1. SYNOPSIS

Name of Sponsor/Company	Janssen Research and Development
Name of Finished Product	DARZALEX
Name of Active Ingredient(s)	JNJ-54767414 (daratumumab)

Protocol No.: 54767414NAP4001

Title of Study: A Post-authorization Safety Study to Evaluate the Incidence of and Risk Factors for Severe and Fatal Infusion-related Reactions in Patients Treated with Daratumumab (Intravenous or Subcutaneous)

Sponsor's Responsible Party: PPD , MD, Executive Medical Director Oncology **(Main Author)**

Keywords: multiple myeloma, daratumumab, infusion-related reaction

EU PAS Register Number: EUPAS49827

Marketing Authorization Holder(s): Janssen Biotech, Inc.

Study Center(s): Brazil, Canada, Czech Republic, France, Germany, Italy, Netherlands, Poland, Spain, United Kingdom, United States including Puerto Rico

Publication (Reference): None

Study Period: 9 December 2022 to 23 September 2025

Rationale and Background: Daratumumab is a first-in-class, human immunoglobulin G1 kappa monoclonal antibody (mAb) that specifically binds to the cell surface molecule cluster of differentiation (CD)38. Daratumumab is being developed for the treatment of multiple myeloma (MM) and other malignancies. This study is being conducted CCI by conducting a prospective, observational, single-arm study to assess the risk of severe (Grades 3 to 4) and fatal (Grade 5) IRRs in patients with MM treated with IV or SC daratumumab.

Research Question and Objectives: This single-arm, prospective, observational study aimed to assess the risk of severe (Grades 3 to 4) and fatal (Grade 5) IRRs in patients treated with IV or SC daratumumab for the treatment of MM in the clinical practice setting and to attempt to identify potential risk factors.

Study Design: This was a prospective, observational, single-arm, multicenter study to assess the incidence of and risk factors for severe (Grades 3 to 4) and fatal (Grade 5) IRRs in patients (anti-CD38-naïve) with MM during or following the first 3 administrations of daratumumab (IV or SC) in a clinical practice setting in accordance with approved local labeling. Administration of daratumumab was provided as part of routine clinical practice and was not influenced by enrollment in the study.

Setting: In this study, data was collected during daratumumab IV and/or SC therapy in routine clinical practice.

Participant Population and Study Size: At each site, the investigators determined the eligibility of patients for data collection in this study based on the protocol-specified selection criteria. Patients must have been at least 18 years old or of legal consenting age per local regulations and must have been starting daratumumab treatment for the first time in accordance with the approved label. Patients must have signed an informed consent form (ICF) allowing source data verification in accordance with local

requirements. The study's goal was to enroll 1,000 patients for a fair estimation of incidence rate of severe and fatal IRRs.

Variables and Data Sources: The primary data source for this study was the medical record of each patient with MM who had provided a signed ICF. The variables collected included demographics, disease characteristics, medical history, laboratory values, current and ongoing treatments and other medications. For each of the first 3 administrations of daratumumab, the investigators specified the date and time of administration and the formulation of daratumumab. All AEs were entered into the eCRF by the investigator, including their start and stop time and date. In this study, the term 'IRRs' referred to both systemic administration-related reactions for patients receiving daratumumab SC and systemic infusion-related reactions for patients receiving daratumumab IV. Local injection-site reactions (eg, bruising, edema at injection-site) were not considered IRRs. A list of key IRR signs/symptoms were provided to investigators. Deaths due to any cause were captured from medical records and from other healthcare professionals and caregivers in the 30-day period (early discontinuation prior to the fourth dose) or 7-day period (follow-up until the fourth dose only) following the last administration of daratumumab for the study.

Statistical Methods: Descriptive summaries were provided for treatment-emergent IRRs, treatment-emergent adverse events (TEAEs), demographics, baseline characteristics, daratumumab exposure, laboratory tests, etc. Continuous variables were summarized in terms of the number of observations, mean, standard deviation (SD), minimum, median, maximum, Q1 and Q3. Categorical variables were summarized by number and percentage in each category.

RESULTS: All analyses were performed on the safety analysis set, which included all patients who received at least 1 administration of daratumumab IV or SC formulation.

Participant Information: Of the 1029 patients screened, 1009 (98.1%) patients met the eligibility criteria and signed the ICF to enroll in the study. A total of 1003 patients received at least 1 dose of daratumumab and were included in the safety analysis set: 38 received daratumumab IV, 959 received daratumumab SC and 6 patients switched from IV to SC formulation during the first 3 administrations. Overall, 33 (3.3%) patients from the safety analysis set prematurely discontinued study participation.

Demographics And Baseline Information: Overall, the median age of patients was 72.0 years (range: [31; 92]), the majority were aged ≥65 years, and 56.6% were male. The race of patients included 858 (85.5%) white, 49 (4.9%) black or African American, 12 (1.2%) Asian, 9 (0/9%) other, 4 (0.4%) Native Hawaiian or other Pacific Islander and 3 (0.3%) each American Indian/Alaska Natives and multiple races. Of the 181 patients enrolled in the United States, 64 (35.4%) patients were from an under-represented minority race/ethnicity, including 33 (18.2%) black or African American and 22 (12.2%) Hispanic or Latino patients. At baseline, 287 (28.6%) patients were classified as ISS Stage I, 308 (30.7%) patients as ISS Stage II and 258 (25.7%) patients as ISS Stage III. The majority of the patients (850 [84.8%] patients) had an ECOG performance score of ≤2. The median time from the first diagnosis of MM to enrollment in the study was 0.09 years (range: [0; 34.3]).

Treatment Information: Overall, in the safety analysis set, 962 (95.9%) patients had received all 3 doses of daratumumab during the study. Daratumumab administration modifications (ie, dose delay; infusion rate increase or decrease; or administration interruption or abortion) were reported for 22/44 (50.0%) patients receiving daratumumab IV and 148/959 (15.4%) patients receiving daratumumab SC. Paracetamol and dexamethasone were the most frequently reported pre-treatment medications. Pre-treatment use of paracetamol was reported by 97.6%, 94.2%, and 91.1% of patients prior to the first, second and third daratumumab administration, respectively and pre-treatment use of dexamethasone was received by 85.6%, 82.7% and 81.4% patients prior to the first, second and third daratumumab administration, respectively. Dexamethasone was the most frequently reported post-treatment medication, received by 24.6%, 23.0%, and 20.7% of patients following first, second, and third daratumumab

administrations, respectively.

Outcomes of Interest:

Treatment-Emergent IRRs: Overall, 72 (7.2%) patients experienced a total of 126 IRR events following daratumumab administration: 16/44 (36.4%) treated with daratumumab IV and 56/959 (5.8%) treated with daratumumab SC. The majority of the events (108/126 [85.7%]) were recovered or resolved. Grade ≥3 IRRs were reported for 1/44 (2.3%) patient treated with daratumumab IV and 5/959 (0.5%) patients treated with daratumumab SC. Of the Grade ≥3 IRRs, all were Grade 3; no Grade 4 or Grade 5 IRRs were reported in this study.

Safety:

Adverse Events: Overall, 560 (55.8%) patients experienced TEAEs, 193 (19.2%) experienced Grade 3 or 4 TEAEs and 105 (10.5%) experienced serious TEAEs. Overall, TEAEs leading to daratumumab dose modifications were reported for 149/1003 (14.9%) patients, including 12/38 (31.6%) patients who received daratumumab IV, 134/959 (14.0%) patients who received daratumumab SC, and 3/6 (50%) patients had switched from IV to SC formulation. TEAEs leading to discontinuation of daratumumab were reported for 28 (2.8%) patients, of whom 3/38 (7.9%) patients had received daratumumab IV and 25/959 (2.6%) patients had received daratumumab SC. TEAEs leading to treatment discontinuation were reported for 19 (1.9%) patients of whom 2/38 (5.3%) had received daratumumab IV and 17/959 (1.8%) had received daratumumab SC. TEAEs leading to death were reported for 13 (1.3%) patients of whom 2 (5.3%) had received daratumumab IV and 11 (1.1%) had received daratumumab SC.

Adverse Events of Clinical Interest: Overall, treatment-emergent cytopenia events were reported for 144 (14.4%) patients and treatment-emergent Grade 3 or 4 cytopenia events were reported for 93 (9.3%) patients. Neutropenia (92 [9.2%] patients), Anemia (55 [5.5%] patients), and Thrombocytopenia (38 [3.8%] patients) were the most frequently occurring cytopenia events.

Overall, 16 (1.6%) patients experienced a treatment-emergent hemorrhage event. Grade 3 or 4 Hemorrhage event was reported for 1 (0.1%) patient.

Overall, treatment-emergent infections were reported for 109 (10.9%) patients and Grade 3 or 4 treatment-emergent infections were reported for 42 (4.2%) patients.

Overall, 17 (1.7%) patients died: 13 (1.3%) patients due to adverse events, 3 (0.3%) patients due to disease progression, and 1 (0.1%) patient due to ‘Other’ reasons.

No secondary primary malignancy was reported.

DISCUSSION AND CONCLUSION:

DISCUSSION: The study population of 1003 patients was generally representative of the population of patients with MM in terms of demographic and disease characteristics. The study has fulfilled enrollment of at least 15% minority and/or underserved populations in the United States as proposed. IRRs during the study were reported for a total of 72/1003 (7.2%) patients, which included 16/44 (36.4%) patients receiving daratumumab IV and 56/959 (5.8%) patients receiving daratumumab SC. Grade 3 IRRs were reported for a total of 6/1003 (0.6%) patients (1/44 [2.3%] received daratumumab IV and 5/959 [0.5%] received daratumumab SC), and no Grade 4 or Grade 5 IRRs were reported. IRRs occurred primarily during the initial infusion, with higher incidence associated with the daratumumab IV formulation and substantially lower incidence with the daratumumab SC formulation. All adverse events assessed as IRRs or severe IRRs by the adjudication committee were also initially assessed and reported as IRRs or severe IRRs by the investigators, suggesting no underreporting of events. This was further supported by the IRR reliability assessment, with moderate overall agreement between investigators and adjudicator assessments as indicated by the Cohen’s kappa coefficient.

CONCLUSIONS: This study was conducted in adult patients with MM treated with daratumumab IV and SC formulations for the first time in routine clinical practice. No IRR-related deaths were observed and severe IRRs were uncommon. The IRR adjudication results further suggest there was no evidence of underreporting of IRR events by investigators. The risk of severe and fatal IRRs observed in this study to date is comparable to that reported in the daratumumab product label. The analysis to identify potential risk factors of severe/fatal IRRs could not be performed due to the small number of severe IRR events observed in this study. The AEs reported during the study were consistent with the known safety profile of daratumumab. There were no new or unexpected safety findings.

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