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Clinical Pharmacology Strategies to Support Dose Optimization of the Recommended Phase 2 Dose Regimen of JNJ-5322, a BCMA×GPRC5D×CD3 Trispecific Antibody, in Relapsed/Refractory Multiple Myeloma

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Key Takeaways

The optimal dose and schedule of ramantamig was a single step-up dose (SUD) of 5 mg subcutaneous (SC) followed by a fixed 100 mg monthly treatment dose, providing a more convenient dosing schedule vs first-generation bispecific antibodies while optimizing safety and efficacy

Population pharmacokinetic (PK) and exposure-response (E–R) analyses guided extensive dose optimization of the ramantamig recommended phase 2 dose (RP2D), a dose which seems to be consistent with initiatives to define the minimally efficacious dose[1]

Conclusions

Clinical response plateaued at exposures at or above the RP2D, with lower exposure associated with inferior response

There was no relationship between exposure and key treatment-emergent adverse events (TEAEs), including weight loss and grade ≥3 infections

A 5-mg SUD before the 100-mg RP2D dose effectively minimized the occurrence of cytokine release syndrome (CRS) following both SUD and treatment doses

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Poster

Supplementary material

hhttps://www.congresshub.com/ASH2025/Oncology/Ramantamig/Nguyen

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Disclosures
AN is an employee of Johnson & Johnson.

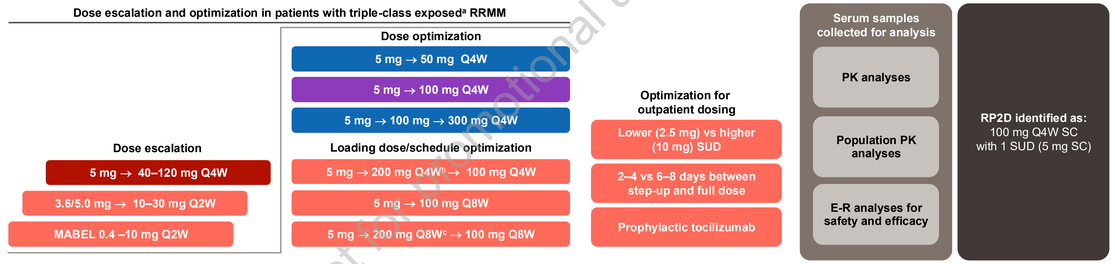
Introduction

- Ramantamig (JNJ-5322) is a next-generation trispecific antibody that contains novel B-cell maturation antigen (BCMA), G protein–coupled receptor class C group 5 member D (GPRC5D), and CD3 binding domains, and has shown potent and selective T-cell–mediated antitumor activity against BCMA- and GPRC5D-expressing cells[2]
- In a first-in-human study (NCT05652335) in patients with relapsed/refractory multiple myeloma (RRMM), ramantamig was characterized by a manageable safety profile and promising efficacy with an overall response rate (ORR) of 100% and 12-month progression-free survival rate of 95% in patients naive to BCMA/GPRC5D therapies[3]

We present pharmacology data supporting the RP2D of 100 mg every 4 weeks (Q4W) with 1 SUD of 5 mg; data collected through Feb 2025

Methods

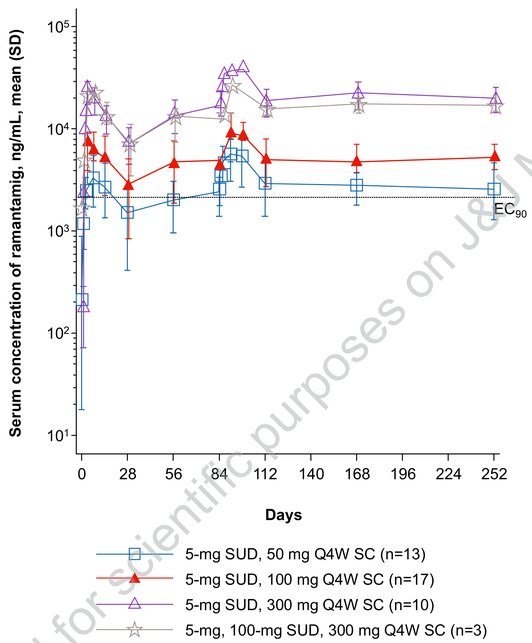
Phase 1 study design and PK analyses



[a]≥1 proteasome inhibitor, ≥1 immunomodulatory drug, and ≥1 anti-CD38 monoclonal antibody. Eligibility criteria in the United States included ≥3 prior lines of therapy or triple-class refractory. [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. MABEL, minimum anticipated biologic effect level; Q2W, every other week; Q8W, every 8 weeks.

Results

Figure 1: At the RP2D (100 mg Q4W), the mean ramantamig serum concentration was maintained at or above the mean concentration associated with the 90% maximal drug effect identified in an ex vivo cytotoxicity assay (EC_{90})



Ramantamig exhibited approximately dose-proportional increases in exposure across all doses; steady state was reached after 12 weeks with an estimated steady state half-life of 17 days

Population PK and covariate analyses revealed that no dose adjustments were required based on the clinically relevant covariates tested (eg, body weight, tumor burden)

Figure 2: E–R analyses for efficacy across all doses showed that a maximal ORR was observed at or above 100 mg Q4W, which was determined to be the RP2D; exposures with lower doses or less frequent dosing (50 mg Q4W or 100 mg Q8W) did not provide efficacy comparable to the RP2D, while exposures at or above the RP2D provided comparable ORR (A) and very good partial response (VGPR) or better (B)

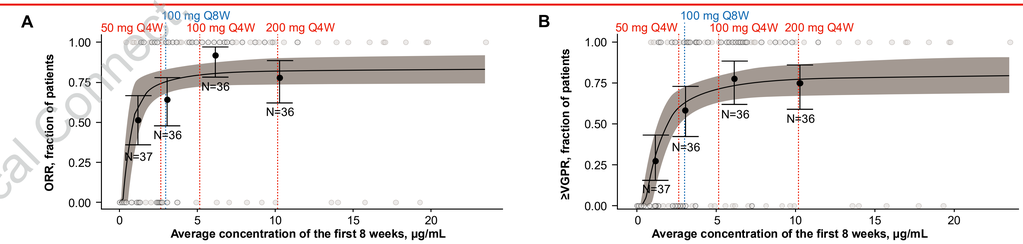
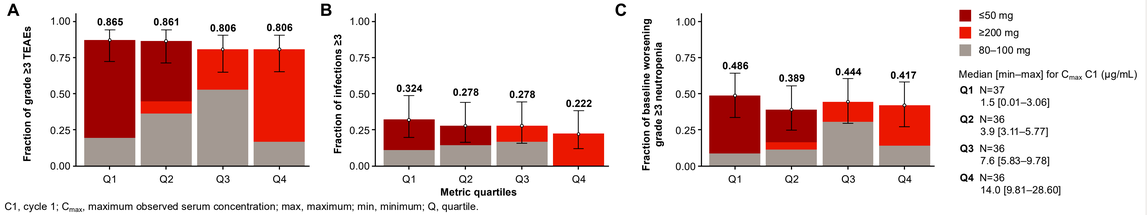
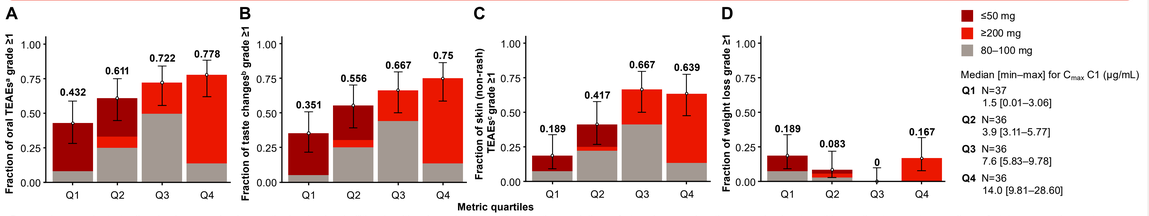


Figure 3: E–R analyses for safety across all doses showed no relationships across grade ≥3 TEAEs (A), grade ≥3 infections (B), and grade ≥3 neutropenia (C); lower drug exposures were not associated with additional safety benefit across the majority of clinically significant TEAEs



C1, cycle 1; C_{max}, maximum observed serum concentration; max, maximum; min, minimum; Q, quartile.

Figure 4: Although there was an E–R relationship observed for GPRC5D-related TEAEs, including oral TEAEs (A), taste changes (B), and skin TEAEs (C), there was no relationship observed with weight loss (D), and the increased TEAE rates from 50- to 100-mg exposure were minimal; 100 mg Q4W was well tolerated and adverse events were manageable[3]



[a]Dysgeusia, ageusia, taste disorder, hypogeusia, dry mouth, dysphagia, cheilitis, glossitis, glossodynia, mouth ulceration, oral discomfort, oral mucosal erythema, oral pain, stomatitis, swollen tongue, tongue discomfort, tongue erythema, tongue edema, and tongue ulceration. [b]Dysgeusia, ageusia, hypogeusia, and taste disorder. [c]Skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome.

E–R analyses substantiated the use of 5 mg as the optimal SUD for the subsequent 100-mg treatment dose that resulted in manageable incidence of CRS; higher SUDs (eg, ≥7.5 mg) increased the incidence of CRS at the SUD, while a lower SUD (2.5 mg) reduced the incidence of CRS after the SUD but increased the overall incidence of CRS during the subsequent 100-mg treatment dose (Supplemental Figure). The risk of grade ≥2 CRS was comparable for all SUDs tested (0.4–20 mg; data not shown)

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1. US Food and Drug Administration. Project Optimus. 2024. Accessed November 5, 2025. https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus. 2. Pillarisetti K, et al. Presented at ASH; December 9–12, 2023; San Diego, CA, USA. 3. van de Donk NWCJ, et al. Presented at ASCO; May 30–June 3, 2025; Chicago, IL, USA & Virtual.

Multiple Myeloma

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