Efficacy and Safety of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From MonumenTAL-1

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INTRODUCTION

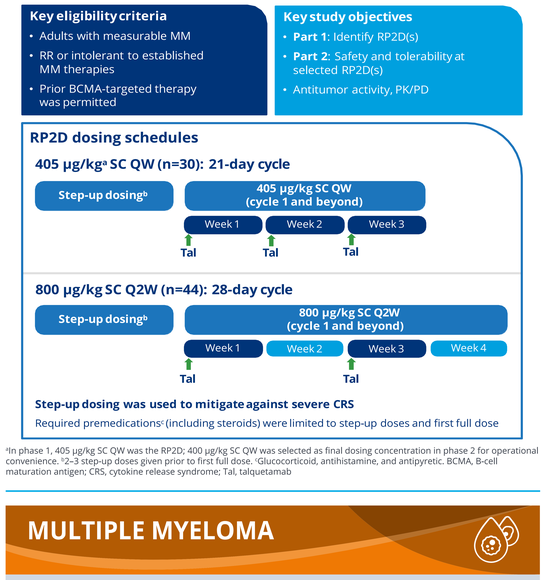
- G protein-coupled receptor family C group 5 member D (GPRC5D) is an orphan receptor that is highly expressed in malignant plasma cells but has limited expression in normal human tissues[1-5]
- Talquetamab (JNJ-64407564) is a first-in-class, off-the-shelf, T-cell redirecting bispecific antibody targeting both GPRC5D and CD3 receptors[6-7]
- MonumenTAL-1 is a first-in-human, phase 1 trial of talquetamab in patients with relapsed/refractory multiple myeloma (RRMM)[8-10]
  - A total of 130 patients received subcutaneous (SC) talquetamab
  - The maximum tolerated dose was not reached[8]
  - Collective safety, efficacy, pharmacokinetic (PK), and pharmacodynamic (PD) data supported two recommended phase 2 doses (RP2Ds) for talquetamab: 405 µg/kg SC weekly (QW) and 800 µg/kg SC every other week (Q2W)[8]
- Here we present updated results of MonumenTAL-1, with longer follow-up for patients treated at each RP2D, and additional patients treated at the 800 µg/kg dose

METHODS

Study design and key eligibility criteria

- MonumenTAL-1 is an ongoing phase 1 (NCT03399799) study of talquetamab in patients with RRMM (**Figure 1**)

FIGURE 1: MonumenTAL-1 study design



[a]In phase 1, 405 µg/kg SC QW was the RP2D; 400 µg/kg SC QW was selected as final dosing concentration in phase 2 for operational convenience. [b]2–3 step-up doses given prior to first full dose. [c]Glucocorticoid, antihistamine, and antipyretic. BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; Tal, talquetamab

MULTIPLE MYELOMA

RESULTS

Patients

- As of April 6, 2022, 74 patients had received talquetamab at the RP2Ds, including 30 patients at 405 µg/kg QW and 44 patients at 800 µg/kg Q2W
- Median (range) follow-up was 13.2 months (1.1–24.0) for 405 µg/kg QW and 7.7 months (0.7–16.0) for 800 µg/kg Q2W
- Baseline characteristics are shown in **Table 1**

TABLE 1: Baseline characteristics

Characteristic	405 µg/kg SC QW[a] n=30	800 µg/kg SC Q2W[a] n=44
Age (years), median (range)	61.5 (46–80)	64.0 (47–84)
Male, n (%)	19 (63.3)	21 (47.7)
Race, n (%)		
White	25 (83.3)	35 (79.5)
Black or African American	4 (13.3)	4 (9.1)
Asian	0	3 (6.8)
Not reported	1 (3.3)	2 (4.5)
Bone marrow plasma cells ≥60%[b], n (%)	6 (20.7)	5 (12.2)
Extramedullary plasmacytomas ≥1[c], n (%)	11 (36.7)	15 (34.1)
High-risk cytogenetics[d], n (%)	3 (11.1)	9 (22.5)
Time since diagnosis (years), median (range)	5.6 (1.7–19.6)	6.4 (0.8–21.3)
Prior lines of therapy, n, median (range)	6 (2–14)	5 (2–17)
Prior stem cell transplantation, n (%)	27 (90.0)	33 (75.0)
Exposure status, n (%)		
Triple-class[e]	30 (100)	43 (97.7)
Penta-drug[f]	24 (80.0)	30 (68.2)
BCMA-targeted therapy[g]	9 (30.0)	12 (27.3)
Refractory status, n (%)		
Triple-class[e]	23 (76.7)	34 (77.3)
Penta-drug[f]	6 (20.0)	12 (27.3)
Refractory to last line of therapy	26 (86.7)	39 (88.6)

[a]With 2–3 step-up doses. [b]Percentages calculated from total n=29 for 405 µg/kg SC QW and n=41 for 800 µg/kg SC Q2W. [c]Soft tissue plasmacytomas not associated with the bone were included. [d]del(17p), t(4:14), and/or t(14;16); calculated from n=27 for 405 µg/kg SC QW and n=40 for 800 µg/kg SC Q2W. [e]≥1 PIs, ≥1 IMiDs, and ≥1 anti-CD38 mAbs. [f]≥2 PIs, ≥2 IMiDs, and ≥1 anti–CD38 mAbs. [g]Includes antibody drug conjugates, bispecific antibodies, and chimeric antigen receptor T cell therapy.

IMiD, immunomodulatory drug; mAb, monoclonal antibody; PI, proteasome inhibitor

Safety

- Overall, the most common adverse events (AEs) were CRS, skin-related events, and dysgeusia
- Cytopenias were mostly confined to step-up and cycle 1–2 doses and generally resolved within 1 week
- Infections occurred in 46.7% of patients at 405 µg/kg QW and 38.6% at 800 µg/kg Q2W (grade 3/4: 6.7%/9.1%)
- CRS events were mostly grade 1/2 and were largely confined to the step-up doses and first full dose
- Dysgeusia was managed with supportive care, and at times with dose adjustments
- No patients died due to drug-related AEs

TABLE 2: Safety profile

AEs (≥20% of total SC population), n (%)	405 µg/kg SC QW[a] n=30		800 µg/kg SC Q2W[a] n=44	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic				
Neutropenia	20 (66.7)	18 (60.0)	18 (40.9)	15 (34.1)
Anemia	17 (56.7)	9 (30.0)	21 (47.7)	12 (27.3)
Lymphopenia	12 (40.0)	12 (40.0)	18 (40.9)	18 (40.9)
Leukopenia	12 (40.0)	9 (30.0)	10 (22.7)	8 (18.2)
Thrombocytopenia	11 (36.7)	7 (23.3)	10 (22.7)	5 (11.4)
Nonhematologic				
CRS	23 (76.7)	1 (3.3)	35 (79.5)	0
Skin-related AEs[b]	20 (66.7)	0	32 (72.7)	1 (2.3)
Dysgeusia	19 (63.3)	N/A	25 (56.8)	N/A
Nail-related AEs[c]	18 (60.0)	0	15 (34.1)	0
Rash-related AEs[d]	14 (46.7)	1 (3.3)	13 (29.5)	7 (15.9)
Dysphagia	12 (40.0)	0	12 (27.3)	0
Pyrexia	11 (36.7)	0	10 (22.7)	0
Fatigue	10 (33.3)	1 (3.3)	12 (27.3)	0
Dry mouth	9 (30.0)	0	25 (56.8)	0
Weight decreased	9 (30.0)	0	19 (43.2)	1 (2.3)
Nausea	9 (30.0)	0	9 (20.5)	0
Diarrhea	9 (30.0)	0	8 (18.2)	0
ALT increased	6 (20.0)	1 (3.3)	14 (31.8)	3 (6.8)
Decreased appetite	7 (23.3)	1 (3.3)	11 (25.0)	1 (2.3)
Headache	7 (23.3)	0	11 (25.0)	0
AST increased	3 (10.0)	0	14 (31.8)	3 (6.8)

AEs were graded by CTCAE v4.03 with CRS events graded per Lee et al 2014 criteria.

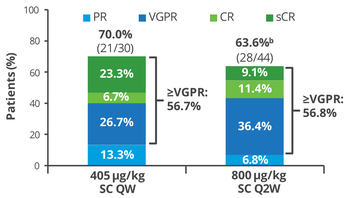
[a]With 2–3 step-up doses. [b]Includes skin exfoliation, pruritus, dry skin, skin ulcer, eczema, skin hyperpigmentation, skin lesion, asteatotic eczema, skin fissures, skin irritation, and skin toxicity. [c]Includes nail disorder, onychomadesis, nail discoloration, nail dystrophy, onycholasis, nail ridging, nail bed disorder, and nail hypertrophy. [d]Includes rash, maculopapular rash, dermatitis acneiform, erythematous rash, vesicular rash, dermatitis, contact dermatitis, and exfoliative generalized dermatitis.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; N/A, not applicable

Efficacy

- Overall response rates (ORRs) are shown in **Figure 2**

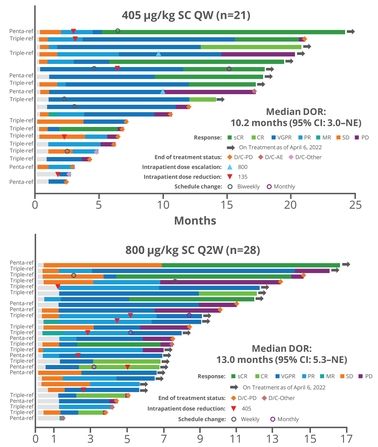
Figure 2: ORR[a]



[a]Investigator assessment of evaluable patients per 2011 IMWG response criteria; includes unconfirmed responses. [b]Due to rounding, individual response rates do not sum to the ORR. CR, complete response; IMWG, International Myeloma Working Group; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

- Median (range) time to first confirmed response was 0.9 months (0.2–3.8) at 405 µg/kg QW and 1.2 months (0.3–6.8) at 800 µg/kg Q2W
- The ORRs in key patient subgroups (405 µg/kg QW and 800 µg/kg Q2W, respectively) were:
  - Triple-class refractory: 65.2% (15/23) and 67.6% (23/34)
  - Penta-drug refractory: 83.3% (5/6) and 75.0% (9/12)
- Responses were durable and deepened over time (**Figure 3**)

FIGURE 3: Durability of response



D/C, discontinued; DOR, duration of response; NE, not estimable; MR, minimal response; PD, progressive disease; Penta-ref, penta-drug refractory; SD, stable disease; Triple-ref, triple-class refractory

Pharmacokinetics and pharmacodynamics

- The RP2Ds had comparable PK and PD profiles
- Antidrug antibodies were detected in 17.6% (13/74) of patients, were generally low titer, and did not appear to impact safety, efficacy, or PK
- Peripheral induction of PD-1+ T cells, which is indicative of T-cell activation, was observed with both RP2Ds
- Both RP2Ds were associated with consistent induction of cytokines (ie, IL-10, IL-6, IL-2Rα)

KEY TAKEAWAY

Talquetamab, a first-in-class, T-cell redirecting bispecific antibody targeting both GPRC5D and CD3 receptors, demonstrated robust efficacy in patients with heavily pretreated RRMM

CONCLUSIONS

- Both RP2Ds of talquetamab (405 µg/kg QW and 800 µg/kg Q2W) have comparable safety, efficacy, PK, and PD profiles
- These data with longer follow-up support the encouraging efficacy of the QW and Q2W schedules, with ORRs of 64–70% across triple-class and penta-drug refractory patients
- A phase 2 expansion study of both RP2Ds is ongoing (NCT04634552) and phase 1 studies are evaluating talquetamab in combination with other agents (NCT04586426; NCT04108195; NCT05050097)

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DISCLOSURES

MM served in a consulting/advisory role for Janssen and has served on speakers' bureaus for Celgene/BMS, Medscape, and Janssen. **AYK** reports leadership with Sutro, has stock/other ownership interests in BMS, has served in a consulting/advisory role for Janssen, BMS, Sanofi, Regeneron, Pfizer, and GSK, served on speakers' bureaus for Takeda, BMS, and GSK, and has received research funding from Janssen. **JGB** has served in a consulting/advisory role for Takeda, BMS, CRISPR therapeutics, Celgene, Kite, a Gilead Company, Janssen, Legend Biotech, Secura Bio, and Bluebird Bio; and has received research funding from Celgene, Takeda, BMS, Amgen, Janssen, Novartis, AbbVie, Bluebird Bio, Teva, Genentech/Roche, Poseida Therapeutics, Sanofi, Acetylon Pharmaceuticals, Lilly, Celularity, CRISPR Therapeutics, EMD Serono, Ichnos Sciences, GSK, and Incyte. **AO** has served in a consulting/advisory role for Celgene, Janssen, Amgen, Sanofi, and GSK, and has served on speakers' bureau for Amgen and Celgene. **NWCJvdD** has received honoraria from BMS/Celgene, has served in a consulting/advisory role for BMS/Celgene, Janssen, Amgen, Takeda, Roche, and Novartis/Bayer/Servier, and has received research funding from Janssen, Amgen, and Cellectis. **PRO** has served in a consulting/advisory role for Janssen, Oncopeptides, Sanofi, GSK, Pfizer, BMS, and has received honoraria from Janssen, Celgene, Amgen, Takeda, Oncopeptides, Sanofi, AbbVie, GSK, Kite, a Gilead Company, and Pfizer. **DM** has received honoraria from Janssen, Takeda, and AbbVie. **MVM** has served in a consulting/advisory role for Takeda, Janssen, Celgene, Amgen, AbbVie, GSK, Pfizer, Regeneron, and Roche/Genentech, and has received honoraria from Janssen, Celgene, Amgen, Takeda, GSK, AbbVie/Genentech, and Sanofi. **LJC** has served in a consulting/advisory role for AbbVie, Amgen, Celgene, and Karyopharm Therapeutics, has served on speakers' bureaus for Amgen, and Sanofi, has received honoraria from Amgen, Celgene, Janssen, Karyopharm Therapeutics, and Sanofi, and research funding from Janssen and Amgen. **JC** has served in a consulting/advisory role for Janssen, Celgene/BMS, and Sanofi; reports patent/royalties/other intellectual property for patent deposition on use of CD-38 binding nanobodies, and has received research funding from Janssen. **DV** is an employee of Janssen and reports stock and other ownership interests in Johnson & Johnson/Janssen. **JM** is an employee of and reports stock/other ownership interests in Johnson & Johnson/Janssen. **SY** is an employee of Johnson & Johnson. **BH** is an employee of and reports stock/other ownership interests in Janssen. **JT** is an employee of, reports stock/other ownership interests in, and has received research funding from Johnson & Johnson/Janssen. **JDG** is an employee of and reports stock/other ownership interests in Janssen. **AC** has served in a consulting/advisory role for Amgen, Janssen, Seagen, Karyopharm Therapeutics, Genzyme, OncoPeptides, Takeda, Antengene, GlaxoSmithKline, Secura Bio, Shattuck Labs, Genentech, AbbVie, and BMS/Celgene, and has received research funding from Celgene, Janssen, Amgen, Seagen, Takeda, and Pharmacyclics.

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