SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K.K.
Name of Investigational Product	JNJ-54767414 (Daratumumab)

Status: Approved
Date: 7 June 2016
Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: 54767414MMY1002

Title of Study: A Phase 1 Study of JNJ-54767414 (Daratumumab) in Japanese Patients With Relapsed or Refractory Multiple Myeloma

NCT No.: NCT02116569

Clinical Registry No.: CR104072

Coordinating Investigator: No coordinating investigator (multicenter)

Study Centers: The study was conducted at 2 centers in Japan.

Publication (Reference): None

Study Period: 28 April 2014 to 25 September 2015

Phase of Development: 1

Objectives:

Primary Objective

- To evaluate the tolerability and safety of daratumumab in Japanese subjects with relapsed or refractory multiple myeloma (MM).

Secondary Objectives

- To evaluate the pharmacokinetic (PK) profile of daratumumab.
- To evaluate the generation of antibodies to daratumumab (immunogenicity).
- To evaluate the preliminary efficacy of daratumumab.

Exploratory Objective

- To explore biomarkers predictive of response to daratumumab.

Methodology:

This was a Phase 1, open-label, nonrandomized, multicenter, dose escalation study to evaluate the safety and tolerability of JNJ-54767414 (daratumumab) in Japanese subjects with relapsed or refractory MM. Study periods and critical study events are described below.

Screening Phase

Screening (up to 21 days) started with signing of the informed consent and ended at Day -1. During this phase, subjects were evaluated for study entry based on the in-/exclusion criteria.

Treatment Phase

The open-label treatment phase started on Day 1 (Week 0) by administration of study agent (as an intravenous [IV] infusion) and extended until study agent discontinuation. The treatment phase consisted of 2 periods: 1) first period consisted of an intense dose regimen (from Weeks 0 to 9); and 2) second period consisted of a less intense dose regimen (from Week 10 until end-of-treatment [EOT]).

In the first period, subjects received the first infusion with a 3-week resting period followed by 6-weekly dosing until Week 8 (a total of 7 infusions). The dose-limiting toxicity (DLT) evaluation period was approximately 5 weeks in duration and began with the first infusion of daratumumab and ended immediately before initiation of the fourth infusion. Dose-limiting toxicity evaluation period was set to evaluate tolerability on a single dose of daratumumab for 3 weeks; thereafter, at least 2 consecutive doses in the most intensive dose period. Subjects had to re-sign a new informed consent form (ICF) provided to them before initiation of the fourth infusion.

In the second period, subjects received the study agent in cycles. Each cycle was 28 days (4 weeks in duration). Starting Week 10, subjects received biweekly (q2w) infusions until Week 24 (a total of 8 infusions, from Cycles 1 to 4), and from Cycle 5 (Week 26), subjects continued to receive monthly (every 4 weeks, [q4w]) infusions until EOT.

In the study, 2 dose levels (8 mg/kg and 16 mg/kg) of daratumumab were assessed. For assessment of dose levels, the subjects were to be recruited sequentially into 2 cohorts (of at least 3 subjects). Subjects in the first cohort were treated with a dose level of 8 mg/kg. The dose level of 16 mg/kg of daratumumab in the other cohort was initiated after the safety and tolerability of the 8 mg/kg dose level in the first cohort were confirmed. Dose modification for individual subjects was not permitted during the first period. Dose delay was permitted in the second period to manage daratumumab-related adverse events (AEs). The dose of study agent for each subject to be administered was calculated based on the subject's body weight.

Treatment with daratumumab was to be continued until disease progression, unmanageable AEs in the treatment phase, or other study treatment discontinuation criteria that marked EOT.

Follow-up Phase

The 8-week follow-up phase started after EOT and continued until 8 weeks after the last administration of study agent, death, lost to follow-up, consent withdrawal for study participation, or study end, whichever occurred earlier.

Number of Subjects (Planned and Analyzed): Planned: A total of 12 subjects were planned to be enrolled in the study, with at least 3 subjects in a cohort. Enrolled: A total of 9 subjects (4 subjects in the 8 mg/kg level and 5 subjects in the 16 mg/kg level) were enrolled in the study. Analyzed: All 9 enrolled subjects were analyzed in the study.

Diagnosis and Main Criteria for Inclusion: Japanese men or women aged 20 years or above, with relapsed or refractory MM were enrolled. Subjects had to have previously received at least 2 prior lines of therapy for MM, proven to have symptomatic MM according to the International Myeloma Working Group (IMWG) diagnostic criteria and measurable disease defined by serum or urine M-protein.

Test Product, Dose and Mode of Administration, Batch No.: Daratumumab was supplied as a colorless to slightly yellow liquid with concentration of 20 mg/mL in a 6 mL vial (with a nominal fill volume of 5 mL) for IV administration (Batch numbers: DHS55 and EBS52). Daratumumab was administered in 2 doses (8 mg/kg and 16 mg/kg). Treatment with daratumumab in the 8 mg/kg cohort was started first and treatment at 16 mg/kg was started after the safety and tolerability of the 8 mg/kg cohort were confirmed.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: Daratumumab was administered as a weekly IV infusion in the first period of the treatment phase (ie, from Week 0 until Week 8 [a total of 7 infusions]) with a 3-week resting period after the first infusion. The second period of the treatment phase continued from Week 10 until EOT with IV infusions administered q2w until Week 24 (a total of 8 infusions); thereafter, infusions were administered q4w until study agent discontinuation or termination of study participation.

Criteria for Evaluation:

Pharmacokinetics: The PK parameters estimated for serum daratumumab were area under the concentration versus time curve (AUC), clearance (CL), maximum observed concentration (C_{max}), predose concentration at steady state (C_{trough}), elimination half-life ($t_{1/2}$), time of maximum concentration (T_{max}), and volume of distribution (V). Following the first dose, all PK parameters were estimated using the actual sampling times by noncompartmental analysis methods. Venous blood samples for PK evaluations were collected during the first period on Days 1, 4, 8, 15, 22, 29, 36, 43, 50, 57, 60, 64 and during the second period on Days 1 and 15 of Cycles 1 to 4, on Day 1 of Cycle 5, at EOT, and at follow-up.

Immunogenicity: Antibodies to daratumumab were assessed at Day 1 of the first period and at follow-up.

Biomarkers: Assessments for biomarkers (natural killer [NK] and T cells) were performed. Blood samples for biomarker evaluations were collected at the following timepoints: Days 1, 8, 15, 22, 29, 43, 57 (first period), Days 1 to 4 of Cycle 1 and Cycle 5 (second period), and at EOT.

Efficacy: Efficacy was not the primary objective of the study. Secondary efficacy endpoints included overall response rate (ORR), progression-free survival (PFS), and duration of follow-up. Other secondary efficacy endpoints included time to response, duration of response, time to disease progression, and M-components evaluations. Efficacy assessments included response to treatment in accordance with the IMWG criteria. Proportion of subjects with response to treatment (stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR]) and quality of response (also included subjects who achieved minimal response [MR]) were summarized.

Safety Evaluations: Safety evaluations were based on the incidence of treatment-emergent AEs (TEAEs), clinical laboratory results, vital signs, physical examination findings, electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) performance status, and direct/indirect Coombs' tests.

Dose-limiting Toxicity: DLTs were based on study agent-related AEs and defined as any of the following events in the DLT evaluation period: infusion-related reaction (IRR), hematologic, and nonhematologic toxicities.

Statistical Methods:

Analysis Sets: The following analysis sets were used for study evaluations:

- All Treated Analysis Population: All subjects who received at least 1 administration of daratumumab and were used for all safety and efficacy analyses unless otherwise stated.
- Response Evaluable Analysis Population: All subjects who received at least 1 administration of daratumumab and have had a disease assessment during treatment to allow for comparison to the baseline assessment.
- PK Analysis Population: All subjects who received at least 1 administration of daratumumab with at least 1 during-treatment-sample collected to determine the concentration.
- Immunogenicity Analysis Population: All subjects who received at least 1 administration of daratumumab with at least 1 during-treatment-sample collected to assess the generation of antibodies to daratumumab.

- DLT Evaluable Population: All subjects in all treated analysis population who did not meet the next subject replacement rule for dose-escalation decision.

Planned Analyses

Pharmacokinetics: Descriptive statistics were used to summarize serum daratumumab concentrations at each sampling timepoint and PK parameters of daratumumab.

Immunogenicity: The incidence of antibodies to daratumumab was summarized for all subjects who received a dose of daratumumab and had appropriate samples for detection of antibodies to daratumumab.

Biomarkers: The counts of NK cells (CD3-CD16+CD56+) were summarized by visit.

Efficacy Evaluations: Major secondary efficacy endpoints (ORR, PFS, and duration of follow-up) and other secondary efficacy endpoints (time to response, time to disease progression, and duration of response) were summarized by dose level. The response evaluable analysis population was used for all response-related analyses, except for time to disease progression analysis and PFS, which used the all treated analysis population. Serum and urine M-protein levels (absolute values and percentage changes from baseline) were summarized.

Safety: Safety analyses included the descriptive statistics and frequency tabulations of all reported TEAEs, deaths, serious adverse events (SAEs), other significant AEs (TEAEs leading to treatment discontinuation, TEAEs leading to dose delay, TEAEs leading to dose reduction and infusion interruption), and AEs of special interest (IRRs and infection and infestations). Laboratory data summarized as shift tables and time series plots for creatinine, hemoglobin, platelets, white blood cells (WBCs), neutrophils, and lymphocytes. Lists of abnormal laboratory observations were presented. The effects of daratumumab on ECGs were evaluated by means of descriptive statistics and frequency tabulations. All other safety data (vital signs, physical examination, and direct/indirect Coombs' Test) were presented in listings or tables.

RESULTS:

STUDY POPULATION:

Of the 13 screened subjects, 9 subjects (4 subjects in the 8 mg/kg level and 5 subjects in the 16 mg/kg level) were enrolled and treated with daratumumab. Subjects were treated with daratumumab 16 mg/kg after the safety and tolerability of daratumumab in the 8 mg/kg cohort were confirmed. All treated subjects permanently discontinued the study agent. Among the 9 treated subjects, 7 subjects (77.8%) discontinued study agent due to progressive disease, 1 subject (11.1%) discontinued study agent due to a protocol violation, and 1 subject (11.1%) due to noncompliance with the study agent.

Demographic characteristics were generally similar between the 2 dose levels. Of the 9 subjects treated, 5 subjects (55.6%) were women and 4 (44.4%) were men. The median age was 65 years (range: 47 to 73 years). At baseline, all subjects had an ECOG performance status score of 0 or 1. The majority of subjects were of MM stage I or II.

The median duration of treatment was 5.6 months (range: 0 to 10.6 months) for the entire study population: 6.3 months (range: 0.7 to 10.6 months) for the 8 mg/kg level and 2.4 months (range: 0 to 9.5 months) for the 16 mg/kg level. Among the 9 treated subjects, 4 subjects (44.4%) received daratumumab for 183 days or longer. The median cumulative dose of daratumumab administered was 127.1 mg/kg (range: 16.3 to 182.1 mg/kg) in the 8 mg/kg level and 122.7 mg/kg (range: 16.2 to 309.7 mg/kg) in the 16 mg/kg level.

EFFICACY RESULTS:

The ORR (sCR, CR, VGPR, and PR) was 25.0% (1 of 4 subjects) in the 8 mg/kg level and 60.0% (3 of 5 subjects) in the 16 mg/kg level; all 4 subjects with ORR achieved a PR. The median PFS (Kaplan-Meier

[KM] estimate) was 6.0 months in the 8 mg/kg level and 9.5 months in the 16 mg/kg level. Of the 9 treated subjects, 7 subjects (all 4 subjects in the 8 mg/kg level and 3 of 5 subjects in the 16 mg/kg level) had disease progression and 2 subjects in the 16 mg/kg level were censored (because the subjects did not reach to disease progression). The median duration of follow-up was 10.5 months (range: 2.3 to 16.4 months) for the 8 mg/kg level and 9.9 months (1.7 to 13.2 months) for the 16 mg/kg level.

The time to response was 2.3 months for 1 responder in the 8 mg/kg level. The median time to response was 1.8 months (range: 1.2 to 1.9 months) for 3 responders in the 16 mg/kg level. The duration of response (KM estimate) was 2.8 months for 1 responder in the 8 mg/kg level and the median duration of response was 7.7 months for 3 responders in the 16 mg/kg level. The median time to disease progression was 6.0 months in the 8 mg/kg level and 9.5 months in the 16 mg/kg level. The majority of subjects (5 of 9 subjects [55.6%]) had reductions in serum M-protein from baseline.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

Pharmacokinetics

Mean daratumumab C_{max} after the first infusion at 16 mg/kg level was approximately 2.3-times that for subjects who received 8 mg/kg level. Mean $t_{1/2}$ values were prolonged (68.163 to 407.379 hours) with increasing dose, while mean CL values were decreased (0.678 to 0.247 mL/h/kg) with increasing dose. Following the 16 mg/kg dose regimen, accumulation of daratumumab continued throughout the weekly dosing, and decreased slightly as subjects entered the q2w dosing period and the subsequent q4w dosing period.

Immunogenicity

All 9 treated subjects were tested for antibodies to daratumumab (4 subjects in the 8 mg/kg level and 5 subjects in the 16 mg/kg level). No subject tested positive for antibodies to daratumumab during the study.

Biomarkers

In both 8 mg/kg and 16 mg/kg levels, a marked decrease in total NK cells was observed until Day 8, and the decrease was sustained throughout the treatment phase irrespective of subjects who were responders or nonresponders.

SAFETY RESULTS:

All subjects had at least 1 TEAE and study agent-related TEAE. There were no deaths or TEAEs leading to study agent discontinuation. There were no TEAEs leading to dose reduction and dose interruption reported in this study. No DLTs were observed in either dose levels during the study.

TEAEs

All 9 treated subjects experienced at least 1 hematologic TEAE. The most frequently reported hematologic TEAEs by preferred term (PT) in the 8 mg/kg (n=4) versus 16 mg/kg (n=5) levels were: lymphopenia (4 versus 5 subjects), neutropenia (2 versus 5 subjects), and leukopenia (0 versus 3 subjects). The most frequently reported study agent-related hematologic TEAEs by PT in the 8 mg/kg versus 16 mg/kg levels were: lymphopenia (4 versus 5 subjects), neutropenia (0 versus 5 subjects), and leukopenia (0 versus 3 subjects). The onset of events was higher during the first 8 weeks of treatment, which decreased over time (from Weeks 8 to 24).

Grade 3 or Higher TEAEs

No Grade 5 TEAEs were reported during the study. The most frequently reported Grade 3 or 4 TEAEs by PT in the 8 mg/kg versus 16 mg/kg levels were: lymphopenia (2 versus 5 subjects), neutropenia (0 versus 4 subjects), and leukopenia (0 versus 3 subjects).

Serious Adverse Events

Overall, 3 of 9 subjects (33.3%) experienced at least 1 treatment-emergent SAE during the study: 1 subject in the 8 mg/kg level had thrombocytopenia, 1 subject in the 16 mg/kg level had headache and pyrexia, and 1 subject in the 16 mg/kg level had pneumonia. The events of headache, pyrexia, and pneumonia were resolved and were considered by the investigator to be possibly related to the study agent. The event of thrombocytopenia was not resolved and was considered by the investigator as not related to the study agent.

Other Significant Adverse Events

There were no TEAEs leading to dose reduction and dose interruption reported in the study. Overall, 1 subject in the 8 mg/kg level had dose delay due to a nonserious Grade 2 TEAE of upper respiratory tract infection. Infusion interruptions due to TEAEs were reported in 2 of 9 subjects (22.2%): 1 subject each in both dose levels.

Adverse Events of Clinical Interest

Of the 4 subjects (1 of 4 subjects in the 8 mg/kg level and 3 of 5 subjects in the 16 mg/kg level) with IRRs, 3 subjects (1 subject in the 8 mg/kg level and 2 subjects in the 16 mg/kg level) experienced IRRs after the first daratumumab infusion and 1 subject in the 16 mg/kg level had IRRs after the second daratumumab infusion. All IRRs were Grade 1 or 2.

Five of 9 subjects (55.6%) experienced TEAEs of infections and infestations (nasopharyngitis, cystitis, pharyngitis, pneumonia, upper respiratory tract infection, and adenoiditis): 2 of 4 subjects in the 8 mg/kg level and 3 of 5 subjects in the 16 mg/kg level. Of these 5 subjects, 1 subject in the 16 mg/kg level had an SAE of Grade 3 pneumonia, which resolved subsequently, and was considered by the investigator to be possibly related to the study agent.

Clinical Laboratory Evaluations

In the 16 mg/kg level, a marked decrease in mean creatinine values was observed at Cycle 1 Day 15 (approximately 45 µmol/L); thereafter, the mean creatinine values were generally maintained at the decreased level throughout the study. Of the 9 subjects, 8 subjects (88.9%) had Grade 3 or 4 hematologic TEAEs; 3 of 4 subjects in the 8 mg/kg level and all 5 subjects in the 16 mg/kg level.

Other Safety Observations

No trend was noted between the incidence of abnormalities in vital sign parameters and the dose of daratumumab (8 mg/kg and 16 mg/kg) in the study. No subject had reported QTcF or QTcB >500 msec or a change from baseline of >60 msec or had an abnormal value of clinical significance. Overall, 8 of 9 subjects (88.9%) experienced a positive result in indirect Coombs' test after having a negative baseline result within 5 hours of the first daratumumab infusion: all 4 subjects in the 8 mg/kg level and 4 of 5 subjects in the 16 mg/kg level.

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

CONCLUSIONS:

- The safety and tolerability of daratumumab therapy at a dose level of 8 mg/kg and 16 mg/kg were confirmed for Japanese subjects with relapsed or refractory MM in this study.
  - No DLTs were observed in the study.
  - No deaths or no study agent discontinuation due to TEAEs were reported up to this dose level. All Grade 3/4 AEs were resolved, except the events of anemia and thrombocytopenia (both events were considered as not related to the study agent by the investigator).

  - All IRRs were Grade 1 or 2 in severity and transient.
  - No subject had reported QTcF or QTcB >500 msec or a change from baseline of >60 msec or had an abnormal value of clinical significance.
  - There was no reported interference with blood transfusion clinical decision making.

- Following the 16 mg/kg dose regimen, accumulation of daratumumab continued throughout the weekly dosing, and decreased slightly as subjects entered the q2w dosing period and the subsequent q4w dosing period. Daratumumab elimination showed nonlinear PK characteristics after the first infusion.
- No subject developed antibodies to daratumumab indicating a low risk of immunogenicity for daratumumab.
- Overall, ORR was 44.4% (4 of 9 subjects); 25.0% (1 of 4 subjects) for 8 mg/kg level and 60.0% (3 of 5 subjects) for 16 mg/kg level.
- A decrease in total NK cells was observed following daratumumab treatment in both dose levels, which supports the observation that NK cells express CD38.

In conclusion, this study showed a favorable benefit/risk profile for daratumumab in the treatment of patients with relapsed and refractory MM.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.