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First-in-Human Study of JNJ-79635322 (JNJ-5322), a Novel, Next-Generation Trispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Initial Phase 1 Results

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Key Takeaway

JNJ-5322, a BCMA×GPRC5D T-cell engaging trispecific antibody, demonstrated manageable safety and an ORR comparable to CAR-T, with convenient, off-the-shelf, Q4W dosing with 1 SUD to facilitate outpatient dosing

Conclusions

JNJ-5322 100 mg Q4W SC with 1 SUD (2–8 days before first full dose) of 5 mg was selected as the RP2D

JNJ-5322 appeared to have an improved or similar safety profile compared with bispecific antibodies targeting BCMA/GPRC5D

- Grade 3/4 infection rate of 28.6% with appropriate infection management
- Improved oral TEAE profile, with minimal to no weight loss
- CRS events were low grade with only 1 SUD; prophylactic tocilizumab data support option for outpatient dosing

ORR of 100% (≥CR, 70.4%) at the RP2D in patients naive to BCMA/GPRC5D

- 12-month PFS of 95.0% at the RP2D in BCMA/GPRC5D-naive patients

Introduction

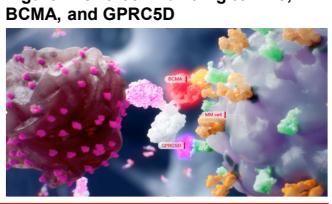
- Based on real-world evidence from a prospective observational study, LocoMMotion, the expected median progression-free survival (PFS) in patients with triple-class exposed relapsed/refractory multiple myeloma (RRMM) is 4.6 months[1]
- T-cell redirecting immunotherapies targeting a single myeloma antigen, including chimeric antigen receptor T-cell (CAR-T) and bispecific antibodies, have improved outcomes in patients with RRMM[2-6]
- Phase 1 RedirecTT-1 results, with an overall response rate (ORR) of 80% at the recommended phase 2 regimen of talquetamab + teclistamab, highlight the promise of dual-antigen targeting, including in patients with complex disease biology such as extramedullary disease[7]
- Despite these advances, there remains potential to further improve efficacy while reducing treatment burden
- We report the first results from an ongoing phase 1 study (NCT05652335) of JNJ-5322 in patients with triple-class exposed RRMM

Methods

Novel binding domains targeting CD3, BCMA, and GPRC5D

Molecule	Implications
Dual-targeted molecule to bind both BCMA and GPRC5D	• Enhanced myeloma cell targeting due to "**double lock-down**" effect of binding 2 myeloma antigens • More comprehensive targeting of myeloma cells • BCMA-/GPRC5D+, BCMA+/GPRC5D-, and dual BCMA+/GPRC5D+
Novel CD3, BCMA, and GPRC5D binding domains	• Prevention of antigen escape • Potential to improve GPRC5D-related safety profile • Manageable CRS profile with only 1 SUD needed

Figure 1: JNJ-5322 binding to CD3, BCMA, and GPRC5D



Key eligibility criteria
- Triple-class exposed RRMM[a]

Key objectives
- Identify RP2D
- Safety, including DLTs
- Preliminary efficacy assessment

N=147 all doses investigated (all SC)

Study design

Dose escalation
- 5 mg → 40–120 mg Q4W
- 3.6/5.0 mg → 10–30 mg Q2W
- MABEL 0.4 –10 mg Q2W

Dose optimization
- 5 mg → 50 mg Q4W
- 5 mg → 100 mg Q4W
- 5 mg → 100 mg → 300 mg Q4W

Loading dose/schedule optimization
- 5 mg → 200 mg Q4W[b] → 100 mg Q4W
- 5 mg → 100 mg Q8W
- 5 mg → 200 mg Q8W[c] → 100 mg Q8W

Optimization for outpatient dosing
- Lower (2.5 mg) vs higher (10 mg) SUD
- 2–4 vs 6–8 days between SUD and full dose
- Prophylactic tocilizumab

RP2D identification
- 5 mg SC → 100 mg Q4W SC

The RP2D with 1 SUD was determined based on safety-, PK-, and efficacy-guided endpoints; the MTD was not reached

[a]≥3 prior LOT or triple-class refractory in the United States. [b]200 mg given Q4W for 4 doses, then switched to 100 mg. [c]200 mg given Q8W for 2 doses, then switched to 100 mg. BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; GPRC5D, G protein–coupled receptor class C group 5 member D; LOT, line of therapy; MABEL, minimum anticipated biological effect level; MTD, maximum tolerated dose; PK, pharmacokinetics; Q2W, every other week; Q4W, every 4 weeks; Q8W, every 8 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous; SUD, step-up dose.

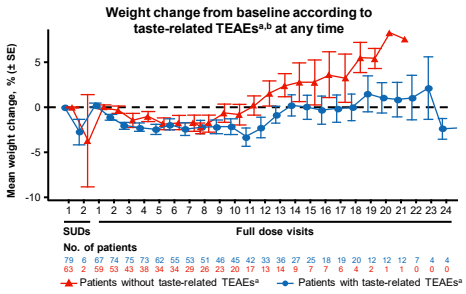
Results

Table 1: Baseline characteristics

Characteristic	RP2D (n=36)	All doses (N=147)
Median FU, months (range)	11.6 (0.4–18.6)	9.3 (0.3–25.8)
Median age, years (range)	67.5 (43–87)	64.0 (39–87)
Male, n (%)	22 (61.1)	87 (59.2)
Race, n (%)		
White	28 (77.8)	110 (74.8)
Black/African American	1 (2.8)	13 (8.8)
Asian	1 (2.8)	7 (4.8)
Multiple	2 (5.6)	2 (1.4)
Unknown/not reported	4 (11.1)	15 (10.2)
Extramedullary plasmacytomas ≥1,[a] n (%)	3 (8.3)	16 (10.9)
High-risk cytogenetics,[b] n (%)	9 (27.3)	39 (31.2)
ISS stage,[c] n (%)		
I	19 (52.8)	77 (53.1)
II	12 (33.3)	50 (34.5)
III	5 (13.9)	18 (12.4)
Years since diagnosis,[d] median (range)	7.0 (0.9–18.7)	6.9 (0.7–31.9)
Median prior LOT, n (range)	4.0 (2–11)	4.0 (1–11)
Exposure status, n (%)		
Triple-class[e]	36 (100.0)	147 (100.0)
Penta-drug[f]	15 (41.7)	72 (49.0)
BCMA/GPRC5D exposed	9 (25.0)	29 (19.7)
BCMA/GPRC5D naive	27 (75.0)	118 (80.3)
Refractory status, n (%)		
PI	19 (52.8)	86 (58.5)
IMiD	36 (100.0)	136 (92.5)
Anti-CD38	36 (100.0)	138 (93.9)
Triple-class[e]	19 (52.8)	79 (53.7)
Penta-drug[f]	2 (5.6)	10 (6.8)
To last LOT	34 (94.4)	132 (89.8)

Data cut-off date: April 15, 2025. RP2D selected as 100 mg Q4W with 1 5-mg SUD. [a]≥1 nonradiated, bone-independent lesion ≥2 cm. Patients with paraskeletal plasmacytomas were permitted but not counted as EMD. [b]FISH or karyotype testing in n=33 (RP2D) and n=125 (total). Defined as del(17p), t(4;14), or t(14;16). [c]In n=145 (total), [d]In n=35 (RP2D) and n=144 (total). [e]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [f]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb. FISH, fluorescence in situ hybridization; FU, follow-up; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor.

Figure 2: GPRC5D oral TEAEs and weight changes

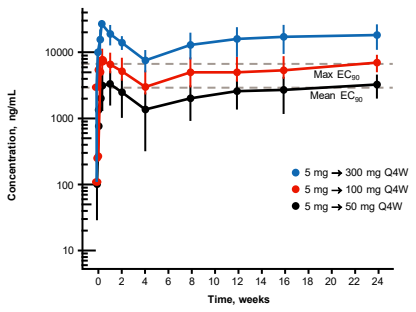


Data cut-off date: April 15, 2025. Median follow-up: 11.6 months (RP2D) and 9.3 months (all doses). RP2D selected as 100 mg Q4W with 1 5-mg SUD. [a]Includes dysgeusia, ageusia, hypogeusia, and taste disorder. [b]Weight measurements were used to assess weight loss, and then the percentage change from baseline was graded per CTCAE. CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Grade 1/2 taste-related AEs occurred in 58% (RP2D or all doses). Grade 1/2 weight loss is usually transient. No grade ≥3 events

Pharmacokinetics
- Exposure: ~ dose-proportional increase across all doses
- Steady state: reached after 12 weeks, estimated half-life ~17 days
- Mean serum concentration: slowly increased across all doses; reached a median maximum after 7 days for Q4W dosing

Figure 3: Mean serum concentration–time profiles



RP2D selected as 100 mg Q4W with 1 5-mg SUD. EC_{90}, 90% maximal effective concentration.

At the RP2D, the mean serum concentration was maintained above the mean EC_{90}

Table 2: Treatment-emergent adverse events

Most common TEAEs,[a] n (%)	RP2D (n=36) Any Grade	RP2D (n=36) Grade 3/4	All doses (N=147) Any Grade	All doses (N=147) Grade 3/4
Hematologic TEAEs (≥10% of total)				
Neutropenia	15 (41.7)	11 (30.6)	72 (49.0)	61 (41.5)
Lymphopenia	16 (44.4)	15 (41.7)	55 (37.4)	52 (35.4)
Anemia	6 (16.7)	3 (8.3)	37 (25.2)	22 (15.0)
Thrombocytopenia	8 (22.2)	3 (8.3)	27 (18.4)	12 (8.2)
Leukopenia	5 (13.9)	3 (8.3)	19 (12.9)	11 (7.5)
Nonhematologic TEAEs (≥30% of total)				
Infections	29 (80.6)	12 (33.3)	111 (75.5)	42 (28.6)
Taste related[b]	21 (58.3)	NA	85 (57.8)	NA
CRS	19 (52.8)	0	83 (56.5)	0
Nail related[c]	22 (61.1)	0	81 (55.1)	0
Skin (nonrash)[d]	23 (63.9)	0	73 (49.7)	1 (0.7)
Hypogammaglobulinemia[e]	10 (27.8)	1 (2.8)	53 (36.1)	4 (2.7)
Diarrhea	11 (30.6)	1 (2.8)	49 (33.3)	5 (3.4)
Fatigue	13 (36.1)	3 (8.3)	48 (32.7)	4 (2.7)

Data cut-off date: April 15, 2025. Median follow-up: 11.6 months (RP2D) and 9.3 months (all doses). RP2D selected as 100 mg Q4W with 1 5-mg SUD. [a]TEAEs graded by CTCAE v5.0; CRS per ASTCT criteria. [b]Dysgeusia, ageusia, hypogeusia, and taste disorder; maximum grade is 2 per CTCAE. [c]Nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxicity, and nail ridging. [d]Skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome. [e]Presented as a TEAE only. NA, not applicable.

- At RP2D: 1 DLT (neutropenia), 1 grade 5 TEAE (pneumonia)
- All other doses: 4 DLTs (maculopapular rash, palmar-plantar erythrodysesthesia syndrome, pneumonia, and respiratory failure), and 4 grade 5 TEAEs (adenoviral encephalitis [drug related], embolic stroke, multiple organ dysfunction syndrome, and pulmonary hemorrhage)

Table 3: CRS and ICANS

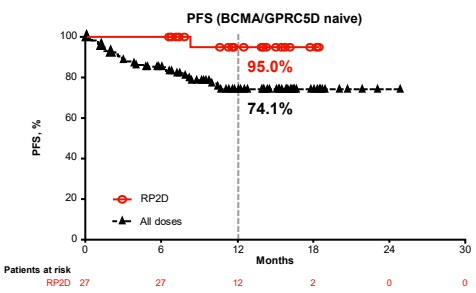
Parameter	100 mg without prophylactic tocilizumab (n=26)	100 mg with prophylactic tocilizumab (n=20)
Patients with CRS,[a] n (%)	18 (69.2)	4 (20.0)
Grade 1	14 (53.8)	4 (20.0)
Grade 2	4 (15.4)	0
Grade 3	0	0
Onset of CRS,[b] days, median (range)	2 (1–4)	1 (1–2)
Duration of CRS, days, median (range)	2 (1–5)	2 (2–2)
Timing of CRS,[c] n (%)		
SUD 1	12 (46.2)	2 (10.0)
First full dose	10 (38.5)	2 (10.0)
≥Second full dose	0	1 (5.0)
Supportive measures for CRS,[d] n (%)	17 (65.4)	4 (20.0)
Tocilizumab	12 (46.2)	2 (10.0)
Oxygen	3 (11.5)	0
Corticosteroids	1 (3.8)	2 (10.0)
Other	14 (53.8)	4 (20.0)
CRS recovered or resolved	18 (100.0)	4 (100.0)

Data cut-off date: April 15, 2025. Median follow-up: 11.6 months (RP2D) and 9.3 months (all doses). RP2D selected as 100 mg Q4W with 1 5-mg SUD. [a]CRS and ICANS graded per ASTCT criteria. [b]Relative to the most recent dose. [c]Patients could experience ≥1 event. [d]Patients could receive ≥1 supportive therapy. ICANS, immune effector cell–associated neurotoxicity syndrome.

- No patients had ICANS at the RP2D

Prophylactic tocilizumab decreased CRS incidence/severity

Figure 7: PFS (BCMA/GPRC5D naive)



12-month PFS 95.0% at the RP2D (74.1% across all doses). PFS data support the RP2D

Table 4: Infections summary

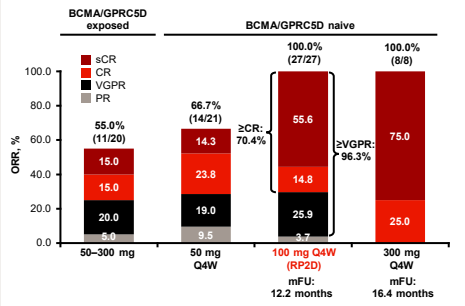
Most common infections (≥10% of total)[a] and hypogammaglobulinemia,[b] n (%)	RP2D (n=36) Any Grade	RP2D (n=36) Grade 3/4	All doses (N=147) Any Grade	All doses (N=147) Grade 3/4
Infections	29 (80.6)	12 (33.3)	111 (75.5)	42 (28.6)
Upper respiratory tract infection	14 (38.9)	1 (2.8)	44 (29.9)	4 (2.7)
Pneumonia	6 (16.7)	4 (11.1)	28 (19.0)	21 (14.3)
COVID-19	5 (13.9)	0	21 (14.3)	1 (0.7)
Nasopharyngitis	4 (11.1)	0	15 (10.2)	0
Urinary tract infection	5 (13.9)	1 (2.8)	15 (10.2)	1 (0.7)
Hypogammaglobulinemia	18 (50.0)		90 (61.2)	
Patients receiving ≥1 dose of IVIG[c]	17 (47.2)		83 (56.5)	

Data cut-off date: April 15, 2025. Median follow-up: 11.6 months (RP2D) and 9.3 months (all doses). RP2D selected as 100 mg Q4W with 1 5-mg SUD. [a]TEAEs graded by CTCAE v5.0. TEAEs listed by descending order of frequency in the total population. [b]Patients with ≥1 TEAE or postbaseline IgG value <400 mg/dL. [c]Includes patients who started IVIG prior to treatment. Ig, immunoglobulin; IVIG, intravenous immunoglobulin.

- 2 patients died due to infections (adenovirus encephalitis, pneumonia) in setting of hypogammaglobulinemia (<200 mg/dL)

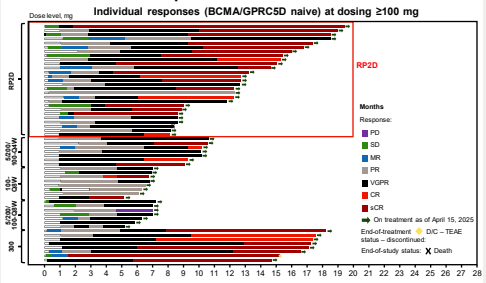
Infections can be managed with monthly IgG monitoring and Ig replacement to maintain IgG ≥400 mg/dL

Figure 4: ORR in patients naive or exposed to BCMA/GPRC5D therapies



Data cut-off date: April 15, 2025. RP2D selected as 100 mg Q4W with 1 5-mg SUD. CR, complete response; mFU, median follow-up; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

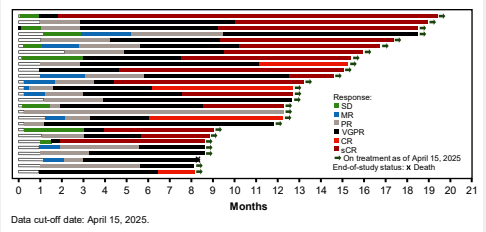
Figure 5: Individual response in patients naive to BCMA/GPRC5D therapies



Data cut-off date: April 15, 2025. RP2D selected as 100 mg Q4W with 1 5-mg SUD. [a]1 patient was in response at time of death. D/C, discontinued; MR, minimal response; PD, progressive disease; SD, stable disease.

Almost all patients remain in response at 12 months of FU[a]

Figure 6: Individual responses (BCMA/GPRC5D naive) at RP2D (100 mg Q4W with 1 5-mg SUD)



Data cut-off date: April 15, 2025.

1 discontinuation at the RP2D (death while in VGPR). No progression or other discontinuations at RP2D to date

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References

1. Mateos MV, et al. *Leukemia* 2024;38:2554-60. 2. Moreau P, et al. *N Engl J Med* 2022;387:495-505. 3. Lesokhin A, et al. *Nat Med* 2023;29:2259-67. 4. Chari A, et al. *Lancet Hematol* 2025;12:E269-E281. 5. Munshi NC, et al. *N Engl J Med* 2021;384(8):705-16. 6. Berdeja JG, et al. *Lancet* 2021;398(10297):314-24. 7. Cohen Y, et al. *N Engl J Med* 2025;9;392:138-49.

Multiple Myeloma

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