SYNOPSIS

Study Title: A Phase 2 Study of Daratumumab Subcutaneous (Dara-SC) Administration in Combination with Carfilzomib and Dexamethasone (DKd) Compared with Carfilzomib and Dexamethasone (Kd) in Participants with Multiple Myeloma who have been Previously Treated with Daratumumab to Evaluate Daratumumab Retreatment

Study Number: 54767414MMY2065

Study Phase: Phase 2

Name of Study Intervention: JNJ-54767414 daratumumab

Trade Name/Device Identification: Darzalex

Name of Sponsor/Company: Janssen Research & Development *

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Status: approved

Date: 25 September 2023

Prepared by: Janssen Research and Development, LLC

Study Name: LYNX

EudraCT	2018-004185-34

Number of Study Center(s) and Countries/Territories:

This study was initiated in 108 sites. Fifty-two sites screened at least 1 patient and 44 sites randomized at least 1 patient. The study was conducted in Belgium, Brazil, Canada, Denmark, Germany, Greece, France, Italy, Netherlands, Poland, Russia, Spain, and United States.

Publications (if any):

None

Study Period:

17 July 2019 (date first participant screened) to 02 February 2023 (date of last observation recorded for this final analysis).

Rationale:

Daratumumab responders who relapse were reported to become re-sensitized (responded again) following an adequate treatment break or by switching to a different daratumumab containing combination regimen. Two patients with triple refractory (IMiDs, PIs, and cytostatics) multiple myeloma were retreated with daratumumab IV with a partial response after relapsing from a prior line of therapy containing daratumumab. A retrospective study of 34 patients at Emory University Hospital, using daratumumab in combination with pomalidomide and dexamethasone, showed that patients with prior daratumumab exposure may be effectively retreated with daratumumab in a re-intensified dosing schedule. These data suggest that retreatment with daratumumab may result in a multiple myeloma disease response. However, the clinical benefit of daratumumab retreatment has not been systematically evaluated. As daratumumab moves into frontline treatment, evidence to support retreatment with daratumumab among patients with disease progression was needed.

Objectives and Endpoints

Objectives	Endpoints
Primary	
Compare the efficacy of Dara-SC in combination with Kd with the efficacy of Kd in participants with RRMM who were previously exposed to daratumumab to evaluate daratumumab retreatment	Rate of VGPR or better as defined by the IMWG criteria
Secondary	
To further characterize the efficacy of Dara-SC in combination with Kd	ORR is defined as the proportion of participants who achieve PR or better responses (ie PR, VGPR, CR, sCR) Rate of CR/sCR PFS OS
To evaluate the MRD negativity rate and durability of MRD negativity status	MRD negativity rate
To characterize the safety of Dara-SC in combination with Kd	
To determine time to next treatment	Time to next treatment
To evaluate the PK of daratumumab	Serum daratumumab concentrations

To determine the immunogenicity of daratumumab and rHuPH20	Prevalence and incidence of anti-daratumumab antibodies and anti-rHuPH20 antibodies

Statistical Analyses:

Sample Size Determination:

The sample size calculation was based on the following assumptions. Based on Study 54767414MMY1001 data, the rate of VGPR or better as the best response was 68% for DKd participants not previously treated with daratumumab. If VGPR or better rate is assumed to be 60% for DKd and 45% for Kd, 230 participants (assigned 1:1) were planned to be enrolled to detect an absolute 15% increase in VGPR or better rate with 70% power using a 2-sided chi-squared test at the 10% significance level.

Efficacy Analyses:

The primary endpoint of VGPR rate or better was defined as the proportion of participants who achieve VGPR, CR, or sCR as the best response according to the IMWG criteria, after initial dose of study intervention and before PD or start of subsequent antimyeloma treatment. The rate of VGPR or better was compared between the treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors were prior PI exposure and daratumumab-free interval (3-6 months, >6 months) at randomization.

Categorical secondary endpoints including ORR, rate of CR/sCR, and MRD negativity rate, were analyzed similar to the primary endpoint. The time-to-event efficacy endpoints, such as PFS, OS, and time to next treatment, were analyzed using the Kaplan-Meier method.

The primary analysis was carried out with a 2-sided alpha level of 0.10. The secondary efficacy analyses were carried out using 2-sided alpha level of 0.10 without multiplicity adjustment.

An interim futility analysis was planned to occur when 40% of participants were enrolled and treated for 6 months. A final analysis was planned to occur at study completion/end of the study to update PFS, survival, second primary malignancy and safety.

Pharmacokinetic Analyses:

The PK analysis set included all participants who received at least 1 dose of daratumumab SC and had at least 1 post-dose PK sample. Descriptive statistics were used to summarize serum daratumumab concentrations at each sampling time point for all participants in the PK analysis set.

Immunogenicity Analyses:

The incidence of anti-daratumumab antibodies was summarized for all participants who received at least 1 dose of daratumumab and had results from at least 1 study sample analyzed for anti-daratumumab antibodies obtained after the first dose of daratumumab. The incidence of anti-rHuPH20 antibodies was summarized for all participants who received at least 1 dose of

daratumumab and had at least 1 sample for detection of anti-rHuPH20 antibodies obtained after the first dose of daratumumab.

Methodology:

This was a Phase 2, open-label, randomized study which enrolled participants in Belgium, Brazil, Canada, Denmark, Germany, Greece, France, Italy, Netherlands, Poland, Russia, Spain, and United States to determine the efficacy of DKd in adult participants with RRMM who had 1 to 3 prior line(s) of treatment including a line containing daratumumab to evaluate daratumumab retreatment. Participants must have completed daratumumab at least 3 months prior to randomization. The study was conducted in 3 phases: Screening, Treatment, and Follow-Up. During the Treatment Phase, participants were randomized to receive Kd or DKd. Participants were stratified by prior PI exposure and daratumumab-free interval (3-6 months, >6 months). Participants in both arms received study intervention until confirmed PD, death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurred first. Follow-up of participants for disease progression and survival continued during the Follow-up Phase.

Number of Participants (planned and analyzed):

The planned total sample size was approximately 115 participants per group. An interim futility analysis was planned after 40% of participants (approximately 92 participants) were enrolled and treated for 6 months. Due to low enrollment, the planned interim futility analysis was redefined for when approximately 80 participants were enrolled and had at least 2 months of treatment to ensure futility was determined in a timely manner. At the interim futility analysis (CCO of 15 August 2022), there were 82 participants enrolled in the study and enrollment was ongoing. At the time of study termination, a total of 88 participants were enrolled in the study. The last observation recorded for this final analysis occurred on 02 February 2023.

The primary and secondary efficacy analyses are based on the ITT analysis set which included 88 randomized participants (ITT analysis set: 44 in the DKd group and 44 in the Kd group).

Summaries of adverse events and other safety data are based on 86 participants (safety analysis set: 43 in the DKd group and 43 in the Kd group), who were randomized, received at least 1 dose of study treatment, and contributed any safety data after the start of study treatment.

Diagnosis and Main Criteria for Inclusion and Exclusion:

This study enrolled participants aged at least 18 years with documented multiple myeloma at screening.

Enrolled participants had to receive 1 to 3 prior line(s) of treatment of which 1 contained daratumumab and completed daratumumab at least 3 months prior to randomization. A single line of therapy could consist of 1 or more agents, and could include induction, HSCT, and maintenance therapy. Radiotherapy, bisphosphonate, or a single short course of corticosteroids (no more than the equivalent of dexamethasone 40 mg/day for 4 days) were not considered prior lines of therapy. Participants must have had evidence of a response to daratumumab containing therapy with response duration of at least 4 months.

Participants must have progressed from or been refractory to their last line of treatment.

Participants were required to have an ECOG performance status score of 0, 1, or 2 to be enrolled in the study.

Study Interventions, Dose, Mode of Administration, and Batch Numbers:

Participants in both treatment arms were to receive carfilzomib at a dose of 20 mg/m^2 intravenously (IV) on Cycle 1 Day 1 and 70 mg/m^2 thereafter on Days 1, 8, and 15 of each cycle, and dexamethasone (oral or IV) at a dose of 40 mg once a week (for participants older than 75 years), the dexamethasone could be administered at a dose of 20 mg weekly). Participants assigned to DKd, were to receive daratumumab SC (1800 mg) weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond). All participants were to continue to receive study treatment until disease progression or unacceptable toxicity.

Duration of Study Intervention:

Participants in both arms received study intervention until confirmed PD, death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurred first.

SUMMARY OF RESULTS AND CONCLUSIONS:

Demographic and Baseline Characteristics:

Of the 88 (100%) participants randomized, 2 (2.3%) participants, 1 in each treatment group, were randomized but did not receive treatment, resulting in 86 (97.7%) participants (43 participants in each of the DKd and Kd groups) who were treated.

The demographic characteristics were comparable between treatment groups. The majority of participants were male (55.7%), and white (85.2%). The median age was 68 years (range 30 to 87 years) with 64.8% of the participants ≥65 years of age.

The majority of participants had measurable disease in serum only (60.2%) with IgG (39.8%) and IgA (20.5%) as the most common types of immunoglobulins observed.

Twelve (30.8%) participants in DKd and 14 (40.0%) participants in the Kd group were high risk for cytogenetic risk. Most participants were described as ISS Stage I in the DKd group (DKd: 24 [54.5%]; Kd: 12 [27.9%]) and ISS Stage II in the Kd group (DKd: 11 [25.0%]; Kd: 19 [44.2%]).

The median number of prior lines of therapy was 2.0. A total of 55 (64.0%) participants were refractory to daratumumab (DKd: 29 [67.4%]; Kd: 26 [60.5%]) as the prior multiple myeloma therapy. Median time since last daratumumab exposure was 223.5 days for the DKd group and 203.0 days for the Kd group.

Exposure:

The median duration of study treatment was 8.77 months (range: 0.1-28.3 months) in the DKd group and 8.05 months (range: 0.3-30.4 months) in the Kd group. The median number of treatment cycles received was 10 in the DKd group and 8 cycles for the Kd group.

Efficacy Results:

The interim futility analysis conducted when 82 participants were enrolled in the study, concluded that the observed rate of VGPR or better was not higher in the DKd treatment group (38.1%) compared with the rate in the Kd group (38.1%), so the study was terminated. At the time of study termination, a total of 88 participants were enrolled in the study. The results of the final analysis were as follows:

- At the time of this final analysis, 20 (45.5%) participants in DKd group and 18 (40.9%) participants in Kd group had VGPR or better (sCR+CR+VGPR) based on computerized algorithm. The results were not statistically significant (odds ratio=1.2, 90% CI: 0.59, 2.46; p-value=0.6757).
- The overall response rate (PR or better) was 70.5% for the DKd group and 56.8% for the Kd group with a p-value of 0.1935, indicating no statistical significance.
- The rate of CR or better (sCR + CR) was 11.4% for the DKd group and 22.7% for the Kd group with a p-value of 0.1723, indicating no statistical significance.
- Twenty-four (54.5%) participants in the DKd group and 27 (61.4%) participants in the Kd group died or had progressive disease based on computerized algorithm. The median PFS in the DKd group was 10.74 months and 10.61 months in the Kd group. The 6-month PFS rate was 83.2% (90% CI: 71.0, 90.6) for the DKd group and 64.1% (90% CI: 49.8, 75.2) for the Kd group. The 18-month PFS rate was 27.4% (90% CI: 14.3, 42.2) for DKd group and 37.1% (90%CI: 23.8, 50.4) for the Kd group.
- With a median follow-up of 18.66 months, a total of 20 deaths (8 [18.2%] in the DKd group and 12 [27.3%] in the Kd group) were observed. The HR for OS (KDd vs Kd) was 0.75 (95% CI: 0.35, 1.60; p=0.5277), demonstrating no statistical significance between the groups. The median OS was not reached in either treatment groups.
- The median time to next therapy was similar for both treatment groups (DKd: 20.14 months [90% CI: 11.33, NE] and Kd: 20.60 months [90% CI: 14.06, 25.40]).
- The MRD negativity rate at the 10^{-5} threshold was 6.8% in the DKd group and 11.4% in the Kd group and was not statistically significant.
- The absolute NK cell numbers were reduced with treatment in the DKd group. The absolute numbers of $CD3^+$ T cells and $CD8^+$ T cells, however, were reduced in both the DKd and Kd groups, suggesting that no T cell expansion occurred with daratumumab treatment.

Safety Results:

- The safety profile at the time of this final analysis was generally consistent with the known safety profiles of daratumumab and the Kd regimen. No new safety concerns were identified.
- The overall incidence of any grade TEAE was 41 (95.3%) participants in the DKd group and 43 (100.0%) participants in the Kd group. The most common TEAEs (≥20% in either treatment group) were COVID-19 (DKd: 23.3%, Kd: 23.3%), upper respiratory tract infections (DKd: 4.7%, Kd: 23.3%), thrombocytopenia (DKd: 37.2%; Kd: 20.9%), anemia (DKd: 27.9%, Kd: 32.6%), diarrhoea (DKd: 9.3%, Kd: 25.6%), and hypertension (DKd: 25.6%, Kd 16.3%).

- The proportion of participants with Grade 3 or 4 TEAEs was 58.1% in the DKd group and 55.8% in the Kd group. The most commonly reported Grade 3 or 4 TEAEs (≥10% in either treatment group) by PT were thrombocytopenia (DKd: 14.0%, Kd: 4.7%), anemia (DKd: 11.6%; Kd: 9.3%), and hypertension (DKd: 18.6%; Kd: 7.0%).
- Twelve (27.9%) participants in the DKd group and 20 (46.5%) in the Kd group had at least 1 treatment-emergent serious AE. The most common treatment-emergent serious adverse events (≥5% in either treatment group) were COVID-19 (DKd: 7.0%, Kd: 2.3%), pneumonia (DKd: 4.7%, Kd 9.3%), and acute kidney injury (DKd: 0%, Kd: 9.3%).
- Four (9.3%) participants in the DKd group and 7 (16.3%) participants in the Kd group had 1 or more TEAEs leading to discontinuation of study treatment. COVID-19 was the only TEAE leading to discontinuation of study treatment that occurred in more than 1 participant (DKd: 2 [4.7%], Kd: 2 [4.7%]).
- The total number of participants with TEAE with outcome of death (Grade 5) was the same for both treatment groups (3 [7.0%] participants in each treatment group).
- A total of 16.3% of participants in the DKd group and 27.9% in the Kd group died during the study. The most common primary cause of death was disease progression, occurring in 9.3% and 14.0% of participants in the DKd and Kd groups, respectively.
- There were no participants in the DKd group with treatment-emergent IRRs and 1 (2.3%) participant in the DKd group had a Grade 1 treatment-emergent injection site reaction of rash erythematous.
- The most common treatment-emergent cytopenias (at least 10% in either treatment group) were thrombocytopenia, anemia, neutropenia, and lymphopenia. The incidence of neutropenia events and thrombocytopenia was higher in the DKd group compared with the Kd group (neutropenia DKd: 18.6%, Kd: 9.3%; thrombocytopenia DKd: 37.2%, Kd: 20.9%). The incidence of anemia and lymphopenia events was lower in the DKd group compared with the Kd group (anemia DKd: 27.9%, Kd: 32.6%; lymphopenia DKd: 7.0%, Kd: 18.6%).
- The incidence of infections and infestations in the DKd group was lower compared with that in the Kd group (DKd: 48.8%, Kd: 74.4%). A similar proportion of participants in each treatment group had Grade 3 or 4 treatment-emergent infections and infestations (DKd: 18.6%, Kd: 20.9%).
- No second primary malignancies were reported for the DKd group and 1 (2.3%) participant in the Kd group had a neoplasm prostate.
- Five (11.6%) participants in each treatment group had 1 or more cardiac events of interest. The most common cardiac TEAE of interest was cardiac failure (DKd: 2.3%, Kd: 9.3%). The incidence of cardiac events related to carfilzomib was 9.3% in the DKd group and 7.0% in the Kd group; related to dexamethasone was 2.3% in both treatment groups; and there were no cardiac events related to daratumumab in the DKd group.

Pharmacokinetic and Immunogenicity Results:

- Serum daratumumab C_{trough} after weekly doses of daratumumab SC in the DKd group increased over time to a maximum mean (SD) value of 849 (329) µg/mL on Cycle 3 Day 1 pre-injection. Serum maximum Ctrough decreased slightly to 715 (381) µg/mL on Cycle 7 Day 1 pre-injection after less frequent dosing (every 2 weeks) in Cycles 3-6.
- Measurable daratumumab concentrations at baseline on Cycle 1 Day 1 pre-injection in the DKd group and the Kd group were observed, attributed to likely previous exposure to daratumumab.

- The observed serum PK profile of daratumumab in participants previously treated with daratumumab was similar to the profile reported in a Phase 2 daratumumab SC study in combination with Kd.
- The C_{trough} at the end of weekly dosing, at steady state (approximately 5 months after the first dose, Cycle 7 Day 1 pre-injection) and at 8 weeks after the last dose observed in this study were comparable with C_{trough} at the same or similar timepoints observed in the other daratumumab SC combination study with Kd.
- None of 35 (0.0%) participants tested positive for treatment-emergent anti-daratumumab antibodies after the first dose of daratumumab in the DKd group, indicating a low incidence of antibodies to daratumumab in participants with daratumumab retreatment.
- One of 35 participants (2.9%) in the DKd group tested positive for treatment-emergent anti-rHuPH20 antibodies with the peak titer of 1:5, indicating a low incidence of anti-rHuPH20 antibodies in participants with daratumumab retreatment. This participant tested negative for neutralizing anti-rHuPH20 antibodies.

Conclusions:

This study examined the combination of Kd with daratumumab SC when used for the treatment of patients with RRMM who were previously exposed to daratumumab. An interim futility analysis was conducted when 82 participants were enrolled. The observed rate of VGPR or better was not statistically higher in the DKd treatment group compared with the Kd group. As such, the null hypothesis (ie, no treatment difference in the rate of VGPR or better) was accepted, and the study was terminated. Enrollment was ongoing up to the time of study termination, when a total of 88 participants were enrolled in the study. No new safety concerns were identified. The observed serum PK profile of daratumumab in participants previously treated with daratumumab was similar to the profile reported in a Phase 2 daratumumab SC study in combination with Kd. The incidence of antibodies to daratumumab or to rHuPH20 was low following daratumumab retreatment.