH-levels were significantly higher in patients who exhibited poor bispecific antibody activity (Figure 13C). Altogether, it is suggested that patient-specific factors can determine response to T-cell redirectors targeting different antigens.

In summary, GPRC5D is a promising target for immunotherapeutic strategies and talquetamab showed marked *ex vivo* anti-MM activity, irrespective of disease stage or

cytogenetic risk. Tumor-related factors (GPRC5D expression) and differences in the composition of the BM microenvironment (including E:T ratio and % of Tregs) were observed, contribute to the variability in response to talquetamab. The data also indicate that strategies aiming at optimizing E:T ratio (e.g. induction therapy) or Treg depletion, can improve response to bispecific antibodies in MM.

Example 2: Nonclinical Pharmacology Studies of Talquetamab

Bispecific antibody talquetamab was generated by controlled fragment antigen binding arm exchange from two parental antibodies; GC5B596, an anti-GPRC5D antibody that originated from mouse immunization using the human GPRC5D DNA and GPRC5D overexpressing rat basophilic leukemia cells; and CD3B219, an anti-CD3 ϵ antibody that originated from a public domain antibody, SP34, which was further humanized and affinity matured. Talquetamab binds to human and cynomolgus CD3 and GPRC5D, and to rodent GPRC5D, but not to rodent CD3 (see e.g., U.S. Patent No. 10,562,968).

Talquetamab Binding to Multiple Myeloma Cell Lines

Talquetamab binds specifically to endogenous GPRC5D-expressing multiple myeloma cell lines in a dose-dependent manner, as measured by flow cytometry for all GPRC5D-positive cell lines that were tested (H929, MM.1R, and OPM-2). In contrast, Talquetamab did not bind to GPRC5D-negative cell lines, NALM-6 and Daudi cells.

Talquetamab-mediated T Cell Dependent Cytotoxicity of GPRC5D-positive Cell Lines *in Vitro*

The T cell-dependent killing potential of talquetamab in multiple myeloma cells was determined in a flow cytometry-based cytotoxicity assay. Increasing concentrations of talquetamab were incubated with pan T cells from 6 healthy donors, 3 GPRC5D-positive and 2 GPRC5D-negative cell lines, at an effector:target (E:T) ratio of 5:1. These findings revealed that talquetamab induced cell death in GPRC5D-positive cell lines after 48 hours with average half maximal effective concentration (EC₅₀) (or 20% maximal effective concentration – EC₂₀) values for H929, MM.1R, OPM-2 of 0.057 (0.029), 0.015 (0.007) and 0.214 (0.091) nM, respectively. No cell lysis was observed in the negative control (GPRC5D-negative) cell lines or with control antibodies bearing an unrelated arm (null) paired with GPRC5D or CD3. To assess the T cell activation potential of talquetamab, cells were harvested from this assay after 48 hours of incubation and analyzed by flow cytometry for the expression of the T cell activation marker (CD25). Talquetamab (but not the negative control null molecules) induced

potent T cell activation with average EC_{50} (EC_{20}) values for H929, MM.1R, OPM-2 of 0.082 (0.035), 0.014 (0.006), and 0.288 (0.168) nM, respectively, when incubated with GPRC5D-positive multiple myeloma cells and healthy donor pan T cells. This was not the case in the 2 negative control cells (NALM-6 and Daudi). *In vitro* cytokine release was assessed in the supernatant from T cell-mediated killing assay (using T cells from 6 healthy donors) with H929 cells. The observed values for the average EC_{50} (EC_{20}) were as follows: interferon (IFN)- γ : 1.120 (0.615) pg/mL; tumor necrosis factor (TNF)- α : 1.545 (0.805) pg/mL; interleukin (IL)-1 β : 0.720 (0.462) pg/mL; IL-2: 1.962 (1.380) pg/mL; IL-4: 1.867 (1.733) pg/mL; IL-6: 0.684 (0.441) pg/mL; IL-8: 0.440 (0.273) pg/mL; IL-10: 1.082 (0.670) pg/mL. Talquetamab did not cause significant activation of T cells in the absence of target GPRC5D-positive cells in *in vitro* or in whole blood assay. These findings demonstrate the specificity of talquetamab. The effect of talquetamab on cytotoxicity, T cell activation, and cytokine release was also tested in an *in vitro* assay using whole blood from healthy donors. Whole blood was incubated with GPRC5D-positive (H929) multiple myeloma cells at an E:T ratio of 5:1 with increasing concentrations of talquetamab for 48 hours. Talquetamab-induced cell death in GPRC5D-positive cell lines after 48 hours. Mean EC_{50} (EC_{20}) values for healthy donors were as follows: cytotoxicity 0.389 (0.131) nM, cytokine IL-10 0.107 (0.032) nM, and T cell activation 0.236 (0.083) nM.

20 Talquetamab-mediated T Cell Dependent Cytotoxicity of Primary Multiple Myeloma Cell Samples

The cytotoxicity effect of talquetamab was also evaluated in an *ex vivo* assay using frozen bone marrow (mononuclear cells) samples from patients with multiple myeloma (n=6) and T cells from healthy donors (at 1:1 ratio). The results revealed that talquetamab promoted a dose-dependent reduction of GPRC5D-positive primary multiple myeloma cells, which correlated with T cell activation after 48 hours. Average EC_{50} (EC_{20}) values were as follows: cytotoxicity 0.127 (0.041) nM; T cell activation 0.061 (0.016) nM. The control null antibodies had no effect on cytotoxicity or T cell activation, suggesting that the induced cell-death effect is specific for talquetamab.

30 Concentration Dependency of Talquetamab on Killing and T Cell Activation

To assess whether high concentrations of talquetamab can lead to epitope saturation on the target cells or T cells and inhibit synapse formation, T cell-mediated cytotoxicity assays were performed using H929 cells with increased concentrations of talquetamab up to 532 nM. Talquetamab showed a dose-dependent cytotoxicity and T

cell activation up to the top concentration of 532 nM and no epitope saturation effect was observed.

Effects of Talquetamab in Multiple Myeloma Xenograft Models *in Vivo*

Efficacy of GPRC5D x CD3 bispecific antibody talquetamab was evaluated in 3
5 GPRC5D-positive human multiple myeloma models in peripheral blood mononuclear cell (PBMNC)-humanized NOD scid gamma (NSG, NOD.Cg-Prkdcscid) mice. Two models were used: a prophylactic model in which treatment was initiated at the time of tumor cell implantation (H929), or an established model in which treatment was initiated after palpable tumors were formed (MM.1S and RPMI 8226).

10 For the H929 prophylactic multiple myeloma model, mice were engrafted with 10 million PBMCs one week prior to tumor inoculation with 5×10^6 H929 cells subcutaneous. Treatment with talquetamab at 0.1, 1, or 10 μg per mouse (corresponding to 0.005, 0.05, or 0.5 mg/kg) was initiated immediately and repeated every 3 to 4 days thereafter for a total of 5 doses. Talquetamab elicited complete blockade of tumor
15 formation at dose levels of either 10 or 1 $\mu\text{g}/\text{mouse}$, and 0.1 $\mu\text{g}/\text{mouse}$ either blocked tumor formation or significantly suppressed growth as compared with phosphate-buffered saline (PBS)-treated control mice (97.6% mean tumor growth inhibition as compared with control mice, $p < 0.01$).

For the established MM.1S multiple myeloma model, NSG mice were inoculated
20 with 1×10^7 cells subcutaneously. One week later 10 million PBMCs were engrafted. Two weeks after tumor cell implantation, treatment with either GPRC5D x CD3 bispecific antibody talquetamab (0.1, 1, 10, or 50 μg per mouse), CD3 x null, or GPRC5D x null (10 μg per mouse) was initiated and repeated every 3 to 4 days thereafter for a total of 7 doses. Antitumor efficacy was observed with 10 and 50 $\mu\text{g}/\text{animal}$ dose
25 levels of talquetamab bispecific antibody, with 10 out of the 10 complete responses (CR) (100% tumor regressions) in each group. Moreover, the 1 μg per mouse dose significantly inhibited tumor growth by 65% as compared with PBS-treated control animals ($p \leq 0.05$), whereas the CD3 x null bispecific antibody nor the GPRC5D x null bispecific antibody failed to suppress tumor growth in the model.

30 A separate regression study using RPMI 8226 target cells expressing minimal GPRC5D protein and human purified T cells from a healthy donor as effector cells showed that talquetamab had no effect on the tumor regression. GPRC5D was present at low levels. Additional studies on preclinical activity and determinants of response of

talquetamab in MM are described in Verkleij et al., *Blood Advances*, 2021, 5(8): 2196-2215, the content of which is incorporated herein by reference in its entirety.

Example 3: Toxicology and Safety Pharmacology

Toxicology

5 Talquetamab was administered IV once weekly for 4 weeks in a non-good laboratory practice (GLP) tolerability study in cynomolgus monkeys and was well tolerated up to 30 mg/kg. There were no talquetamab related clinical signs, significant pharmacodynamic effects (e.g., cytokine release) or adverse effects on safety parameters. Other notable changes were non-adverse and generally consistent with the expected
10 mechanism of action of talquetamab and included transient and mild decreases in lymphocyte counts. It was determined that talquetamab had an approximately 100-fold lower *in vivo* pharmacological activity to GPRC5D in cynomolgus monkeys compared with humans. Based on the poor cross-reactivity, lack of adverse effects, and minimal pharmacodynamic effects observed in this study, further nonclinical safety studies with
15 talquetamab in the cynomolgus monkey were not considered useful for human risk assessment.

Therefore, hazard identification studies in cynomolgus monkey were conducted with the surrogate molecule, talquetamab, which had cross-reactivity to cGPRC5D, and its functional activity in cynomolgus monkey cells was similar to the activity of
20 talquetamab in human cells and was considered pharmacologically relevant in cynomolgus monkey. In an exploratory 2-week tolerability study (2 weekly doses of 0, 0.3, 3, and 10 mg/kg) and a pivotal 1-month GLP study that included safety pharmacology assessments (4 weekly doses of 0, 10, and 30 mg/kg), talquetamab was well tolerated and no effects were noted on safety pharmacology parameters
25 (cardiovascular, respiratory, or central nervous system function).

Overall, there was no robust pharmacodynamic or toxicological response in cynomolgus monkey with the study drug (talquetamab) that is typically expected from this class of molecule at the high doses tested. The minimal pharmacodynamics response with the surrogate molecule is potentially due to low target expression or low
30 target cell (plasma cells) numbers in healthy cynomolgus monkeys. Hence, the results highlight the limitations of the cynomolgus monkey to provide useful information about risk assessment associated with targeting GPRC5D in patients with multiple myeloma (i.e., limited translatability of these nonclinical toxicity findings to patient who may carry a greater target cell burden).

Local Tolerance

In a local tolerance study, a single subcutaneous (SC) injection of talquetamab (20 mg) was well tolerated in male New Zealand White rabbits. There were no adverse dermal observations at the injection sites (evaluated up to 72 hours post-dose), and no gross or microscopic findings at the injection sites or in draining lymph nodes. As the rabbit is not a pharmacologically relevant species for targeting of GPRC5D by talquetamab, this study only assessed the tolerability of the formulation.

Tissue Cross-reactivity, Serum, Hemolytic, and Cytokine Potential (*in Vitro* Studies)

An *in vitro* GLP tissue cross-reactivity study in human tissues showed biotinylated talquetamab staining on the membrane and cytoplasm of mononuclear leukocytes (likely due to binding to CD3) in human lymphoid tissues (lymph node, spleen, thymus, tonsil, bronchus-associated lymphoid tissue in the lung, and gut-associated lymphoid tissue in the gastrointestinal tract), and select non-lymphoid tissues (mononuclear cells in bladder, breast, colon, fallopian tube, kidney, liver, ovary, parathyroid, peripheral nerve, pituitary, placenta, prostate, salivary gland, thyroid, ureter, and uterus (cervix, endometrium)). No unanticipated cross-reactivity was observed. The ability of talquetamab to induce cytokine release in human donor blood was assessed using the soluble phase assay format assay. A solid phase assay format was also tested. In the soluble phase format, talquetamab induced statistically significant, dose-dependent increases in IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-13, IFN γ , and TNF α , relative to control.

Estimates of population EC₂₀ values of talquetamab were: 346.39 nM for IL-1 β , 195.49 nM for IL-2, 519.20 nM for IL-8, 6616.99 nM for IFN γ , and 859.97 nM for TNF α . EC₂₀ values could not be calculated for IL-6, IL-10, and IL-13 due to lack of a 4-parameter curve fit. In the solid phase format assay relative to control, talquetamab induced statistically significant release in 9 of the 10 cytokines (IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IFN γ , and TNF α). However, population EC₂₀ estimates could not be calculated for any of the cytokines induced due to lack of a 4-parameter curve fit. Because of the nature of response (e.g., biphasic response, poor curve fitting, and similar profile to the negative control), the biological relevance of the solid phase assay is unclear. Talquetamab did not cause hemolysis in whole human blood and was compatible with human serum at concentrations between 0.10 and 10 mg/mL.

In cynomolgus monkeys, systemic talquetamab exposure (maximum observed serum concentration [C_{max}] and area under the serum concentration versus time curve [AUC]) increased with dose in an approximately dose-proportional manner following IV

administration of talquetamab as a single dose of 0.5 and 5 mg/kg in an rHSA formulation or 0.5 mg/kg in formulation buffer in a pharmacokinetic study. Talquetamab exposure also increased with dose in an approximately dose-proportional manner following weekly doses of 0.5 to 30 mg/kg in an exploratory 4-week tolerability study.

- 5 The serum half-life of talquetamab was estimated at 9 to 12 days in cynomolgus monkeys.

Example 4: Nonclinical Immunogenicity

- A preliminary evaluation on immunogenicity risk for talquetamab was conducted. Given the similarity of talquetamab to native human monoclonal antibodies,
- 10 the risk of immunogenicity is expected to be low to moderate, similar to other human therapeutic monoclonal antibodies. In the non-GLP single-dose pharmacokinetic study of talquetamab, immunogenicity results showed that 8 out of the 12 animals treated with talquetamab tested positive for anti-drug antibody (ADA). In the non-GLP multiple-dose studies of talquetamab, data suggest the presence of ADA (2 out of the 12 animals).
- 15 However, ADA was not monitored in either of these studies. When compared to the ADA-negative animals in the same dose group, all ADA-positive animals exhibited either lower drug exposure prior to the last dose on Day 22 or faster concentration decrease after the dose.

Example 5: Phase 1 Study of Talquetamab Administered as Monotherapy for Relapsed or Refractory Multiple Myeloma

- A first-in-human (FIH), phase 1, open-label, multicenter study of talquetamab administered to adult subjects with relapsed or refractory multiple myeloma was carried out (NCT03399799). The study was conducted in 2 parts, separately for IV and SC administration: dose escalation (Part 1) and dose expansion (Part 2). The overall aim of
- 25 the study was to evaluate the safety of talquetamab. Safety was monitored by a Study Evaluation Team (SET). A diagram of the dose escalation scheme is provided in Figure 1.

Subject Population

- The inclusion and exclusion criteria for enrolling subjects in this study are
- 30 described below.

Inclusion Criteria

≥18 years of age.

Documented initial diagnosis of multiple myeloma according to International Myeloma Working Group (IMWG) diagnostic criteria.

Subjects with measurable multiple myeloma who have progressed on, or could not tolerate, all available established therapies.

Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

Clinical laboratory values at screening:

Hematology	
Hemoglobin	≥ 8.0 g/dL (≥ 5 mmol/L) (must be without red blood cell [RBC] transfusion within 7 days prior to the laboratory test; recombinant human erythropoietin use is permitted).
Platelets	$\geq 50 \times 10^9$ /L (must be without transfusion support or platelet stimulating factor in the 7 days prior to the laboratory test)
Absolute Neutrophil Count (ANC)	$\geq 1.0 \times 10^9$ /L (prior growth factor support is permitted but must be without support in the 7 days prior to the laboratory test)
Chemistry	
Aspartate Aminotransferase or Alanine Aminotransferase	$\leq 3.0 \times$ upper limit of normal (ULN)
Creatine	≥ 40 mL/min/1.73 m ² based upon Modified Diet in Renal Disease formula calculation.
Total bilirubin	$\leq 2.0 \times$ ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin $\leq 1.5 \times$ ULN is required)
Corrected serum calcium	≤ 14 mg/dL (≤ 3.5 mmol/L) or free ionized calcium < 6.5 mg/dL (< 1.6 mmol/L).

5

Women of childbearing potential (WOCBP) must have a negative pregnancy test at screening and prior to the first dose of study drug using a highly sensitive pregnancy test either serum (β human chorionic gonadotropin [β -hCG]) or urine.

Before the first dose of study drug: Women of childbearing potential and fertile men who are sexually active must agree to use a highly effective method of contraception ($< 1\%$ / year failure rate) during the study and for 100 days after the last dose of study drug.

Sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to and able participate in the study.

Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard of care for the subject's disease.

15

Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

- 5 Prior Grade 3 or higher CRS related to any T cell redirection (e.g., CD-3 redirection technology or CAR-T cell therapy) or any prior GPRC5D targeting therapy.
- Prior antitumor therapy as follows, prior to the first dose of study drug:
 - Gene modified adoptive cell therapy (e.g., chimeric antigen receptor modified T cells, natural killer [NK] cells) within 3 months.
 - Targeted therapy, epigenetic therapy, or treatment with an investigational drug or an
 10 invasive investigational medical device within 21 days or at least 5 half-lives, whichever is less.
 - Monoclonal antibody treatment for multiple myeloma within 21 days.
 - Cytotoxic therapy within 21 days.
 - Proteasome inhibitor therapy within 14 days.
 - 15 Immunomodulatory agent therapy within 7 days.
 - Radiotherapy within 21 days. However, if the radiation portal covered $\leq 5\%$ of the bone marrow reserve, the subject is eligible irrespective of the end date of radiotherapy.
 - Vaccinated with live, attenuated vaccine within 4 weeks or as recommended by the
 20 product manufacturer prior to the first dose, during treatment, or within 100 days of the last dose of talquetamab.
 - Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy.
 - Received a cumulative dose of corticosteroids equivalent to ≥ 140 mg of prednisone
 25 within the 14-day period before the first dose of study drug.
 - Received either of the following:
 - An allogenic stem cell transplant within 6 months before first dose of study drug.
 - Subjects who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks without signs of GVHD.
 - 30 An autologous stem cell transplant ≤ 12 weeks before first dose of study drug.
 - Central nervous system (CNS) involvement or clinical signs of meningeal involvement of multiple myeloma. If either is suspected, negative whole brain magnetic resonance imaging (MRI) and lumbar cytology are required.

- Plasma cell leukemia ($>2.0 \times 10^9/L$ plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein [M-protein], and skin changes), or primary amyloid light chain (AL) amyloidosis.
- 5 Known to be seropositive for human immunodeficiency virus or acquired immune deficiency syndrome.
- Hepatitis B infection as defined according to the American Society of Clinical Oncology guidelines. In the event the infection status is unclear, quantitative levels are necessary to determine the infection status. Active Hepatitis C infection as
- 10 measured by positive HCV-RNA testing. Subjects with a history of Hepatitis C virus antibody positivity must undergo HCV-RNA testing.
- Pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.
- Known allergies, hypersensitivity, or intolerance to talquetamab or its excipients.
- 15 Any serious underlying medical condition, such as:
- Evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection;
- Active autoimmune disease or a documented history of autoimmune disease
- Psychiatric conditions (e.g., alcohol or drug abuse), severe dementia, or altered mental status; and
- 20 Any other issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
- 25 Pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 100 days after the last dose of study drug.
- Plans to father a child while enrolled in this study or within 100 days after the last dose of study drug.
- Major surgery within 2 weeks of the first dose, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate
- 30 in the study or within 2 weeks after the last dose of study drug administration. (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate).

The subjects must agree to not donate blood or blood components during the study and for 100 days after the last doses of study drug.

NOTE: All study inclusion/exclusion criteria were ensured to have been met at screening and prior to the first dose of study drug. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug was given such that he or she no longer meets all eligibility criteria, supportive treatment might be administered according to local standards of care, if necessary, so that eligibility criteria might be met and laboratory test(s) might be repeated once, to determine if the subject qualified for the study. If inclusion/exclusion criteria were not met after further evaluation, the subject should be excluded from participation in the study.

Pharmacokinetics, Immunogenicity, and Receptor Occupancy

Evaluations

Blood and serum samples were collected for talquetamab pharmacokinetics, receptor occupancy (RO), and immunogenicity (antibodies to talquetamab assessment). Also, a pharmacokinetic/immunogenicity sample would be collected any time a suspected infusion-related reaction (IRR) or cytokine release syndrome (CRS) event (in case of a CRS event, samples will be collected at onset, 24 hours, and 72 hours) was observed during the study. In addition, pharmacokinetic and immunogenicity samples were collected at the End-of-Treatment visit following study drug discontinuation. The exact dates and times of blood sampling were recorded on the laboratory requisition forms. Collected samples were stored under specified controlled conditions for the temperatures indicated in the Laboratory Manual.

Venous blood samples were collected for measurement of serum concentrations of talquetamab. The serum sample would be evenly divided into 2 aliquots (1 for pharmacokinetics; 1 for backup). At timepoints where serum concentration and antibodies to talquetamab would be evaluated, 1 blood draw was collected and the serum was evenly divided into 3 aliquots (1 each for pharmacokinetics, antibodies to study drug, and a backup).

Blood samples were collected for RO. Bone marrow aspirate might also be analyzed for pharmacokinetics, if feasible. Data were used for mechanistic pharmacokinetic/pharmacodynamic modeling. Samples collected for analyses of talquetamab serum concentration and antibody to talquetamab might be used to evaluate soluble B cell maturation antigen (sBCMA) or to evaluate safety or efficacy aspects that

address concerns arising during or after the study period for further characterization of immunogenicity.

Analytical Procedures

Pharmacokinetics: Serum samples were analyzed to determine concentrations of talquetamab using a validated, specific, and sensitive assay method by or under the supervision of the sponsor.

Immunogenicity: The detection and characterization of anti-talquetamab antibodies were performed using a validated or appropriately qualified assay methods by or under the supervision of the sponsor. All samples collected for detection of antibodies to talquetamab would also be evaluated for talquetamab serum concentration to enable interpretation of the antibody data.

Pharmacokinetic Parameters

Blood samples were collected from all subjects for the measurement of serum talquetamab concentration for pharmacokinetic analyses. Pharmacokinetic parameters were estimated for individuals, and descriptive statistics were calculated for each dose level. $C_{\max}$ and AUC with dose might also be explored. Pharmacokinetic parameters include, but were not limited to, AUC_{inf} , $AUC_{(0-t)}$, AUC_{tau} , $C_{\max}$, $T_{1/2}$, time to reach the $C_{\max}$ ($T_{\max}$), CL (for IV administration), CL/F (for SC administration), volume of distribution at steady-state (V_{ss} for IV administration); and V_{ss} /F (for SC administration) parameters were calculated if sufficient data were available for estimation. (AUC: area under the serum concentration versus time curve; AUC_{inf} : area under the serum concentration versus time curve from time 0 to infinity with extrapolation of the terminal phase; $AUC_{(0-t)}$: area under the concentration-time curve from time zero to time t; AUC_{tau} : area under the serum concentration versus time curve during a dose interval time period (tau) at steady-state; $C_{\max}$: maximum observed serum concentration; $T_{1/2}$: half-life; $T_{\max}$: time to reach the $C_{\max}$ (multiple doses); CL: total systemic clearance of drug after intravenous administration; V_{ss} : volume of distribution at steady-state).

Immunogenicity Assessments / Antibodies to Talquetamab

Antibodies to talquetamab were evaluated in serum samples collected from all subjects according to schedules. Additionally, serum samples were also collected at the final visit from subjects who were discontinued from treatment or withdrawal from the study. These samples were tested by the sponsor or sponsor's designee.

Serum samples were screened for antibodies binding to talquetamab and the titer of confirmed positive samples were reported. The ADA-positive (anti-drug antibody-positive) samples were tested for neutralizing antibodies to talquetamab. Immune response analysis might be conducted on pharmacokinetic samples collected at other
5 timepoints, if deemed necessary.

Receptor Occupancy (RO)

Whole blood samples were analyzed for RO via flow cytometry. Samples were collected to evaluate RO to quantify the binding of therapeutics to CD3 on the cell surface. RO samples were collected in Part 2 if the RO sample results from Part 1 were
10 comprehensive and meaningful for drug response. Sample was collected from all subjects, based on emerging data, prior to the first intravenous (IV) priming dose and for some subjects treated with higher subcutaneous (SC) dosing.

Biomarker Evaluations

Biomarker evaluations were completed in both Part 1 and Part 2. The biomarker
15 assessments focused on several main objectives: 1) evaluate cytokine production in response to study drug administration; 2) evaluate the immune responses indicative of T cell redirection for potential contributions to study drug response; 3) determine the clinical benefit of study drug in subjects with cytogenetic modifications (del17p, t(4;14), t(14;16), or other high-risk molecular subtypes); and 4) determine the ability of study
20 drug to reduce minimal residual disease (MRD) in subjects who had at least a complete response (CR). All biomarker assessments were performed at a central laboratory. If it became necessary, additional biomarker samples might be collected to help understand an unexplained event and specifically additional sample(s) for cytokines would be collected any time a suspected IRR or CRS event was observed or reported during the
25 study.

Biomarker analyses were dependent upon the availability of appropriate biomarker assays and might be deferred or not performed, if during or at the end of the study, it became clear that the analysis would not have sufficient scientific value for biomarker evaluation, or if there were not enough samples or responders to allow for
30 adequate biomarker evaluation. In the event the study was terminated early or showed poor preliminary clinical antitumor activity, completion of biomarker assessments was based on justification and intended utility of the data.

Additional Collections

Based on emerging scientific evidence, the sponsor might request additional material from previously collected bone marrow samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

5 *Pharmacodynamic Markers*

Serum samples were collected before and at multiple time points after talquetamab administration at step-up or full treatment doses as scheduled. Cytokine were detected and measured using multi-plexed analyte panels (Luminex or MEsoScaleDiscovery technology). Analyses monitored included, but were not limited to
10 TNF- α , IL-2, IL-6, INF- γ , IL-10, and IL-2R α , which can inform on relative activation of immune cells.

Whole blood samples and bone marrow aspirate samples might be analyzed to evaluate tumor and immune cell populations by flow cytometry and/or cytometry by time of flight (CyTOF) in order to determine if treatment with talquetamab results in
15 increased antitumor activity by redirected T cell-mediated killing of GPRC5D-positive multiple myeloma cells and increased activation of cytotoxic T cells. Whole blood T cell functionality assays might also be performed to study how this could affect drug response.

For these analyses, whole blood samples collected pre- and post-talquetamab
20 administration were analyzed using multi-color flow cytometry to assess immune populations, including, but not limited to, CD8+, CD4+ total and regulatory T cells, as well as naïve and memory T cell subsets. In addition, activation/exhaustion markers including CD25, PD-1, TIM-3, LAG-3, HLA-DR and CD38 were also measured on CD8+ and CD4+ total and naïve/memory T cell sub.

25 *Predictive Biomarkers*

Some genetic mutations/translocations are known to confer a poor prognosis in multiple myeloma therapy and resistance. Therefore, DNA/RNA sequencing from tumor cells might be performed, for translocation/mutation/genomic analysis to assess whether specific molecular subgroups such as del17p, t(4;14), t(14;16) or other risk associated
30 mutations/translocations were responsive to treatment and to identify potential predictive biomarkers of response and/or resistance.

GPRC5D and PD-L1 expression on plasma cells at baseline may also be measured by flow cytometry on multiple myeloma cells in bone marrow samples to

determine if antigen expression level or checkpoint ligand upregulation is a predictive biomarker of response.

- Baseline immunophenotyping, including, but not limited to, frequency and activation/exhaustion of T cell subsets may also be performed on bone marrow aspirates to determine potential predictive biomarkers of response and/or resistance.

Minimal Residual Disease

- Minimal residual disease negativity was being evaluated in the field as a potential surrogate for progression-free survival (PFS). Baseline bone marrow aspirates will be used to define the myeloma clones, and posttreatment samples would be used to evaluate MRD negativity in those subjects who experience a CR/stringent complete response (sCR). A fresh bone marrow aspirate was to be collected at screening, where clinically feasible. If bone marrow aspirate was not available at screening, non-decalcified diagnostic tissue, such as non-decalcified slides (bone marrow aspirate, touch preparation or clot selection) or formalin-fixed, paraffin-embedded block (clot section only, no bone marrow biopsy), must be supplied for MRD assessment instead. Minimal residual disease would be monitored in subjects using next generation sequencing on bone marrow aspirate DNA. If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment might be utilized.

Pharmacokinetic/Pharmacodynamic Evaluations

- Pharmacokinetic/pharmacodynamic modeling was explored to understand and characterize the exposure-response relationship.

Efficacy Evaluations

- Disease evaluations were performed at the end of each treatment cycle and prior to the start of the next cycle. Disease evaluations scheduled for treatment days should be collected before study drug is administered. Disease evaluations would be performed by a central laboratory until disease progression. This study would use the 2016 IMWG-based response criteria. If it was determined that the study drug interferes with the immunofixation assay, CR would be defined as the disappearance of the original M-protein associated with multiple myeloma on immunofixation, and the determination of CR would not be affected by unrelated M-proteins secondary to the study drug. Subjects who relapse should not be taken off treatment and disease evaluations would continue until disease progression is confirmed.

Disease progression must be consistently documented across clinical study sites. Note: the onset of new or increased size of soft tissue plasmacytomas and lytic bone

lesions observed during Cycle 1 would not be considered disease progression. The sponsor would use a validated computer algorithm to assess response to treatment.

Myeloma Protein Measurements in Serum and Urine

- Blood and 24-hour urine samples for M-protein measurements were analyzed by
- 5 the central laboratory. The following tests were required:
- Serum protein electrophoresis;
 - Serum immunofixation electrophoresis at screening and thereafter when M-protein is non-quantifiable;
 - Serum FLC assay;
 - 10 24-hour urine M-protein quantitation by electrophoresis;
 - Urine immunofixation electrophoresis at screening and thereafter when M-protein is non-quantifiable;
 - Serum β -microglobulin at screening; and
 - Serum quantitative immunoglobulins (IgG, IgA, IgM, IgE, and IgD) at screening.

- 15 Samples for serum quantitative immunoglobulins (IgG, IgA, IgM, IgE, and IgD) were also collected at screening and every 4 weeks thereafter to be analyzed locally. Blood and 24-hour urine samples were collected until the development of confirmed disease progression. Disease progression based on one of the laboratory tests alone were confirmed by at least 1 repeat investigation performed 1 to 3 weeks later. Disease
- 20 evaluations would continue beyond relapse from CR until disease progression was confirmed. Serum and urine immunofixation and serum free light chain (FLC) assay would be performed at screening and thereafter when a CR was suspected (when serum or 24-hour urine M-protein electrophoresis [by serum protein electrophoresis or urine M-protein quantitation by electrophoresis (UPEP)] were 0 or non-quantifiable). Both serum
- 25 and urine immunofixation test would be performed routinely for subjects with light chain multiple myeloma.

Serum Calcium Corrected for Albumin

- Blood samples for calculating serum calcium corrected for albumin were collected and analyzed at the central laboratory until the development of confirmed
- 30 disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL [>2.8 mmol/L]) could indicate disease progression or relapse if it was not attributable to any other cause. Calcium bound to albumin and only the unbound (free) calcium was biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium").

Measurement of free ionized calcium was an acceptable alternative to corrected serum calcium for determining hypercalcemia. Free ionized calcium levels greater than the upper limit of normal (ULN) are considered to be hypercalcemic for this study.

Bone Marrow Examination

- 5 For all subjects, bone marrow aspirate or biopsy were performed for clinical assessments and biomarker evaluations. Clinical staging (morphology, cytogenetics, and immunohistochemistry or immunofluorescence or flow cytometry) might be done by a local laboratory. A bone marrow aspirate sample was required to confirm CR and sCR; the sample must be collected and the results obtained prior to the next scheduled dose of
- 10 study drug. A bone marrow aspirate sample was also collected at Cycle 3 Day 1 and at the time of disease progression, if clinically indicated.

In addition, MRD might be evaluated at the time of suspected CR/sCR, and for subjects with confirmed CR/sCR, an additional bone marrow aspirate was obtained 12 months post C1D1 (± 1 month) and yearly (± 1 month) thereafter.

15 *Skeletal Survey*

- A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) was to be performed during the screening phase and evaluated locally by either roentgenography or low dose CT scans without the use of IV contrast.
- 20 During the treatment phase, and before disease progression was confirmed, X-rays, or CT scans would be performed locally, whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging was an acceptable method for evaluation of bone disease and might be included at the discretion of the investigator; however, it would not replace the skeletal survey. If a radionuclide bone
- 25 scan was used at screening in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. Note: a radionuclide bone scan would not replace a complete skeletal survey.

- Subjects might present with disease progression manifested by symptoms of pain due to bone changes. Therefore, disease progression might be documented, in these
- 30 cases, by skeletal survey or other radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression was obvious by radiographic investigations, then no confirmatory X-rays were necessary. In instances in which changes were subtler, a repeat X ray might be needed in 1 to 3 weeks.

Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the screening phase. Clinical examination or MRI might be used to document extramedullary sites of disease. CT scan evaluations were an acceptable alternative if there is no contraindication to the use of IV contrast. Positron emission tomography (PET)-CT was allowed if CT alone was not available. Ultrasound tests were not acceptable to document the size of extramedullary plasmacytomas.

Extramedullary plasmacytomas were assessed for all subjects with a history of plasmacytomas or if clinically indicated at screening, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease would be performed, measured, and evaluated locally every 4 weeks (for physical examination) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects until development of confirmed CR or confirmed disease progression. If assessment could only be performed radiologically, then evaluation of extramedullary plasmacytomas might be done every 12 weeks ($\pm$ 2 weeks). For every subject, the methodology used for evaluation of each disease site was consistent across all visits. Irradiated or excised lesions would be considered not measurable and would be monitored only for disease progression.

To qualify for partial response (PR) or minimal response (MR), the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50% or 25%, respectively, and new plasmacytomas must not have developed. To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50% or a new plasmacytoma must have developed, except in Cycle 1. In the cases where not all existing extramedullary plasmacytomas were reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, this would also qualify as disease progression.

Criteria for Response to Multiple Myeloma Treatment

Response	Response Criteria
Stringent complete Response (sCR)	CR as defined below, <i>plus</i> Normal FLC ratio, <i>and</i> Absence of clonal PCs by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry
Complete response (CR)*	Negative immunofixation on the serum and urine, <i>and</i> Disappearance of any soft tissue plasmacytomas, <i>and</i> <5% PCs in bone marrow

Very good partial Response (VGPR)*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal response (MR)	≥25% but ≤49% reduction of serum M-protein, <i>and</i> Reduction in 24-h urine M-protein by 50-89% In addition to the above criteria, if present at baseline, a 25% to 49% reduction in the size of soft tissue plasmacytomas also is required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or PD
Progressive disease (PD)†	Increase of 25% from lowest response value in any one of the following: Serum M-component (absolute increase must be ≥0.5 g/dL) Urine M-component (absolute increase must be ≥200 mg/24 hours) Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder
CR=complete response; FLC=free light chain; IMWG=International Myeloma Working Group; M-protein=monoclonal paraprotein; MR=minimal response; PC=plasma cell; PD=progressive disease; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response	
All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases	

of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

*Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a >90% decrease in the difference between involved and uninvolved FLC levels.

†Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in subjects without measurable disease by M-protein and by FLC levels; “25% increase” refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the “lowest response value” does not need to be a confirmed value.

^a Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

Clinical Relapse

Clinical relapse is defined using the definition of clinical relapse in IMWG criteria (Durie 2006; Kumar 2016, Rajkumar 2011). In IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, MRI, or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL; >2.875 mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥ 177 mM/L)
6. Hyperviscosity

In some subjects, bone pain may be the initial symptom of relapse in the absence of any of the above features. However, bone pain without imaging confirmation is not adequate to meet these criteria in studies.

Objectives and Endpoints

Objectives	Endpoints
Primary	
Part 1 (Dose Escalation): To characterize the safety of talquetamab and recommend the Phase 2 dose(s) and schedule Part 2 (Dose Expansion): To further characterize the safety of talquetamab at the recommended Phase 2 dose(s) (RP2Ds)	Part 1 (Dose Escalation): Frequency and type of DLT, and frequency and severity of adverse events, serious adverse events, and laboratory abnormalities Part 2 (Dose Expansion): Frequency and severity of adverse events, serious adverse events, and laboratory abnormalities
To characterize the pharmacokinetics and pharmacodynamics of talquetamab	Pharmacokinetic parameters and pharmacodynamic markers including but

To assess the immunogenicity of talquetamab To evaluate the preliminary antitumor activity of talquetamab at the RP2D(s) in Part 2	not limited to depletion of GPRC5D expressing cells, systemic cytokine concentrations, and markers of T cell activation Presence of anti-talquetamab antibodies Assess the ORR (at least a PR or better); CBR; DOR and TTR; and PFS, as defined by the IMWG response criteria
Secondary	
To explore the relationships between pharmacokinetics, pharmacodynamics, adverse event profile, and clinical activity of talquetamab. To investigate predictive biomarkers of response or resistance to talquetamab. To investigate the immunoregulatory activity of talquetamab. To quantify receptor occupancy (RO), when feasible. To evaluate MRD negativity rates. To evaluate the exposure-response relationship.	

CBR: clinical benefit rate; DOR: duration of response; TTR: time to response; PFS: progression-free survival; MRD: minimal residual disease.

Part 1 (Dose Escalation Part) – Dosing Schedule

- 5 IV administration: A whole blood *in vitro* assay system from healthy human donors was used to estimate the minimum anticipated biologic effect level (MABEL)-based starting dose. A dose of 0.5 µg/kg IV administered over approximately 4-hours once every 2 weeks was selected based on the lowest mean EC₂₀ from the most relevant assay among T cell activation, cytotoxicity, and cytokine release. Subsequent bi-weekly
- 10 IV dose levels were selected based on the review of all available data including, but not limited to, pharmacokinetic, pharmacodynamic, safety, and preliminary antitumor activity data. Preliminary first dose pharmacokinetic results from 3 subjects (dose range 0.5 to 1.0 µg/kg) following bi-weekly IV dosing with talquetamab showed that T_{1/2} ranged from 2.12 to 6.47 days. Based on the safety profile and preliminary
- 15 pharmacokinetic data, weekly IV dosing with talquetamab was initiated. Subsequent dose levels were selected based on a statistical model using all available data to identify safe and tolerable putative RP2D(s), defined as the dose(s) and schedule(s) of talquetamab for characterization in Part 2.

- 20 SC administration: talquetamab was administered subcutaneously (SC) on a weekly dosing schedule. Dose escalation for the SC dosing cohort began with a 1.5 µg/kg priming dose administered SC on Day -7, followed by a full dose of 5 µg/kg administered SC on Days 1, 8, and 15 of a 21-day cycle. Subsequent SC dose levels were selected based on a statistical model using all available data to identify safe and

tolerable putative RP2D(s), defined as the dose(s) of talquetamab for characterization in Part 2.

The following dosage levels had been tested in 182 patients and the cut-off date for the analyses was April 18, 2021:

5

Bi-weekly IV (N=26)	Weekly IV (N=76)	Weekly SC (N=63)	Bi-weekly SC (N=22)
Cohort 1 (0.5 µg/kg) = 1 Cohort 2 (1.0 µg/kg) = 2 Cohort 3 (1.5 µg/kg) = 10 Cohort 4 (2.25 µg/kg) = 11 Cohort 5 (3.38 µg/kg) = 2	Cohort 6 (2.25 µg/kg) = 12 Cohort 7 (1.5 µg/kg) = 6 Cohort 8 (1.5+3.38 µg/kg) = 12 Cohort 9 (1.5+5 µg/kg) = 12 Cohort 10 (1.5+7.5 µg/kg) = 10 Cohort 11 (1.5+11.25 µg/kg) = 6 Cohort 13 (1.5/1.5+20 µg/kg) = 3 Cohort 14 (1.5/10+20 µg/kg) = 6 Cohort 19 (1.5/10+60 µg/kg) = 6 Cohort 21 (1.5/10/60+180 µg/kg) = 3	Cohort 12 (1.5+5 µg/kg) = 4 Cohort 15 (5+15 µg/kg) = 4 Cohort 16 (10+45 µg/kg) = 6 Cohort 17 (10/45+135 µg/kg) = 5 Cohort 18 (10/45+135 µg/kg) = 3 Cohort 20 (10/60+405 µg/kg) = 12 Cohort 22 (10/60/300+800 µg/kg) = 11 Cohort 23 PT 2 (10/60 + 405 µg/kg) = 18	Cohort 24 (10/60/300 + 800 µg/kg) = 15 Cohort 26+27 PT2 (10/60/300 + 800 µg/kg) = 8 Cohort 28 (10/60/300 + 1200 µg/kg) = 9

See also Fig. 1B for the study design.

Results of Part 1 (Dose Escalation) (Cut-off Date for Analyses October 24, 2020)

10 Eligible patients have measurable MM per International Myeloma Working Group (IMWG) criteria and have progressed on or could not tolerate established therapies. The primary objectives of the dose escalation phase are to characterize the safety of talquetamab and to identify a recommended phase 2 dose (RP2D). Escalating doses of IV or SC talquetamab (0.5-800 µg/kg) with and without step-up dosing were

assessed. Key secondary objectives include characterizing the pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of talquetamab. Adverse events (AEs) were graded using the Common Terminology Criteria for AE, v4.03, and cytokine release syndrome (CRS) was graded according to Lee et al (Blood 2014;124:188).

5 Response was assessed by the investigator according to IMWG criteria. Among the subjects evaluated, 102 received talquetamab by IV and 29 received talquetamab by SC. Median age was 65 years (range 33 – 80; 32% were ≥ 70) and 23% had International Staging System stage III disease. Median number of prior therapies was 6 (range 2-20), 87% of subjects were refractory to last line of therapy, 80% triple-
10 class refractory, 75% penta-class exposed, and 33% penta-class refractory. Thirteen (10%) subjects had prior selinexor therapy, and 21 (15%) had prior BCMA-directed therapy.

 Most common all-grade hematologic AEs were anemia (52%), neutropenia (47%), and lymphopenia (41%). Most common all-grade nonhematologic AEs were
15 CRS (47%), dysgeusia (33%), and fatigue (32%). Two dose-limiting toxicities of clinically asymptomatic grade 4 increased lipase in the setting of a pancreatic plasmacytoma (7.5 $\mu\text{g/kg}$ IV; unresolved) and grade 3 maculopapular rash (135 $\mu\text{g/kg}$ SC; resolved after 3 days) were reported. Treatment-related grade 3-4 AEs were reported in 50% of patients, with lymphopenia (21%) and neutropenia (16%) being most
20 frequent. Infections were reported in 38% of patients, and treatment-related infusion/injection site reactions (IV and SC) were reported in 16%.

 CRS was reported in 48% of patients, and all events were grade 1-2 except for 4 (3%) events of grade 3 severity. CRS was generally confined to the first cycle, and the severity appears to be mitigated by implementation of step-up dosing and SC
25 administration. Neurotoxicity was reported in 7 (5%) patients; 4 had grade 1-2 events and 3 had grade 3 delirium (n=2) and confusion (n=1). Neurotoxicity events occurred in the context of CRS in 4 patients.

 PK results from IV dosing indicated that the half-life of talquetamab supports weekly dosing. SC results showed lower C_{max} with comparable trough levels than that of
30 IV dosing (at a similar dose) which makes it a favorable administration option.

 Talquetamab treatment led to pharmacodynamic changes supporting mechanism of action, including increases in T cell activation and cytokines such as IL-10, IL-2R α and IL-6. Comparable induction of pharmacodynamic markers was seen with IV and SC dosing.

Overall response rates were 32% and 36% for IV and SC cohorts, respectively.

In the more recent dose escalation cohorts, the response rates have continued to improve (IV: 20 µg/kg [67%], 60 µg/kg [100%]; SC: 135 µg/kg [50%], 405 µg/kg [100%]).

- Responses were noted early at the 1.0 µg/kg dose, and stringent complete responses were achieved starting at the 1.5 µg/kg dose.

Table 5: Summary of Best Overall Response

	IV (Q2W and QW)				SC (QW)		
Response, n (%)	0.5-11.25 µg/kg (n=83)	20 µg/kg (n=9)	60 µg/kg (n=6)	180 µg/kg (n=2)	5-45 µg/kg (n=13)	135 µg/kg (n=8)	405 µg/kg (n=3)
ORR	21 (25)	6 (67)	6 (100)	1 (50)	2 (15)	4 (50)	3 (100)
≥VGPR	10 (12)	5 (56)	4 (67)	0	0	1 (13)	1 (33)
Best Response							
sCR	4 (5)	0	1 (17)	0	0	0	0
CR	1 (1)	0	0	0	0	0	0
VGPR	5 (6)	5 (56)	3 (50)	0	0	1 (13)	1 (33)
PR	11 (13)	1 (11)	2 (33)	1 (50)	2 (15)	3 (38)	2 (67)
MR	2 (2)	0	0	0	0	0	0
SD	39 (47)	1 (11)	0	1 (50)	9 (69)	3 (38)	0
PD	16 (19)	2 (22)	0	0	2 (15)	1 (13)	0

CR: complete response; IV: intravenous; MR: minimal response; QW, weekly; Q2W: every 2 weeks; ORR: overall response rate; PD: progressive disease; PR: partial response; SC: subcutaneous; sCR: stringent complete response; SD: stable disease;

- 10 VGPR: very good partial response.

Table 6: Summary of Overall Best Confirmed Response based on Investigator Assessment; Modified Intent-to-treat Analysis Set (Part 1, IV, Q2W)

	IV Bi-weekly (µg/kg)				
	0.5	1.0	1.5	2.25	3.38
Analysis set: Modified intent-to-treat	1	2	10	10	2
Response category					
Stringent complete response (sCR)	0	0	2 (20.0%)	0	0
Complete response (CR)	0	0	0	0	0
Very good partial response (VGPR)	0	1 (50.0%)	1 (10.0%)	1 (10.0%)	0
Partial response (PR)	0	0	0	2 (20.0%)	0
Minimal response (MR)	0	0	1 (10.0%)	2 (20.0%)	0
Stable disease (SD)	0	1 (50.0%)	3 (30.0%)	4 (40.0%)	0
Progressive disease (PD)	1 (100.0%)	0	3 (30.0%)	1 (10.0%)	2 (100.0%)
Not evaluable (NE)	0	0	0	0	0
Overall response (sCR+CR+VGPR+PR)	0	1 (50.0%)	3 (30.0%)	3 (30.0%)	0
Clinical benefit (Overall response + MR)	0	1 (50.0%)	4 (40.0%)	5 (50.0%)	0
VGPR or better (sCR + CR + VGPR)	0	1 (50.0%)	3 (30.0%)	1 (10.0%)	0

Note: Response was assessed by investigators, based on International Uniform Response Criteria Consensus Recommendations. Percentages were calculated with the number of subjects in each group as denominator.

5

Table 7: Summary of Overall Best Confirmed Response based on Investigator Assessment; Modified Intent-to-treat Analysis Set (Part 1, IV, QW)

	IV Weekly (µg/kg)								
	2.25	1.5	1.5 then 3.38	1.5 then 5	1.5 then 7.5	1.5 then 11.25	1.5/1.5 then 20	1.5/10 then 20	1.5/10 then 60
Analysis set: Modified intent-to-treat	12	6	12	12	10	6	3	6	6
Response category									
Stringent complete response (sCR)	1 (8.3%)	0	0	0	0	1 (16.7%)	0	0	1 (16.7%)
Complete response (CR)	1 (8.3%)	0	0	0	0	0	0	0	0
Very good partial response (VGPR)	0	0	0	1 (8.3%)	1 (10.0%)	0	2 (66.7%)	3 (50.0%)	2 (33.3%)
Partial response (PR)	2 (16.7%)	0	2 (16.7%)	1 (8.3%)	2 (20.0%)	2 (33.3%)	0	1 (16.7%)	2 (33.3%)
Minimal response (MR)	0	0	0	0	0	0	0	0	0
Stable disease (SD)	6 (50.0%)	6 (100.0%)	6 (50.0%)	6 (50.0%)	5 (50.0%)	2 (33.3%)	0	1 (16.7%)	1 (16.7%)
Progressive disease (PD)	2 (16.7%)	0	4 (33.3%)	4 (33.3%)	2 (20.0%)	1 (16.7%)	1 (33.3%)	1 (16.7%)	0
Not evaluable (NE)	0	0	0	0	0	0	0	0	0
Overall response (sCR+CR+VGPR+PR)	4 (33.3%)	0	2 (16.7%)	2 (16.7%)	3 (30.0%)	3 (50.0%)	2 (66.7%)	4 (66.7%)	5 (83.3%)
Clinical benefit (Overall response + MR)	4 (33.3%)	0	2 (16.7%)	2 (16.7%)	3 (30.0%)	3 (50.0%)	2 (66.7%)	4 (66.7%)	5 (83.3%)
VGPR or better (sCR + CR + VGPR)	2 (16.7%)	0	0	1 (8.3%)	1 (10.0%)	1 (16.7%)	2 (66.7%)	3 (50.0%)	3 (50.0%)

Note: Response was assessed by investigators, based on International Uniform Response Criteria Consensus Recommendations. Percentages are calculated with the number of subjects in each group as denominator.

10

Table 8: Summary of Overall Best Confirmed Response based on Investigator Assessment; Modified Intent-to-treat Analysis Set (Part 1, SC, QW)

	IV		SC							
	Weekly (µg/kg)	IV	Weekly (µg/kg)							
	1.5/10/60 then 180		1.5 then 5	5 then 15	10 then 45	10/45 then 135	10/60 then 405	10/60/300 then 800	Total	Total
Analysis set: Modified intent-to-treat	2	100	4	3	6	8	3	1	25	125
Response category										
Stringent complete response (sCR)	0	5 (5.0%)	0	0	0	0	0	0	0	5 (4.0%)
Complete response (CR)	0	1 (1.0%)	0	0	0	0	0	0	0	1 (0.8%)
Very good partial response (VGPR)	0	12 (12.0%)	0	0	0	1 (12.5%)	1 (33.3%)	0	2 (8.0%)	14 (11.2%)
Partial response (PR)	0	14 (14.0%)	1 (25.0%)	0	1 (16.7%)	3 (37.5%)	2 (66.7%)	0	7 (28.0%)	21 (16.8%)
Minimal response (MR)	0	3 (3.0%)	0	0	0	0	0	0	0	3 (2.4%)
Stable disease (SD)	2 (100.0%)	43 (43.0%)	3 (75.0%)	3 (100.0%)	3 (50.0%)	3 (37.5%)	0	1 (100.0%)	13 (52.0%)	56 (44.8%)
Progressive disease (PD)	0	22 (22.0%)	0	0	2 (33.3%)	1 (12.5%)	0	0	3 (12.0%)	25 (20.0%)
Not evaluable (NE)	0	0	0	0	0	0	0	0	0	0
Overall response (sCR+CR+VGPR+PR)	0	32 (32.0%)	1 (25.0%)	0	1 (16.7%)	4 (50.0%)	3 (100.0%)	0	9 (36.0%)	41 (32.8%)
Clinical benefit (Overall response + MR)	0	35 (35.0%)	1 (25.0%)	0	1 (16.7%)	4 (50.0%)	3 (100.0%)	0	9 (36.0%)	44 (35.2%)
VGPR or better (sCR + CR + VGPR)	0	18 (18.0%)	0	0	0	1 (12.5%)	1 (33.3%)	0	2 (8.0%)	20 (16.0%)

Note: Response was assessed by investigators, based on International Uniform Response Criteria Consensus Recommendations. Percentages are calculated with the number of subjects in each group as denominator.

Further data analysis provided pharmacokinetics data support for RP2D (e.g., Figures 2A, 3A, and 3B), overall response rate for SC doses, and duration responses (e.g., Figures 5A-5D). The mean PK profile following first treatment dose (Figure 2A) shows that the exposure was dose-proportional following first dose in 5-405 $\mu\text{g/kg}$ SC cohorts. 405 $\mu\text{g/kg}$ SC cohorts had lower peak/trough ratio than 60 $\mu\text{g/kg}$ IV cohorts and maintained exposure over the maximum EC₉₀. Thus, there is opportunity for less frequent SC dosing. In addition, ADA (anti-drug antibody) rate in patients was 12% (11/95) for IV and 8% (3/38) for SC. ADA did not appear to impact safety, PK, or efficacy. And as demonstrated by Figures 3A and 3B, consistent induction of cytokines (IL-10, IL-6, IL2R α) was observed at doses >45 $\mu\text{g/kg}$ SC; PD-1⁺ T cells were induced in the periphery, indicative of T cell activation; and consistent T cell activation was observed at RP2D of 405 $\mu\text{g/kg}$ SC.

The data analysis also demonstrates that, 1) at most active doses of 20-180 $\mu\text{g/kg}$ IV and 235-800 $\mu\text{g/kg}$ SC, the ORR was 66% (33/50), $\geq$ VGPR was 42%, and the responses deepened over time; 2) at the RP2D of 405 $\mu\text{g/kg}$ SC, the ORR was 69% (9/13), the median time to first confirmed response was 1 month (1-2), 6/9 (67%) of the responders were triple-class refractory, and 2/9 (22%) of the responders were penta-drug refractory. Additionally, duration of response (DPR) data (Figure 5A, the data for IV cohorts were more mature at time of analysis) shows that the responses were durable and deepened over time and the median time to first confirmed response across all doses was 1 month (0.2-3). In responders with duration of >12 months, 9/10 were still in response, with 6 $\geq$ CR and 4 with DOR of >2 years. 1 of 6 responders at doses ≥ 60 $\mu\text{g/kg}$ IV, had progressed at median 7.4-month (5.1-7.8) follow-up. None of the 17 responders at doses ≥ 405 $\mu\text{g/kg}$ SC, had progressed at median 3.7-month (1.4-6.5) follow-up.

Part 1 (Dose Escalation Part): Additional Patients and Longer Follow-up for The SC Administration (Cut-off Date for Analyses April 18, 2021)

Subcutaneous (SC) administration of escalating doses of talquetamab (5-800 $\mu\text{g/kg}$) with and without step-up dosing were assessed in additional cohorts and longer follow-up time using the same study design described above (Figure 1B). Patients must have had measurable disease and have progressed on or could not tolerate all available established therapies. Prior BCMA-targeted therapy was allowed. Premedications (i.e., glucocorticoid, antihistamine, and antipyretic) were limited to step-up doses and the first full dose; however, there was no steroid requirement after the first full dose.

Among the 82 in total SC subjects evaluated, 30 received talquetamab by SC, once weekly (QW), at the RP2D of 405 $\mu\text{g/kg}$ with step-up doses of 10 and 60 $\mu\text{g/kg}$. The other patients received SC, QW or biweekly doses of 5, 15, 45, 135, or 800 $\mu\text{g/kg}$ talquetamab. Median age range for the 82 subjects evaluated was 63 years (range 42 – 80; 27% were ≥ 70), median time since diagnosis was 5.9 years (range 1 – 20 years), and 16% had International Staging System stage III disease. Median number of prior therapies was 6 (range 2 -17), 84% of subjects were refractory to last line of therapy, 76% triple-class refractory, 78% penta-class exposed, and 28% penta-class refractory. Twenty (24%) of subjects had prior BCMA-directed therapy. A summary of the subjects' demographics and disease characteristics is shown in Table 9.

Table 9: Summary of Patient Demographics and Disease Characteristics (SC, QW)

Characteristic	SC Total n=82	RP2D (405 $\mu\text{g/kg}$ SC QW) ^a n=30
Median age (range), y	63.0 (42-80)	61.5 (46-80)
Aged ≥ 70 y, n (%)	22 (27)	7(23)
Sex, n (%)		
Male	47 (57)	19 (63)
Female	35 (43)	11 (37)
Median time since diagnosis (range), y	5.9 (1-20)	5.6 (2-20)
Extramedullary plasmacytomas ≥ 1 , N (%) ^b	27 (33)	10 (33)
Bone marrow plasma cells $\geq 60\%$, n(%) ^c	13(17)	6(21)
ISS stage, n (%) ^d		
I	26(32)	12(40)
II	36(44)	13(43)
III	13(16)	3(10)
Prior transplantation, n (%)	71(87)	27(90)
Median no. prior lines of therapy (range)	6.0 (2-17)	6.0 (2-14)
Exposure status, n (%)		
Prior BCMA therapy ^e	20 (24)	8 (27)
Triple-class ^f	81 (99)	30 (100)
Penta-drug ^g	64 (78)	24 (80)
Refractory Status, n (%)		
Pi ^h	69 (84)	25 (83)
Carfilzomib	54 (66)	19 (63)
IMiD ⁱ	76 (93)	28 (93)

Pomalidomide	67 (82)	26 (87)
Anti-CD38 mAb ⁱ	77 (94)	30 (100)
BCMA ^e	14 (17)	5 (16)
Triple-class ^f	62 (76)	23 (77)
Penta-drugs ^g	23 (28)	6 (20)
To last line of therapy	69 (84)	26 (87)

BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor T-cell; IMiD=immunomodulatory drug; ISS=International Staging System; mAb=monoclonal antibody; PI=proteasome inhibitor; QW=weekly; RP2D=recommended phase 2 dose; SC=subcutaneous
^aStep-up doses of 10 and 60 µg/kg. ^bSoft-tissue component of a bone-based plasmacytoma not included. ^cPercentages calculated from n=76 for SC total and n=29 at RP2D. ^dPercentages calculated from n=66 SC for total and n=27 at RP2D. ^eBCMA CAR-T therapy or BCMA non-CAR-T therapy. ^f≥1 PI, ≥1 IMiD, and 1 anti-CD38 mAb. ^g≥2 PI, ≥2 IMiD, and 1 anti-CD38 mAb. ^hBortezomib, carfilzomib, and/or ixazomib. ⁱThalidomide, lenalidomide, and/or pomalidomide. ^jDaratumumab and/or isatuximab.

The study showed that talquetamab has a tolerable safety profile at the RP2D of 405 µg/kg. No dose-limiting toxicities and deaths due to AEs were observed at the RP2D. Cytopenias were mostly confined to the step-dosing and to the first and second treatment cycles. Neutropenias generally resolved within a week and were limited to the first and second treatment cycles. Infections were observed in 37% of the patients evaluated (9% for grade 3 or 4) and in 32% of patients at the RP2D (3% for grade 3 or 4). Neurotoxicities were observed in 4 patients with SC dosing (all grade 1 or 2) and in 2 patients (7%) at the RP2D. Injection-site reactions occurred in 17% of patients, including at the RP2D, but were mild and manageable (all grade 1 or 2). Skin-related AEs (includes skin exfoliation, pruritis, rash, and nail disorders) occurred in 67% of patients and in 77% of patients at the RP2D (majority grade 1 or 2). Nail disorders (includes onychomadesis and nail dystrophy) occurred in 21% of patients (27% of patients at the RP2D).

Most common all-grade hematologic AEs were neutropenia (57% at any grade, 49% at grade 3 or 4), anemia (45% at any grade, 28% at grade 3 or 4), leukopenia (26% at any grade, 20% at grade 3 or 4), and thrombocytopenia (28% at any grade, 18% at grade 3 or 4). Most common all-grade nonhematologic AEs were CRS (67% at any grade, 1% at grade 3 or 4), dysgeusia (46% at any grade, not applicable at grade 3 or 4), and fatigue (32% at any grade, 0% at grade 3 or 4). Most common all-grade nonhematologic AEs observed at the RP2D of 405 µg/kg were CRS (73% at any grade, 2% at grade 3 or 4), dysgeusia (60% at any grade, NA at grade 3 or 4), and dysphagia

(37% at any grade, 0% at grade 3 or 4). A summary of the data for the safety profile of talquetamab is shown in Table 10.

Table 10: Safety Profile of Talquetamab (Part 2, SC, QW)

AE ($\geq$ 20% of Total SC), n (%)	SC Total n = 82		RP2D (405 μ g/kg SC QW) ^a n=30	
	Any Grade	Grade $\geq$ 3/4	Any Grade	Grade 3/4
Hematologic				
Anemia	37 (45)	23 (28)	17 (57)	8 (27)
Neutropenia	47 (57)	40 (49)	20 (67)	18 (60)
Lymphopenia	19 (23)	19 (23)	9 (30)	9 (30)
Thrombocytopenia	23 (28)	15 (18)	10 (33)	6 (20)
Leukopenia	21 (26)	16 (20)	11 (37)	8 (27)
Nonhematologic				
CRS	55 (67)	1 (1)	22 (73)	1 (2)
Dysgeusia	38 (46)	NA	18 (60)	NA
Fatigue	26 (32)	0	9 (30)	0
Headache	19 (23)	1 (1)	7 (23)	0
Pyrexia	23 (28)	1 (1)	7 (23)	1 (2)
Dry mouth	22 (27)	0	8 (27)	0
Dysphagia	21 (26)	0	11 (37)	0
Diarrhea	18 (22)	0	7 (23)	0
Nausea	12 (22)	0	7 (23)	0

5 AEs=adverse events, CRS=cytokine release syndrome; DLT=dose-limiting toxicity; NA=not applicable; RP2D=recommended phase 2 dose; SC=subcutaneous

^aStep-up doses of 10 and 60 μ g/kg. ^bincludes skin exfoliation, pruritis, rash, and nail disorders

^cincludes nail disorders, onychomadesis and nail dystrophy.

10 CRS was generally limited to grade 1 or 2 in all subjects (with the exception of one patient with grade 3 CRS) and the severity appears to be mitigated by implementation of step-up dosing and SC administration (Figure 14). Median time to CRS onset was 2 days (range 1-22 days) and median duration of CRS was 2 days (range 1-7 days). Out of the 82 patients treated with SC talquetamab, 67% received supportive

15 measures to treat their CRS (e.g., tocilizumab, steroids, low-flow oxygen by nasal cannula, and vasopressor). The majority of patients only had 1 dose of tocilizumab as a supportive measure for CRS. A summary of the data pertaining to patients that experienced CRS is shown in Table 11.

Table 11: Cytokine Release Syndrome that Occurred Following Treatment with Talquetamab (Part 2, SC, QW)

Parameter	SC total n=82	RP2D (405 μ g/kg SC QW) ^a n=30
Patients with CRS, n (%)	55 (67)	22 (73)
Median time to onset (range), days ^b	2 (1-22)	2 (1-22)
Median duration (range), days	2 (1-7)	2 (1-3)

Supportive measures, n (%) ^c	55 (67)	22 (73)
Tocilizumab ^d	43 (52)	18 (60)
Steroids	5 (6)	1 (3)
Low-flow oxygen by nasal cannula	6 (7)	1 (3)
Vasopressor	2 (2)	1 (3)

CRS=cytokine release syndrome; QW=weekly; RP2D=recommended phase 2 dose; SC=subcutaneous

^aStep-up doses of 10 and 60 µg/kg. ^bRelative to the most recent dose. ^cA patient could receive >1 supportive therapy. ^dTocilizumab was allowed for grade 1 CRS ^eGraded according to Lee et al.

5 *Blood*. 2014.124:188.

The RP2D of 405 µg/kg SC QW was administered to 30 patients with a median follow-up of 6.3 months (range 1.4-12 months) for the responders. The data analysis (Figure 4) demonstrates that for the escalating doses of talquetamab (5-800 µg/kg) in 75 patients, note that not all 82 patients were available for evaluation) the ORR was 53.3% (40/75) and $\geq$ VGPR was 44%; 2) at the RP2D of 405 µg/kg SC, the ORR was 70% (21/30), $\geq$ VGPR was 60%, the median time to first confirmed response was 1 month (range 0.2-3.8 months), 15/23 (65.2%) of the responders were triple-class refractory, and 5/6 (83.3%) of the responders were penta-drug refractory. The ORR was assessed in 15 evaluable patients who had $\geq$ 1 dose of talquetamab and $\geq$ 1 post-baseline disease evaluation per the 2011 International Myeloma Working Group response criteria. Out of 6 evaluable patients across the IV and SC cohorts, 4 had negative MRD CR/sCR at 10^{-6} , including 1 subject in the RP2D cohort. Negative MRD was sustained 7 months post-complete response in 1 evaluable patient.

20 Additionally, duration of response data (Figure 5B) show that the responses were durable and deepened over time in 40 patients treated with SC doses of talquetamab ranging from 45 to 800 µg/kg. At the RP2D of 405 µg/kg SC QW (Figure 5C), median duration of response was not reached and after median follow-up of 6.3 months (range 1.4-12.2+ months), 17/21 responders (81%) were alive and remained on talquetamab 25 treatment. Across all SC cohorts, after median follow-up of 6.8 months (range 1.4-16.3+ months) 31/40 responders (78%) remained on talquetamab treatment. The data for IV cohorts (Figure 5A) was more mature and even at subtherapeutic doses, responses were ongoing at 22+ months in patients with longer follow-up.

30 Further data analysis provided pharmacokinetics (PK) data support for the SC RP2D of 405 µg/kg (Figure 2B). The RP2D exhibited a low peak/trough ratio and

maintained exposure over the maximum EC₉₀. In 6 out of 50 patients (12%) treated with SC talquetamab, the patients exhibited anti-drug antibodies that generally were of low titer. Additionally, the anti-drug antibodies did not appear to impact safety, PK, or efficacy. Post-talquetamab administration, PD-1 positive T cells were induced in the periphery, which indicated T cell activation (Figure 3B). Consistent induction of PD-1+ T cells was observed in the RP2D cohorts. Moreover, consistent induction of cytokines (i.e., IL-10, IL-6, IL-2R α) was observed at doses greater than 45 μ g/kg SC.

In addition to 405 μ g/kg, 800 μ g/kg of talquetamab was also well tolerated and highly effective. Patients were treated weekly or biweekly with 800 μ g/kg of talquetamab.

Conclusion, First Data Cutoff

Talquetamab had a manageable safety profile across all doses assessed: most CRS events (67%) were grade 1–2 and generally confined to first step-up and full doses; step-up dosing mitigated high-grade CRS; there was a low incidence of neurotoxic events which were predominantly grade 1-2. Talquetamab specific skin-related AEs (includes skin exfoliation, pruritis, rash, and nail disorders) occurred in 67% of patients.

Greater responses were reached at higher doses: the data analysis demonstrates that for the escalating doses of talquetamab (5-800 μ g/kg) in 75 patients, note that not all 82 patients were available for evaluation the ORR was 53.3% (40/75) and >VGPR was 44%; 2) at the RP2D of 405 μ g/kg SC, the ORR was 70%. Additionally, duration of response data shows that the responses were durable and deepened over time.

Part 1 and 2: Additional Patients and Longer Follow-up for The SC Administration (Cut-off Date for Analyses July 19, 2021)

As of 19 July 2021, 97 subjects have been enrolled in Parts 1 and 2 for talquetamab SC dosing and received at least 1 dose of talquetamab. Thirty subjects (including Part 2 subjects) have been enrolled to receive 10 and 60 μ g/kg step-up doses followed by a 405 μ g/kg SC weekly treatment dose (the first selected RP2D). Twenty-three subjects (including Part 2 subjects) have been enrolled to receive 10, 60 and 300 μ g/kg step-up doses followed by a 800 μ g/kg SC biweekly treatment dose (the second selected RP2D).

The median age for the 30 subjects receiving talquetamab SC at the RP2D of 405 μ g/kg SC weekly was 61.5 years (range: 46 to 80 years), with 7 (23.3%) subjects $\geq$ 70 years of age. The median number of prior therapeutic regimens was 6 (range: 2 to 14). All 30 subjects (100%) were prior triple-exposed (prior therapy included PI, IMiD,

and anti-CD38 monoclonal antibody) and 80.0% were prior penta-exposed (prior therapy included 2 or more PIs, 2 or more IMiDs, and an anti-CD38 monoclonal antibody).

Notably, all 30 subjects were refractory to anti-CD38 monoclonal antibody therapy, 76.7% were triple-refractory, and 20.0% were penta-refractory.

5 The median age for the 23 subjects receiving talquetamab SC at the RP2D of 800 µg/kg SC biweekly was 60.0 years (range: 47 to 84 years), with 7 (30.4%) subjects ≥70 years of age. The median number of prior therapeutic regimens was 5 (range: 1 to 17). Twenty-two subjects (95.7%) were prior triple-exposed (prior therapy included PI, IMiD, and anti-CD38 monoclonal antibody) and 69.6% were prior penta-exposed (prior
10 therapy included 2 or more PIs, 2 or more IMiDs, and an anti-CD38 monoclonal antibody). Notably, 78.3% were refractory to anti-CD38 monoclonal antibody therapy, 65.2% were triple-refractory, and 21.7% were penta-refractory.

 The median age for the 97 subjects receiving talquetamab SC at any dosage was 64.0 years (range: 39 to 84 years), with 28 (28.9%) subjects ≥70 years of age. The
15 median number of prior therapeutic regimens was 6 (range: 1 to 17). Ninety-six subjects (99.0%) were prior triple-exposed (prior therapy included PI, IMiD, and anti-CD38 monoclonal antibody) and 78.4% were prior penta-exposed (prior therapy included 2 or more PIs, 2 or more IMiDs, and an anti-CD38 monoclonal antibody). Notably, 90.7% of subjects were refractory to anti-CD38 monoclonal antibody therapy, 71.1% were
20 triple-refractory, and 22.7% were penta-refractory.

 Another 102 subjects have been treated with talquetamab IV doses in this study. The efficacy and safety profiles of talquetamab IV are comparable to those of talquetamab SC.

Efficacy

25 Talquetamab RP2D of 405 µg/kg SC Weekly

 Disease assessment was done by investigator based on 2011 IMWG response criteria. As of the data cutoff, all 30 subjects treated with talquetamab at the RP2D of 405 µg/kg SC weekly had ≥1 postdose disease evaluation (i.e., response evaluable population). The median follow-up as of the data cutoff for the 30 subjects was
30 11.27 months (range of 4.2 to 15.2 months), and the ORR was 70.0% (Table 12). Among them, 2 subjects (6.7%) had sCR, 1 subject (3.3%) had CR, 14 subjects (46.7%) had VGPR, and 4 subjects (13.3%) had PR as the best confirmed response. No subject had progressive disease as the best confirmed response, and 9 subjects (30.0%) had stable disease (Table 12). Among responders, the median time to first confirmed response (PR

or better) was 0.92 months (range: 0.2 to 5.4 months), and the median duration of response as of the data cutoff has not been reached.

Talquetamab RP2D of 800 µg/kg SC Biweekly

Among the 23 subjects receiving talquetamab at the RP2D of 800 µg/kg SC biweekly, 18 subjects were response evaluable by investigators. The median follow-up of the data cutoff for the 30 subjects was 3.65 months (range of 0.0 to 12.0 months), and the ORR was 66.7% (Table 12). Among them, 2 subjects (11.1%) had sCR, 2 subjects (11.1%) had CR, 5 subjects (27.8%) had VGPR, and 3 subjects (16.7%) had PR as the best confirmed response. No subject had progressive disease as the best confirmed response, and 6 subjects (33.3%) had stable disease (Table 12). Among responders, the median time to first confirmed response (PR or better) was 1.17 months (range: 0.4 to 11.1 months), and the median duration of response was 5.62 months (95% CI 3.71, NE).

All Talquetamab SC Cohorts

Among the 97 subjects receiving any dose of talquetamab SC (with a median follow-up of 7.46 months [range of 0.0 to 18.0 months]), 84 were response evaluable by investigators. The ORR was 56.0% for these 84 subjects. Among them, 6 subjects (7.1%) had sCR, 4 subjects (4.8%) had CR, 26 subjects (31.0%) had VGPR, and 11 subjects (13.1%) had PR as the best confirmed response (Table 12). Among responders, the median time to first confirmed response (PR or better) was 1.15 months (range: 0.2 to 11.1 months), and the median duration of response as of the data cutoff has not been reached.

Table 12 Summary of Overall Best Confirmed Response Based on Investigator Assessment; Response Evaluable Responder Subjects by Investigators (data cutoff 19 July 2021)

	SC Weekly 10/60 then 405* (SC20 and SC23) (µg/kg)	SC Biweekly 10/60/300 then 800* (SC24, SC26 and SC27) (µg/kg)	SC Total
Analysis set: Response evaluable by investigator for subjects	30	18	84
Response category			
Stringent complete response (sCR)	2 (6.7%)	2 (11.1)	6 (6.1%)
Unconfirmed	0	1	1
Complete response (CR)	1 (3.3%)	2 (11.1)	4 (4.8%)
Very good partial response (VGPR)	14 (46.7%)	5 (27.8)	26 (31.0%)
Partial response (PR)	4 (13.3%)	3 (16.7)	11 (13.1%)
Unconfirmed	0	0	1
Minimal response (MR)	0	0	0
Stable disease (SD)	9 (30.0%)	6 (33.3)	34 (40.5%)
Progressive disease (PD)	0	0	3 (3.6%)
Not evaluable (NE)	0	0	0

Table 12 Summary of Overall Best Confirmed Response Based on Investigator Assessment; Response Evaluable Responder Subjects by Investigators (data cutoff 19 July 2021)

	SC Weekly 10/60 then 405* (SC20 and SC23) (µg/kg)	SC Biweekly 10/60/300 then 800* (SC24, SC26 and SC27) (µg/kg)	SC Total
Overall response (sCR+CR+VGPR+PR)	21 (70.0%)	12 (66.7%)	47 (56.0%)
Clinical benefit (Overall response + MR)	21 (70.0%)	12 (66.7%)	47 (56.0%)
CR or better (sCR + CR)	3 (10.0%)	4 (22.2%)	10 (11.9%)
VGPR or better (sCR + CR + VGPR)	17 (56.7%)	9 (50.0%)	36 (42.9%)

Note: Response evaluable subjects by investigators: Subjects have received at least one study treatment and have at least one post-baseline response evaluation by investigator.

Response was assessed by investigators, based on IMWG Criteria.

Percentages are calculated with the number of subjects in each group as denominator.

*Includes Part 2 subjects.

Safety

Treatment-emergent Adverse Events

- Talquetamab was evaluated in both IV and SC administration routes, which exhibited similar safety profiles. SC administration provides a more convenient treatment option for patients and healthcare workers, only the SC administration is being developed moving forward. Therefore, data presented below summarize the experience with talquetamab SC administration.

Talquetamab RP2D of 405 µg/kg SC Weekly

- All 30 subjects receiving talquetamab at the RP2D of 405 µg/kg SC Weekly as of the data cutoff date had at least 1 TEAE (Table 13).

- The most frequently reported TEAEs for subjects treated with talquetamab at the RP2D of 405 µg/kg SC Weekly ($\geq 20\%$ of subjects) were cytokine release syndrome (CRS) (76.7%); neutropenia (66.7%); anemia, dysgeusia (60.0% each); lymphopenia, leukopenia (40.0% each); thrombocytopenia, dysphagia, skin exfoliation (36.7% each); fatigue, nail disorder (30.0% each); dry mouth, hypophosphatemia, pruritus (26.7% each); headache, diarrhea, nausea, rash, weight decreased (23.3% each); pyrexia, dry skin, alanine aminotransferase increased, gamma-glutamyltransferase increased, oropharyngeal pain (20.0% each).
- No subject receiving the RP2D of 405 µg/kg SC Weekly had a TEAE that led to treatment discontinuation (Table 13).

Talquetamab RP2D of 800 µg/kg SC Biweekly

Among the 23 subjects receiving talquetamab at the RP2D of 800 µg/kg SC biweekly as of the data cutoff date, 91.3% had at least 1 TEAE (Table 13).

The most frequently reported TEAEs for subjects treated with talquetamab at the RP2D of 800 µg/kg SC biweekly (≥20% of subjects) were CRS (78.3%); neutropenia, dry mouth (43.5% each); dysgeusia, fatigue, skin exfoliation, aspartate aminotransferase increased (30.4% each); anemia, dry skin, alanine aminotransferase increased (26.1% each); and lymphopenia, thrombocytopenia, decreased appetite, hypokalaemia (21.7% each).

No subject receiving the RP2D of 800 µg/kg SC biweekly had a TEAE that led to treatment discontinuation (Table 13).

All Talquetamab SC Cohorts

Among the 97 subjects receiving any dose of talquetamab SC as of the data cutoff, 95.9% had at least 1 TEAE (Table 13).

The most frequently reported TEAEs (≥20% of subjects) were CRS (70.1%); neutropenia (54.6%); anemia (46.4%); dysgeusia (45.4%); thrombocytopenia, skin exfoliation (30.9% each); lymphopenia, leukopenia, fatigue (28.9% each); dry mouth (25.8%); pyrexia (23.7%); dysphagia, alanine aminotransferase increased (22.7% each); nausea, nail disorder (21.6% each); diarrhea, weight decreased (20.6% each).

Two subjects (2.1%) had a TEAE that led to treatment discontinuation (Table 13): 1 subject experienced Grade 3 cardiac failure related to prior chemotherapy regimens (not related to study drug), and 1 subject experienced Grade 1 maculopapular rash (related to study drug; the worst grade was Grade 3; the subject withdrew consent while the event improved to Grade 1).

Table 13. Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (data cutoff 19 July 2021)

	SC Weekly (µg/kg) 10/60 then 405*	SC Biweekly (µg/kg) 10/60/300 then 800*	SC Total
Analysis set: Safety	30	23	97
Any TEAE	30 (100.0%)	21 (91.3%)	93 (95.9%)
Drug-related	30 (100.0%)	21 (91.3%)	89 (91.8%)
Number of events	516	236	1236
Relatedness			
Possible	284	104	652
Probable	69	27	177
Very likely	163	105	407
Doubtful	28	32	93

Table 13. Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (data cutoff 19 July 2021)

	SC Weekly (µg/kg) 10/60 then 405*	SC Biweekly (µg/kg) 10/60/300 then 800*	SC Total
Not related	177	72	667
Unassigned	0	0	10
Maximum severity of any TEAE			
Grade 1	0	1 (4.3%)	3 (3.1%)
Grade 2	5 (16.7%)	3 (13.0%)	11 (11.3%)
Grade 3	8 (26.7%)	13 (56.5%)	42 (43.3%)
Grade 4	17 (56.7%)	3 (13.0%)	35 (36.1%)
Grade 5	0	1 (4.3%)	2 (2.1%)
Any serious TEAE	10 (33.3%)	5 (21.7%)	37 (38.1%)
Number of events	12	5	61
Drug-related	5 (16.7%)	1 (4.3%)	13 (13.4%)
Number of events	6	1	17
Treatment discontinuation due to TEAE ^a	0	0	2 (2.1%)
Drug-related	0	0	1 (1.0%)
Any dose-limiting toxicity TEAE	0	1 (4.3%)	3 (3.1%)
Number of events	0	1	3
Any CRS	23 (76.7%)	18 (78.3%)	68 (70.1%)
Number of events ^b	34	25	93
Serious events ^b	2	0	6
Maximum severity of any CRS			
Grade 1	18 (60.0%)	12 (52.2%)	49 (50.5%)
Grade 2	4 (13.3%)	6 (26.1%)	18 (18.6%)
Grade 3	1 (3.3%)	0	1 (1.0%)
Grade 4	0	0	0
Grade 5	0	0	0
Drug-related	23 (76.7%)	18 (78.3%)	68 (70.1%)
Death due to TEAE ^c	0	1 (4.3%)	2 (2.1%)
Drug-related	0	0	0
Potential Neurotoxicity Events ^d	5 (16.7%)	1 (4.3%)	16 (16.5%)
Maximum Severity of Potential Neurotoxicity Events ^d			
Grade 1	2 (6.7%)	1 (4.3%)	9 (9.3%)
Grade 2	3 (10.0%)	0	7 (7.2%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Serious	1 (3.3%)	0	3 (3.1%)
Neurotoxicity (related) ^e	2 (6.7%)	0	5 (5.2%)
Grade 3 or higher	0	0	0
Infection-related TEAE	11 (36.7%)	3 (13.0%)	32 (33.0%)
Grade 3 or higher	1 (3.3%)	1 (4.3%)	9 (9.3%)
Drug-related	6 (20.0%)	0	11 (11.3%)
Grade 3 or higher	0	0	1 (1.0%)
Infusion/Injection Reaction			
TEAE	5 (16.7%)	3 (13.0%)	15 (15.5%)
Drug-related	5 (16.7%)	3 (13.0%)	15 (15.5%)
Grade 1 or 2	5 (16.7%)	3 (13.0%)	15 (15.5%)

Table 13. Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (data cutoff 19 July 2021)

	SC Weekly (µg/kg) 10/60 then 405*	SC Biweekly (µg/kg) 10/60/300 then 800*	SC Total
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Keys: TEAE = treatment-emergent adverse event, CRS = cytokine release syndrome,.

^aTreatment discontinuation due to adverse event on the end of treatment CRF page.

^bCRS events are linked for the same subject after the same infusion. If one CRS event is followed by another with an onset date the same as or 1 day after the end date of the previous CRS and any features of the CRS (i.e.: toxicity grades/seriousness/action taken) are different between the CRS events, these CRS events are linked together and considered as one event.

^cDeath due to adverse event on the adverse event CRF page.

^dThe preferred terms identified as potential neurotoxicity events are Amnesia, Aphonia, Bradyphrenia, Confusional state, Delirium, Depressed level of consciousness, Disorientation, Dysarthria, Encephalopathy, Feeling abnormal, Hallucination, Lethargy, Memory impairment, Pyrexia, Somnolence, Vith nerve paralysis.

^eNeurotoxicity is defined as a potential neurotoxicity event that was considered related by investigator.

Percentages are calculated with the number of subjects in each group as denominator.

*Includes Part 2 subjects.

Dose-Limiting Toxicity (DLT)

DLTs were evaluated in Part 1 (dose escalation) only. In Part 1, no subject who received talquetamab at the RP2D of 405 µg/kg SC weekly experienced a DLT, and 1 subject who received talquetamab at the RP2D of 800 ug/kg SC biweekly experienced a DLT (Table 13). No subjects in Part 2 experienced TEAEs meeting DLT criteria.

Three DLTs have been reported in subjects receiving any dose of SC talquetamab (Table 13). One subject reported a SAE of Grade 3 maculopapular rash (deemed very likely related to talquetamab) after receiving two 135 µg/kg weekly treatment doses of talquetamab SC. The SAE improved to Grade 1 as of the data cutoff. One subject experienced a Grade 3 maculopapular rash after receiving a single 800 µg/kg treatment dose (weekly schedule) of talquetamab SC that was considered possibly related. One subject experienced a Grade 3 rash after receiving a single 800 ug/kg treatment dose (biweekly schedule) that was considered very likely related. Both events resolved and subjects continued on treatment and remain on treatment as of the data cutoff.

Grade 3 or Higher Treatment-Emergent Adverse Events

Talquetamab RP2D of 405 µg/kg SC Weekly

Twenty-five (83.3%) subjects receiving talquetamab at RP2D of 405 µg/kg SC Weekly had a Grade 3 or higher TEAE. Grade 3 CRS and infection-related TEAE were reported for 1 subject each (3.3%) receiving the RP2D of 405 µg/kg SC Weekly. No subject had a Grade 3 or higher neurotoxicity event, or infusion/injection reaction. No subject had a fatal (Grade 5) TEAE (Table 13).

Talquetamab RP2D of 800 µg/kg SC Biweekly

- Seventeen (73.9%) subjects receiving talquetamab at RP2D of 800 µg/kg SC biweekly had a Grade 3 or higher TEAE. Grade 3 infection-related TEAE were reported for 1 subject (4.3%) receiving the RP2D of 800 µg/kg SC biweekly. No subject had a
- 5 Grade 3 or higher CRS, neurotoxicity event, or systemic administration related reaction, or local injection site reaction. One subject had a Grade 5 TEAE (Table 13).

All Talquetamab SC Cohorts

- Seventy-nine (81.4%) subjects receiving any dose of SC talquetamab had a Grade 3 or higher TEAE. Grade 3 or higher CRS and infection-related TEAEs were reported
- 10 for 1 (1.0%) subject and 9 (9.3%) subjects, respectively. No subject had a Grade 3 or higher neurotoxicity event, infusion/injection reaction (Table 13). One subject had a Grade 5 neuroendocrine carcinoma that the investigator did not consider related to study treatment and 1 subject had Grade 5 TEAE (Table 13).

Serious Adverse Events

- 15 Talquetamab RP2D of 405 µg/kg SC Weekly

Among the 30 subjects receiving talquetamab SC at the RP2D of 405 µg/kg SC Weekly, serious TEAEs were reported for 10 subjects (33.3%). The only event reported as serious in more than 1 subject was CRS (2 subjects, 6.7%).

Talquetamab RP2D of 800 µg/kg SC Biweekly

- 20 Among the 23 subjects receiving talquetamab SC at the RP2D of 800 µg/kg SC biweekly, serious TEAEs were reported for 5 subjects (21.7%). The only event reported as serious in more than 1 subject was pyrexia (2 subjects, 8.7%).

All Talquetamab SC Cohorts

- Serious TEAEs were reported for 37 subjects (38.1%) receiving talquetamab SC
- 25 (Table 13). Serious adverse events reported by more than 1 subject were CRS (6 subjects, 6.2%), pyrexia (5 subjects, 5.2%), hypercalcemia, febrile neutropenia, bone pain (3 subjects, 3.1%), influenza, urinary tract infection, somnolence (2 subjects, 2.1%). Thirteen (13.4%) subjects had a study drug-related serious adverse event; among them, CRS (7.3%) and pyrexia (3.7%) were reported by more than 1 subject.

- 30 *Deaths*

All Talquetamab SC Cohorts

Seven subjects receiving talquetamab SC died as of the data cutoff date: 3 subjects due to disease progression, 1 due to the TEAE of neuroendocrine carcinoma that

was considered not related to study drug, and 3 subjects within 100 days of last dose without subsequent anticancer therapy due to unknown reasons.

Cytokine Release Syndrome (CRS)

The mechanism of action of talquetamab is based on the binding and activation of T cells and the release of cytokines in the tumor environment, thus CRS is expected in patients receiving talquetamab and CRS is an important identified risk for talquetamab with mitigation strategies in place in all ongoing and planned clinical studies. To reduce the risk of CRS, subjects receive step-up doses of talquetamab, and premedications (glucocorticoid, antihistamine, and antipyretic) prior to each step-up dose and the first treatment dose of talquetamab per protocol.

Talquetamab RP2D of 405 µg/kg SC Weekly

CRS was reported in 23 subjects (76.7%) receiving the RP2D of 405 µg/kg SC Weekly, mostly Grade 1 (60.0%) or Grade 2 (1033%) (Table 13). One patient (3.3%) experienced a Grade 3 CRS event; the patient recovered and continued treatment. CRS was only seen during early doses in Cycle 1, and the median duration of CRS was 2 days (range: 1 to 3 days). Twenty-two subjects (73.3%) received supportive measures as treatment for CRS (18 [60%] received tocilizumab, 1 subject [3.3%] each received corticosteroids, vasopressors, and supplemental oxygen).

Talquetamab RP2D of 800 µg/kg SC Biweekly

CRS was reported in 18 subjects (78.3%) receiving the RP2D of 800 µg/kg SC biweekly, all either Grade 1 (52.2%) or Grade 2 (26.1%) (Table 13). CRS was only seen during early doses in Cycle 1, and the median duration of CRS was 2 days (range: 1 to 5 days). Seventeen subjects (73.9%) received supportive measures as treatment for CRS (15 [65.2%] received tocilizumab, 1 subject [4.3%] each received corticosteroids, and supplemental oxygen).

All Talquetamab SC Cohorts

CRS was reported in 70.1% of subjects receiving talquetamab SC, mostly Grade 1 (50.5%) or Grade 2 (18.6%) (Table 13). One subject (1.0%) exhibited a Grade 3 CRS event. The incidence of CRS and associated symptoms appeared to be dose dependent. CRS was only seen during early doses in Cycle 1, and the median duration of CRS was 2 days (range: 1 to 5 days). Sixty-five subjects (67.0%) received supportive measures as treatment for CRS (50 [51.5%] received tocilizumab, 4 subjects [4.1%] received steroids, 2 subjects [2.1%] received vasopressors, and 8 subjects [8.2%] received supplemental oxygen).

Neurological Adverse Events

Based on the mode of action of talquetamab, neurotoxicity is identified as an important potential risk. In June 2018, members of the ASTCT developed a severity grading system for CRS and ICANS events induced by CAR-T cells and may be applied to other biologics. It was published in April of 2019. This study began in January 2018; consequently, TEAEs in Part 1 and Part 2 of this study were not coded using the ASTCT guidelines. To manage this retrospectively, potential neurotoxicity events (regardless of investigator-assessed relatedness) were identified by the applicant's medical team via review of TEAEs reported in the system organ classes of Nervous System Disorders and Psychiatric Disorders against a predetermined list. The subset of these events that were judged by the investigator as talquetamab-related were considered neurotoxicity events. TEAEs in Part 3 of this study and other ongoing or planned studies will be coded following the ASTCT guidelines and use the term ICANS for neurotoxicity reporting.

Talquetamab RP2D of 405 µg/kg SC Weekly

Among the 30 subjects receiving talquetamab SC at the RP2D of 405 µg/kg SC Weekly, neurotoxicity events were reported in 2 (6.7%) subjects. Of the neurotoxicity events reported, none were reported by more than one subject.

Talquetamab RP2D of 800 µg/kg SC Biweekly

Among the 23 subjects receiving talquetamab SC at the RP2D of 405 µg/kg SC Weekly, there were no neurotoxicity events reported.

All Talquetamab SC Cohorts

Among the 97 subjects receiving any dose of talquetamab SC as of the data cutoff, neurotoxicity events were reported in 5 (5.2%) subjects. Of the neurotoxicity events reported, none were reported by more than one subject.

Pharmacokinetics

As of 25 March 2021 (cutoff for PK data in this study), PK data are available from 69 subjects treated with SC talquetamab at doses ranging from 5 to 800 µg/kg weekly and 800 µg/kg biweekly from MonumenTAL-1. PK data are also available from 100 subjects treated with IV talquetamab at doses ranging from 0.5 to 3.38 µg/kg biweekly and 1.5 to 180 µg/kg weekly. Based on the safety, efficacy and PK, 405 µg/kg weekly SC administration was identified as the putative RP2D and being evaluated in the Part 2 and Part 3 (400 µg/kg for operational convenience) of MonumenTAL-1.

Following IV administration, preliminary results demonstrated that C_{max} occurred at the end of IV infusion. Talquetamab levels declined quickly with an elimination half-

life ($t_{1/2}$) of approximately 7 days. Exposure increased in an approximately dose proportional manner following IV treatment across the range of 1.5 to 180 $\mu\text{g/kg}$.

The PK of talquetamab was further evaluated after talquetamab was subcutaneously administered weekly or biweekly. Following weekly SC administration, the concentration-time profiles demonstrated a less fluctuated and more sustained pattern. The preliminary results suggested the individual T_{max} occurred on Day 2 to Day 8. At the similar dose level of talquetamab, C_{max} was approximately 5.6-fold lower than that of IV treatment; talquetamab trough levels were comparable between IV and SC administration. The sponsor acknowledges that 400 $\mu\text{g/kg}$ SC weekly will result in higher mean C_{trough} , lower mean C_{max} and similar mean C_{avg} at steady state compared to those at 800 $\mu\text{g/kg}$ SC biweekly. However, the inter-subject variability in talquetamab PK was substantial, eg, the CV for most PK parameters were higher than 50%. Consequently, the C_{trough} and C_{max} at steady state overlapped substantially between 400 $\mu\text{g/kg}$ SC weekly and 800 $\mu\text{g/kg}$ SC biweekly. Both 400 $\mu\text{g/kg}$ SC weekly and 800 $\mu\text{g/kg}$ SC biweekly were identified as RP2D based on the observed efficacy and safety. Due to the unique and novel mechanism of action of talquetamab, it is not clear whether the C_{max} is the driving force for the efficacy. However, the talquetamab C_{trough} from both dose regimens was comparable or higher than the maximum effect (EC_{90}) values identified in an ex vivo cytotoxicity assay. In addition, at the dose levels equal to or higher than 405 $\mu\text{g/kg}$ weekly and 800 $\mu\text{g/kg}$ biweekly, the mean talquetamab concentrations were higher than the maximum EC_{90} obtained from ex vivo cytotoxicity assay using bone marrow mononuclear cells from multiple myeloma patients ($n=6$). This assay assessed the ability of talquetamab to induce killing using mononuclear cells from the bone marrow samples of patients with multiple myeloma in co-culture with T cells from healthy donors. Based on the available steady-state data in Cycle 3, the mean accumulation ratio (based on AUC_{tau}) following SC weekly dosing ranged from 1.7 to 5.1. Furthermore, preliminary population PK analysis and non-compartmental analysis showed that the mean bioavailability following SC weekly administration was 48%.

A summary of talquetamab PK parameters, as of 25 March 2021, on Cycle 1 and Cycle 3 following multiple SC weekly (400 $\mu\text{g/kg}$) and biweekly (800 $\mu\text{g/kg}$) dosing is provided in Table 14.

Table 14. Preliminary Summary of Talquetamab PK Parameters on Cycle 1 and Cycle 3 Following Multiple SC Weekly Dosing (400 µg/kg) and Biweekly Dosing (800 µg/kg) of Talquetamab

Cohort	Dose Regimen	C _{max} [ng/mL]	AUC _{tau} [ng.h/mL] ^a	AR _{AUC}	C _{trough} [ng/mL]
Talquetamab PK parameters [mean(SD)] (Cycle 1)					
Cohorts 20 and 23 ^b (N=25)	400 q1w	1363 (992)	139903(106157)		876(698) (N=19)
Cohort 24 (N=12)	800 q2w	2395 (1647)	606614 (386533)		1203 (688) (N=10)
Talquetamab PK parameters [mean(SD)] (Cycle 3)					
Cohorts 20 and 23 ^b (N=17)	400 q1w	3243(1567)	499243 (241097)	4.7(3.0)	2805(1460) (N=14)
Cohort 24 (N=8)	800 q2w	3901 (1408)	1015793 (378659)	2.4 (2.2)	2211 (657) (N=7)

^a For q1w, AUC_{tau}= AUC_{0-168 hr}; For q2w, AUC_{tau}=AUC_{0-336 hr}

^b PK parameters from Cohorts 20 and 23 were combined

Immunogenicity

As of 7 April 7 2021 (cutoff for immunogenicity data in Study 5 64007957MMY1001), samples from 161 subjects (IV and SC treatment) were evaluated for the immunogenicity. Preliminary results showed 12 of 100 subjects (12%) for IV administration (up to 180 µg/kg) and 7 of 61 subjects (11%) for SC administration (up to 800 µg/kg) were positive for ADAs against talquetamab. The titers in majority of the subjects were low (equal to the minimum required dilution of the assay [20]), except for 10 2 subjects. Based on the preliminary evaluation, ADAs do not appear to impact the exposure of talquetamab.

As part of the initial scientific advice, CHMP highlighted the need to provide 1-year data on immunogenicity for marketing authorization. Immunogenicity data have already been obtained from this study (Parts 1 and 2) and will be collected from Part 3 15 (Phase 2). At the time of submission, 1-year data will be available from subjects in Part 1 and Part 2 who are still in the study after 1 year. In addition, approximately 6 months of immunogenicity data from subjects in Part 3 of this study will be included.

Pharmacodynamics

As of data cutoff of 5 February 2021, pharmacodynamic data are available for 28 20 participants treated at the RP2D in MomenTAL-1. Subjects who received 405 µg/kg SC talquetamab demonstrated pharmacodynamic changes consistent with the proposed mechanism of action. These included consistent increases in cytokines such as IL-10 (median maximum fold change 8.582; range: [1.42-73.82]), IL-2Rα (3.866; 1.47-27.84), and IL-6 (87.800; 1.45-1841.25). In addition, induction of T cell activation, as evidenced

by increased expression of activation markers on CD3+ T cells such as CD25 (median maximum fold change 1.87 [range: 0.72 to 9.76]), PD-1 (1.94; 1.09-6.51), HLA-DR (1.324; 0.76-5.64), CD38 (2.952; 0.6-11.30), LAG-3 (3.221; 1.16-11.36), TIM-3 (3.442; 1.06-15.09) and T cell redistribution as indicated by changes in total T cell absolute counts (0.623; 0.2-4.18) were also observed in the 405 µg/kg cohort.

Conclusions Updated Data Cutoff

As of July 19, 2021, 95 patients have received SC talquetamab. The RP2D was originally identified as a weekly SC dose of 405 µg/kg talquetamab with step-up doses of 10 and 60 µg/kg. Alternative dosing schedules that require less frequent administration continue to be investigated. A biweekly RP2D was also identified as a SC dose of 800 µg/kg talquetamab with step-up doses of 10, 60, and 300 µg/kg.

30 patients received the 405 µg/kg weekly dosing schedule (median age: 61.5 years [range: 46–80]; 63% male; 100% triple-class exposed; 80% penta-drug exposed; 77% triple-class refractory, 20% penta-drug refractory; 30% prior BCMA-directed therapy). 23 patients received the 800 µg/kg biweekly dosing schedule (median age: 60.0 years [range: 47–84]; 52% female; 96% triple-class exposed; 70% penta-drug exposed; 65% triple-class refractory, 22% penta-drug refractory; 17% prior BCMA-directed therapy).

There were no treatment discontinuations due to AEs at either of the RP2Ds. The most common AEs at the 405 µg/kg weekly dose were CRS (73%; grade 3/4: 3%), neutropenia (67%; grade 3/4: 60%), and dysgeusia (60%; all grade 1/2); skin-related AEs occurred in 77% (nail disorders: 30%) of patients, and infections occurred in 37% of patients (grade 3/4: 3%). The most common AEs at the 800 µg/kg biweekly dose were CRS (78%; all grade 1/2), dry mouth (44%; all grade 1/2), and neutropenia (44%; grade 3/4: 35%); skin-related AEs occurred in 65% of patients (nail disorders: 17%) and infections occurred in 13% of patients (grade 3/4: 4%).

At a median follow-up of 7.5 months (range: 0.9–15.2), the overall response rate (ORR) was 70% (very good partial response or better [≥VGPR]: 57%) in 30 response-evaluable patients treated with the 405 µg/kg weekly dose. At a median follow-up of 3.7 months (range 0.0–12.0), the ORR was 71% (≥VGPR: 53%) in the 17 response-evaluable patients who received 800 µg/kg biweekly doses. Responses were durable and deepened over time in both cohorts (Figure); Median duration of response was not reached. The majority of responses were maintained at 6 months, with 66% (10/15) and 85% (7/8) of patients continuing on treatment in the 405 µg/kg weekly and 800 µg/kg

biweekly cohorts, respectively. Serum trough levels of talquetamab were comparable at both RP2Ds. Pharmacodynamic data from cohorts treated at both dose levels showed consistent peripheral T cell activation and induction of cytokines, demonstrating the mechanism of action for talquetamab.

- 5 These findings indicate that SC talquetamab is well tolerated and highly effective at both RP2Ds. Preliminary data from the 800 µg/kg biweekly cohort indicate that less frequent, higher doses of SC talquetamab do not have a negative impact on the previously described safety profile.

Pharmacokinetics Simulation

- 10 Further data simulation provided pharmacokinetics (PK) data support for the RP2D of 800 µg/kg administered at cycles 1 and 2. Based on the simulation results, the maximum mean serum concentration (C_{max}) for patients treated with cycle 2 of 800 µg/kg was 4233.4 ng/mL (range 1247.4-12710.1 ng/mL) and the lowest mean concentration of talquetamab in the blood (C_{min}) was 2670.4 ng/mL (range 662.7 -
- 15 8100.4 ng/mL). A summary of the simulated exposure metrics (C_{max} , C_{min} , and AUC (area under the curve)) for 4 different doses of talquetamab (including 800 µg/kg) at cycle 2 are shown in Table 15.

Table 15: Summary of the simulated exposure metrics mean C_{max} , C_{min} , and AUC across different dosing regimens of talquetamab at cycle 2.

Dose Regimen	C_{max} , ng/mL	C_{min} , ng/mL	AUC, ng × day/mL [over a dosing interval]	AUC ₀₋₁₄
800 Q1W ^a	4233.4 (1247.4 - 12710.1)	2670.4 (662.7 - 8100.4)	25574.8 (7349.3 - 77736.2)	51149.6
400 Q1W ^a	2116.7 (623.7 - 6355.1)	1335.2 (331.3 - 4050.2)	12787.4 (3674.6 - 38868.1)	25574.8
800 Q2W ^a	2469.4 (772.9 - 6894.6)	1094.0 (178.6 - 3711.2)	26277.8 (7562.2 - 80807.8)	26277.8
1200 Q2W ^a	3704.1 (1159.3 - 10341.9)	1641.1 (268.0 - 5566.9)	39416.7 (11343.3 - 121211.8)	39416.7

1600 Q2W ^a	4938.8 (1545.7 - 13789.2)	2188.1 (357.3 - 7422.5)	52555.6 (15124.4 - 161615.7)	52555.6
1600 Q3W ^b	3606.3 (1188.8 - 9222.1)	994.0 (127.5 - 3607.2)	50509.1 (14585.4 - 149449.3)	33672.7
1600 Q4W ^a	3403.7 (1099.1 - 8626.6)	703.8 (60.5 - 2982.0)	54714.5 (15290.0 - 171443.3)	27357.3

Median (5th and 95th percentiles) of prediction

^aExposure metrics calculated for 2nd Cycle

^bExposure metrics calculated after 2nd dose

- 5 The mean C_{max} for patients treated with 800 µg/kg of talquetamab at a steady state was 4808.9 ng/mL (range 1329.0 - 18938.7 ng/mL) and the mean C_{min} was 3908.3 ng/mL (range 751.2 - 16766.7 ng/mL). A summary of the simulated exposure metrics (C_{max}, C_{min}, and AUC) across different dosing regimens of talquetamab (including 800 µg/kg) at a steady state are shown in Table 16.

10 **Table 16: Summary of exposure metrics mean C_{max}, C_{min}, and AUC across different dosing regimens of talquetamab at a steady state.**

Dose Regimen	C _{max} , ng/mL	C _{min} , ng/mL	AUC, ng × day/mL [over a dosing interval]	AUC ₀₋₁₄
800 Q1W	4808.9 (1329.0 - 18938.7)	3908.3 (751.2 - 16766.7)	31419.9 (7783.8 - 127114.7)	62839.8
400 Q1W	2404.4 (664.5 - 9469.4)	1954.2 (375.6 - 8383.4)	15709.9 (3891.9 - 63557.3)	31419.8
800 Q2W	2816.6 (828.6 - 9947.7)	1578.7 (192.6 - 7730.7)	31426.7 (7783.8 - 127687.7)	31426.7
1200 Q2W	4224.9 (1242.9 - 14921.5)	2368.1 (289.0 - 11596.0)	47140.0 (11675.7 - 191531.6)	47140.0
1600 Q2W	5633.4 (1657.2 - 19895.4)	3157.4 (385.3 - 15461.4)	62853.4 (15567.6 - 255375.4)	62853.4
1600 Q3W	4498.9 (1345.3 - 14159.5)	1686.1 (152.3 - 9719.1)	62854.1 (15567.6 - 255468.4)	41902.2
1600 Q4W	3940.9 (1167.6 - 11640.4)	1040.8 (64.9 - 6866.8)	62858.8 (15567.6 - 257793.1)	31429.4

Median (5th and 95th percentiles) of prediction

Part 2 (Dose Expansion Part)- Dosing Schedule

Subjects are treated in Part 2 (NCT04634552) after a putative RP2D(s) for talquetamab was identified in Part 1.

5 SC administration: Upon identification of the putative RP2D for SC administration, subjects were treated with 405 µg/kg as the SC QW RP2D in dose expansion (with step-up doses of 10 and 60 µg/kg) to further demonstrate safety and to characterize preliminary antitumor activity. Another subset of subjects were treated with 800 µg/kg as the SC biweekly RP2D dose in dose expansion (with step-up doses of 10, 60, and 300 µg/kg).

10 In Part 2, up to 40 subjects can be enrolled and treated with IV or SC talquetamab at an RP2D of 405 µg/kg or 800 µg/kg. Additionally, the same dosing schedules recommended in Part 1 may be used to further characterize preliminary antitumor activity and safety in additional subjects at the RP2D doses of interest. The same supportive care measures used in Part 1 of the study will be applied to the subjected
15 treated in Part 2. The SET (Study Evaluation Team) may stop further enrollment into the dose expansion cohorts pending the outcome of any SET reviews, or if treatment-emergent toxicity is determined to result in an unfavorable change in subject risk or benefit.

Stopping Rule

20 For each route of administration in Part 2, dose-limiting toxicity (DLT) data will be evaluated after approximately every 5 subjects (e.g., 5th, 10th, etc.) at a putative RP2D complete Cycle 1 of treatment or discontinue earlier. A BLRM model will be fitted, including all cumulative data for subjects from Part 1 (dose escalation) and Part 2 (dose expansion). If the posterior probability that the DLT rate is in the range of [0.25-1] is
25 great than or equal to 25% (i.e., $\text{Prob}[p(\text{TOX, putative RP2D}) > 0.25 \mid \text{data}] \geq 0.25$), the sponsor will stop additional enrollment for the specific putative RP2D cohort. All DLTs that have occurred during Cycle 1 or Cycle 2 up to the current time point will be considered when fitting the BLRM model to calculate the posterior probability. If enrollment to the current putative RP2D is stopped based on SET reviews, other
30 expansion cohorts at lower dose levels may be explored.

Part 3 (Phase 2, Study Name: MonumenTAL-1)

In Part 3, three different cohorts will be enrolled, Cohort A, Cohort B, and Cohort C. Cohorts A, B, and C are representative of the subset of relapsed/refractory multiple

myeloma patients who have limited treatment options. These cohorts are defined as follows:

5 Cohort A (400 µg/kg weekly SC) will enroll subjects with multiple myeloma who have previously received ≥ 3 prior lines of therapy that included at least one proteasome inhibitor (PI), one immunomodulatory imide drug (IMiD), and an anti-CD38 monoclonal antibody, and have not been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies.

10 Cohort B (400 µg/kg weekly SC) will enroll subjects with multiple myeloma who have previously received ≥ 3 prior lines of therapy that included at least one PI, one IMiD, and an anti-CD38 monoclonal antibody, and have been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies.

15 Cohort C (800 µg/kg bi-weekly SC) will enroll subjects with multiple myeloma who have previously received ≥ 3 prior lines of therapy that included at least one PI, one IMiD, and an anti-CD38 monoclonal antibody, and have not been exposed to T cell redirection therapies such as CAR-T or bispecific antibodies.

20 Cohorts A and B will be enrolled after approximately 20 subjects have been treated with SC talquetamab at the RP2D of 400 µg/kg or 800 µg/kg for at least one cycle. The sponsor may also determine that additional subjects are required to further evaluate safety and dose prior to proceeding to Part 3. Enrollment for Cohort C will begin after 20 subjects have been treated with SC talquetamab at an RP2D of 800 µg/kg bi-weekly for at least 1 cycle. In contrast to Part 2, the selected RP2Ds for Part 3 are 400 µg/kg weekly and 800 µg/kg biweekly SC talquetamab until progressive disease. The putative RP2Ds in Part 2 are 405 µg/kg weekly and 800 µg/kg biweekly SC talquetamab until progressive disease.

25 In Part 3, subjects will be allowed to switch from a weekly 400 µg/kg SC dosing schedule to a biweekly 800 µg/kg SC dosing when a subject exhibits a complete response (CR) or better for a minimum of 6 months. The change in dosing schedule also must be approved by the sponsor, based on comparable preliminary PK, safety, and efficacy data of these 2 dosing schedules. The priming dose schedule in Part 3 will consist of 2 doses (10 and 60 µg/kg), each separated by 2 to 4 days and will be completed 2 to 4 days prior to the first treatment dose (i.e., if there are no delays in treatment, the first priming dose (10 µg/kg) is to be administered 5 to 8 days before the first treatment dose and the second priming dose (60 µg/kg 2 to 4 days before the first treatment dose). The biomarkers of the patients in Part 3 also will be evaluated.

An adverse event of special interest for Part 3 is a neurotoxicity grade ≥ 2 (i.e., ICANS (immune effector cell-associated neurotoxicity syndrome), symptoms of ICANS, and non-ICANS neurotoxicity). Regarding the T&E neurological examination for Part 3, an assessment occurs at priming dose 1 and there is no assessment at screening.

5 Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

10 The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

What is claimed:

1. A method of treating a hematological malignancy, preferably a multiple myeloma, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof, wherein the subject is relapsed or refractory to treatment with a prior anti-cancer treatment.
2. The method of claim 1, wherein the GPRC5DxCD3 bispecific antibody is administered intravenously or subcutaneously at a dose of about 0.2 µg/kg to about 2400 µg/kg.
3. The method of claim 2, comprising:
 - (1) administering to the subject the GPRC5DxCD3 bispecific antibody intravenously or subcutaneously at a first priming dose of 0.5 µg/kg to 10 µg/kg, such as 0.5 µg/kg, 1.0 µg/kg, 1.5 µg/kg, 2.25 µg/kg, 2.5 µg/kg, 2.75 µg/kg, 3.0 µg/kg, 3.25 µg/kg, 3.38 µg/kg, 3.5 µg/kg, 3.75 µg/kg, 4 µg/kg, 4.5 µg/kg, 5 µg/kg, 6 µg/kg, 7 µg/kg, 8 µg/kg, 9 µg/kg, 10 µg/kg, or any value in between, preferably every 2 to 4 days, and
 - (2) subsequently administering to the subject the GPRC5DxCD3 bispecific antibody subcutaneously at a treatment dose higher than the first priming dose, in the range of 1.5 µg/kg to 2400 µg/kg or 1.5 µg/kg to 1000 µg/kg, such as 1.5 µg/kg, 5 µg/kg, 10 µg/kg, 15 µg/kg, 30 µg/kg, 45 µg/kg, 100 µg/kg, 135 µg/kg, 200 µg/kg, 300 µg/kg, 400 µg/kg, 405 µg/kg, 500 µg/kg, 600 µg/kg, 700 µg/kg, 800 µg/kg, 900 µg/kg, 1000 µg/kg, 1200 µg/kg, 1600 µg/kg, 2000 µg/kg, 2400 µg/kg, or any value in between, preferably monthly, tri-weekly, bi-weekly, weekly or twice a week,optionally, the method further comprising administering to the subject the GPRC5DxCD3 bispecific antibody subcutaneously at one or more additional priming doses higher than the first priming dose but lower than the treatment dose, wherein the one or more additional priming doses are administered after the first priming dose but before the administration of the treatment dose.
4. The method of claim 2, wherein the GPRC5DxCD3 bispecific antibody is administered intravenously at a dose of about 0.2 µg/kg to about 500 µg/kg, preferably about 1 µg/kg to about 300 µg/kg, most preferably about 10 µg/kg to about 200 µg/kg, such as about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130,

140, 150, 160, 170, 180, 190, 200 µg/kg, or any value in between, preferably monthly, tri-weekly, bi-weekly, weekly, or twice a week.

5. The method of claim 4, comprising:

(1) administering to the subject the GPRC5DxCD3 bispecific antibody intravenously at a first priming dose of 0.5 µg/kg to 5 µg/kg, such as 0.5 µg/kg, 1.0 µg/kg, 1.5 µg/kg, 2.25 µg/kg, 2.5 µg/kg, 2.75 µg/kg, 3.0 µg/kg, 3.25 µg/kg, 3.38 µg/kg, 3.5 µg/kg, 3.75 µg/kg, 4 µg/kg, 4.5 µg/kg, 5 µg/kg, or any value in between preferably every 2 to 4 days, and

(2) subsequently administering to the subject the GPRC5DxCD3 bispecific antibody intravenously at a treatment dose higher than the first priming dose, in the range of 1.5 µg/kg to 200 µg/kg, such as 1.5 µg/kg, 2.25 µg/kg, 3.38 µg/kg, 5 µg/kg, 7.5 µg/kg, 11.25 µg/kg, 20 µg/kg, 40 µg/kg, 60 µg/kg, 80 µg/kg, 100 µg/kg, 120 µg/kg, 140 µg/kg, 160 µg/kg, 180 µg/kg, 200 µg/kg, or any value in between, preferably monthly, tri-weekly, bi-weekly, weekly or twice a week,

optionally, the method further comprising administering to the subject the GPRC5DxCD3 bispecific antibody intravenously at one or more additional priming doses higher than the first priming dose but lower than the treatment dose, wherein the one or more additional priming doses are administered after the first priming dose but before the administration of the treatment dose.

6. The method of claim 2, wherein the GPRC5DxCD3 bispecific antibody is administered subcutaneously at a dose of about 0.5 µg/kg to about 2400 µg/kg, or about 1 µg/kg to about 2400 µg/kg, or about 10 µg/kg to about 2400 µg/kg, such as about 10, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1600, 2000, 2400 µg/kg, or any value in between, preferably monthly, tri-weekly, bi-weekly, weekly, or twice a week.

7. The method of claim 6, comprising:

(1) administering to the subject the GPRC5DxCD3 bispecific antibody at one or more priming doses of 0.3 µg/kg to 400 µg/kg, preferably every 2 to 4 days, and

(2) subsequently administering to the subject the GPRC5DxCD3 bispecific antibody at a treatment dose higher than the priming doses, such as 1 µg/kg to 2400 µg/kg, preferably monthly, tri-weekly, bi-weekly, weekly or twice a week.

8. A method of treating a multiple myeloma in a subject in need thereof, comprising subcutaneously administering to the subject 405 µg/kg of a GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof weekly or biweekly, wherein the

subject is relapsed or refractory to treatment with a prior anti-cancer treatment, preferably the initial administration of the 405 µg/kg GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof occurs after the subject is administered with one or more priming doses of the antibody or antigen binding fragment thereof, such as one or more priming doses of 10, 60, and 300 µg/kg administered subcutaneously weekly or biweekly.

9. A method of treating a multiple myeloma in a subject in need thereof, comprising subcutaneously administering to the subject 800 µg/kg of a GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof weekly or biweekly, wherein the subject is relapsed or refractory to treatment with a prior anti-cancer treatment, preferably the initial administration of the 800 µg/kg GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof occurs after the subject is administered with one or more priming doses of the antibody or antigen binding fragment thereof, such as one or more priming doses of 10, 60, and 300 µg/kg administered subcutaneously weekly or biweekly.
10. The method of any one of claims 1 to 9, wherein the GPRC5DxCD3 bispecific antibody or antigen binding fragment thereof comprises a GPRC5D binding domain comprising the HCDR1 of SEQ ID NO: 4, the HCDR2 of SEQ ID NO: 5, the HCDR3 of SEQ ID NO: 6, the LCDR1 of SEQ ID NO: 7, the LCDR2 of SEQ ID NO: 8 and the LCDR3 of SEQ ID NO: 9, and a CD3 binding domain comprising the HCDR1 of SEQ ID NO: 14, the HCDR2 of SEQ ID NO: 15, the HCDR3 of SEQ ID NO: 16, the LCDR1 of SEQ ID NO: 17, the LCDR2 of SEQ ID NO: 18 and the LCDR3 of SEQ ID NO: 19.
11. The method of any one of claims 1 to 10, wherein the GPRC5D binding domain comprises a heavy chain variable region (VH) having the amino acid sequence of SEQ ID NO: 10 and a light chain variable region (VL) having the amino acid sequence of SEQ ID NO: 11, and the CD3 binding domain comprises a VH having the amino acid sequence of SEQ ID NO: 20 and a VL having the amino acid sequence of SEQ ID NO: 21.
12. The method of any one of claims 1 to 11, wherein the GPRC5DxCD3 bispecific antibody is an IgG4 isotype and comprises phenylalanine at position 405 and arginine at position 409 in a first heavy chain (HC1) and leucine at position 405 and lysine at position 409 in a second heavy chain (HC2), wherein residue numbering is according to the EU Index.

13. The method of any one of claims 1 to 12, wherein the GPRC5DxCD3 bispecific antibody further comprises proline at position 228, alanine at position 234 and alanine at position 235 in both the HC1 and the HC2.
14. The method of any one of claims 1 to 13, wherein the GPRC5DxCD3 bispecific antibody comprises the HC1 having the amino acid sequence of SEQ ID NO: 12, a first light chain (LC1) having the amino acid sequence of SEQ ID NO: 13, the HC2 having the amino acid sequence of SEQ ID NO: 22 and a second light chain (LC2) having the amino acid sequence of SEQ ID NO: 23.
15. The method of any one of claims 1 to 14, wherein the GPRC5DxCD3 bispecific antibody is talquetamab.
16. The method of any one of claims 1 to 15, wherein the treatment achieves a complete response, stringent complete response, very good partial response, partial response, minimal response or stable disease status, and can be continued until disease progression or lack of patient benefit.
17. The method of claim 16, wherein the treatment achieves the complete response that is characterized by negative minimal residual disease (MRD) status, preferably negative MRD status at 10^{-6} cells, as determined by next generation sequencing (NGS), or an overall response rate of at least 20%, such as at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or any value in between.
18. The method of any one of claims 1 to 17, wherein the treatment results in an exposure of GPRC5DxCD3 bispecific antibody at a steady state mean C_{max} of 10 to 25,000 ng/ml, such as 100 to 20,000 ng/ml or 1000-10,000 ng/ml, and a steady state mean AUC_{0-14d} of 1000 to 1,500,000 ng h/ml, such as 5000 to 1,000,000 ng h/ml or 10,000 to 1,000,000 ng h/mL.
19. The method of any one of claims 1 to 18, wherein the prior anti-cancer treatment is selected from the group consisting of thalidomide, lenalidomide, pomalidomide, bortezomib, ixazomib, carfilzomib, panobinostat, pamidronate, zoledronic acid, daratumumab, elotuzumab, melphalan, selinexor, belantamab mafodotin-blmf, Venetoclax, CC-92480, CAR-T therapies, other BCMA-directed therapies, other CD38-directed therapies, and combinations of two or more thereof.
20. The method of any one of claims 1 to 19, wherein the subject is a human in need of a treatment of multiple myeloma and is relapsed or refractory to treatment with the prior treatment of the multiple myeloma.

21. The method of any one of claims 1 to 20, further comprising administering to the subject one or more additional anti-cancer therapies.
22. The method of claim 21, wherein the one or more additional anti-cancer therapies are selected from the group consisting of autologous stem cell transplants (ASCT), radiation, surgery, chemotherapeutic agents, CAR-T therapies, cellular therapies, immunomodulatory agents, targeted cancer therapies, a therapy that reduces or depletes Treg, and combinations of two or more thereof.
23. The method of claim 21, wherein the one or more additional anti-cancer therapies are selected from the group consisting of selinexor, belantamab mafodotin-blmf, isatuximab, venetoclax, lenalidomide, thalidomide, pomalidomide, bortezomib, carfilzomib, elotozumab, ixazomib, melphalan, dexamethasone, vincristine, cyclophosphamide, hydroxydaunorubicin, prednisone, rituximab, imatinib, dasatinib, CC-92480, nilotinib, bosutinib, ponatinib, bafetinib, saracatinib, tozasertib, danusertib, cytarabine, daunorubicin, idarubicin, mitoxantrone, hydroxyurea, decitabine, cladribine, fludarabine, topotecan, etoposide 6-thioguanine, corticosteroid, methotrexate, 6-mercaptopurine, azacitidine, arsenic trioxide and all-trans retinoic acid, and combinations of two or more thereof.