SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-54767414 (daratumumab)

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Status:	Approved
Date:	31 October 2017
Prepared by:	Janssen Research & Development, LLC

Protocol No.: 54767414MMY3007

Title of Study: A Phase 3, Randomized, Controlled, Open-label Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination with VMP (D-VMP), in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High-dose Therapy

Study Name: ALCYONE

EudraCT Number: 2014-002272-88

NCT No.: NCT02195479

Clinical Registry No.: CR104761

Principal Investigator: Maria Victoria Mateos Manteca, MD, PhD, University of Salamanca, Salamanca; Spain

Study Center(s): Argentina (3 sites), Australia (6 sites), Belgium (6 sites), Brazil (6 sites), Bulgaria (7 sites), Croatia (2 sites), Czech Republic (5 sites), Georgia (3 sites), Germany (2 sites), Greece (5 sites), Hungary (5 sites), Italy (12 sites), Japan (17 sites), Korea (7 sites), Macedonia (3 sites), Poland (10 sites), Portugal (2 sites), Romania (4 sites), Russian Federation (10 sites), Serbia (4 sites), Spain (18 sites), Turkey (7 sites), Ukraine (7 sites), United Kingdom (8 sites), United States of America (3 sites).

Publication (Reference): None

Study Period: The first subject was randomized on 09 Feb 2015; the data cut-off date for the second interim analysis was 12 Jun 2017.

Phase of Development: 3

Objectives: Primary: to compare the efficacy of daratumumab when combined with VMP to that of VMP in terms of progression-free survival (PFS) in subjects with previously untreated multiple myeloma who are ineligible for high dose therapy. The key secondary objectives were to determine if the combination of daratumumab with VMP would improve clinical outcome as measured by overall response rate (ORR) (defined as partial response [PR] or better), very good partial response (VGPR) or better rate, complete response (CR) or better rate, minimal residual disease (MRD) negativity rate, overall survival (OS), and safety and tolerability. Additional secondary endpoints included best M-protein response, time to disease progression (TTP), time to response, time to subsequent antimyeloma treatment, PFS2, and patient-reported outcomes (PROs).

The exploratory objectives were to assess biomarkers predictive of response and resistance to therapy and to assess durability of MRD negativity.

Methodology: This was a randomized, open-label, parallel-group, controlled, multicenter study to compare the efficacy of daratumumab when combined with VMP (D-VMP) to that of VMP in terms of progression-free survival (PFS) in subjects with previously untreated multiple myeloma who are ineligible for high-dose therapy. Eligible subjects were to be stratified by International Staging System (ISS; I vs II vs III), region (Europe vs Other), and age (<75 vs ≥75) and then randomized in a 1:1 ratio. An Independent Data Monitoring Committee (IDMC) reviewed data at 2 predetermined interim analyses, and the IDMC continues to review safety data at regular intervals during the study (ie, every 6 months). The first interim analysis, with a purpose to evaluate safety, was performed after a total of approximately 100 subjects had been treated for at least 2 cycles or discontinued the study treatment. The second interim analysis (reported in this CSR), with a purpose to evaluate cumulative interim safety and efficacy data, was performed when approximately 216 PFS events, which is 60% of the total planned PFS events, had been accumulated. The final PFS analysis was originally planned to occur when approximately 360 PFS events have been observed. The end of the study was planned to occur when 330 subjects have died, or 5 years after the last subject is randomized, whichever comes first.

Number of Subjects (planned and analyzed):

Planned: Approximately 700 subjects were planned to be enrolled in the study (350 per treatment arm). Analyzed: 706 subjects randomized (intent-to-treat [ITT]: 350 D-VMP and 356 VMP) and 700 subjects treated (safety analysis set: 346 D-VMP and 354 VMP).

Diagnosis and Main Criteria for Inclusion: Subject had to be at least 18 years of age with documented multiple myeloma as defined by the criteria below:

- Diagnostic criteria of calcium elevation, renal insufficiency, anemia, and bone abnormalities (CRAB)
- Monoclonal plasma cells in the bone marrow ≥10% at some point in their disease history or presence of a biopsy proven plasmacytoma.
- Measurable disease at Screening as defined by any of the following:
  - IgG multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
  - IgA, IgD, IgE, IgM multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
  - Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.
- Newly diagnosed and not considered candidate for high-dose chemotherapy with SCT due to:
  - Being age ≥65 years, Or
  - In subjects <65 years: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. Sponsor review of these comorbid conditions and approval is required before randomization.
- Subject must have had an ECOG Performance Status score of 0, 1, or 2.

Test Product, Dose and Mode of Administration, Batch No.: DARZALEX® (daratumumab) 16 mg/kg IV. Batch numbers (expiry dates) for daratumumab were: 4370081 (02OCT2015), 4370200 (21NOV2015), 4370287 (16OCT2015), 4370394 (13NOV2015), 4370395 (04JUN2016), 4370490 (13JUN2016), 4370491 (05SEP2016), 4370592 (02OCT2016), 4370649 (03SEP2016), 4370774 (27NOV2016), 4370845 (13NOV2016), 4370945 (11DEC2016), 4370945 (06NOV2017), 4371280 (03SEP2016), 4371371 (21NOV2016), 4371374 (01APR2017), 4371503 (21NOV2016), 4371676 (23APR2017), 4371707 (09APR2017), 4371737 (21MAY2017), 4371932 (16JUL2017), 4371933 (22JUL2017), 4371934 (28JUL2017), 4372473 (21APR2017), 4372763 (28NOV2017), B212815 (26FEB2017), B212816 (19MAR2017) B212837 (29OCT2016), B216226 (28APR2017), B216227 (28APR2017), B216228 (28APR2017), B216229 (28APR2017), B218277 (28MAY2017), B218278 (28MAY2017), B219222 (28APR2017), B223121 (30DEC2017), B223122 (30DEC2017), B223123 (30DEC2017), B223136 (30DEC2017).

Reference Therapy, Dose and Mode of Administration, Batch No.:

- VELCADE® (bortezomib) 1.3 mg/m^2 SC: Batch numbers (expiry dates) for bortezomib were: 4370082 (31JUN2016), 4370201 (31DEC2016), 4370492 (30APR2017), 4370903 (28FEB2017), 4371089 (31MAY2017), 4371681 (31MAY2017), 4372034 (31AUG2017), 4372463 (30JUN2018), 4373544 (31AUG2017),
- Melphalan 9 mg/m^2, oral. Batch numbers (expiry dates) for melphalan were: 4370421 (31NOV2016), 4370783 (31JAN2017), 4371043 (31MAY2017), 4371504 (31MAY2017), 4371736 (31JAN2018), 4372014 (31JAN2018), 4372464 (31JAN2018), 4373081 (28FEB2019), 4373081 (28FEB2020).
- Prednisone 60 mg/m^2, oral. Batch numbers (expiry dates) for prednisone were: 4370217 (31OCT2018), 4370387 (31OCT2018), 4371073 (31JUL2019), 4371841 (31OCT2019), 4370216 (30APR2019), 4370388 (30APR2019), 4371050 (30APR2019), 4371840 (30JUN2020).

Duration of Treatment:

All subjects were to receive up to 9 cycles of the VMP regimen (1 cycle = 6 weeks) with or without daratumumab. Subjects in both treatment arms were to receive bortezomib twice weekly (Weeks 1, 2, 4, and 5) in Cycle 1 followed by once weekly (Weeks 1, 2, 4, and 5) in Cycles 2 to 9. Melphalan and prednisone were to be self-administered on Day 1-4 of each bortezomib cycle. For subjects randomized to the Treatment Arm B, 20 mg of dexamethasone was to be substituted for the planned dose of prednisone on Day 1 of each cycle. In this setting, dexamethasone was utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab infusion. Daratumumab 16 mg/kg was to be administered to subjects in Treatment Arm B once every week for 6 weeks (Cycle 1; 1 bortezomib cycle); then once every 3 weeks for 16 additional doses (Cycles 2-9). After completion of the VMP cycles, subjects in Arm A were to enter the Follow-up Phase. Subjects in Arm B were to continue to receive daratumumab every 4 weeks until documented progression, unacceptable toxicity, or the study ends (see below for definition). Subjects who needed to discontinue treatment with any one component of study treatment (bortezomib, melphalan, prednisone, or daratumumab) could continue to receive treatment with the other components of study treatment, as assigned. Upon discontinuation of daratumumab, subjects in Arm B were also to enter the Follow-up Phase.

Criteria for Evaluation: Assessments of tumor response and disease progression were conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. The primary efficacy endpoint was PFS based on a computerized algorithm. PFS was defined as the duration from the date of randomization to either progressive disease, according to the IMWG criteria, or death, whichever occurred first. Assessment of MRD was conducted on bone marrow samples using a validated NGS sequencing assay in accordance with the IMWG MRD guidelines. Safety evaluations included AE monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters

(hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status assessment. Blood samples were drawn for assessment of pharmacokinetics and immunogenicity. Additional assessments included patient-reported outcomes (PRO), biomarkers, and medical resource utilization (MRU).

Statistical Methods: The sample size calculation was based on the assumption that the median PFS for the VMP group in this study was estimated to be approximately 21 months, and that the addition of daratumumab would reduce the risk of the disease progression or death by 27.6%, ie, assuming the hazard ratio (D-VMP vs VMP) of 0.724, which translates to a median PFS of 29 months for the D-VMP group. A total of 360 PFS events would be needed to achieve a power of 85% to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 20-month accrual period and an additional 21-month follow-up, the total sample size needed for the study was approximately 700 (350/treatment group) subjects. Two interim analyses were planned. The first interim analysis was to evaluate safety only after a total of approximately 100 subjects were treated for at least 2 cycles or discontinued the study treatment. The second interim analysis was planned after approximately 216 PFS events (death or PD; 60% of the total planned PFS events), and was actually conducted with 231 PFS events (64% of total planned PFS events). The corresponding exact significance level was 0.0103 (2-sided) at the second interim analysis per the O'Brien-Fleming alpha spending function. The primary treatment comparison of the distribution of overall PFS was based on a stratified log-rank test. Hazard ratio and its 95% confidence interval were estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. Distributions were summarized with the use of the Kaplan-Meier method. The following secondary endpoints were sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach: ORR, VGPR or better rate, CR or better rate, MRD negativity rate, and OS.

RESULTS:

The study was unblinded at the recommendation of the IDMC based on the pre-specified interim analysis of PFS, conducted when 64% of the total PFS events (360) had occurred, which crossed the O'Brien-Fleming boundary for statistical significance. Thus, the results presented in this report represent the final analysis of the primary PFS endpoint.

STUDY POPULATION: The median age was 71 years and 54% of subjects were female. Most (85%) subjects were white, 13% of subjects were Asian, and 1% of subjects were black or African American. The majority (83%) of subjects were enrolled at sites in Europe. The percentage of subjects with an ECOG performance status score of 0, 1, or 2 at baseline was 25%, 50%, and 25%, respectively. Baseline disease characteristics were similar between the 2 treatment groups. The majority of subjects had measurable disease in the serum only, with IgG the most common immunoglobulin isotype (40%), and IgA the second most common (14%); 19% had ISS Stage I, 42% had ISS Stage II, and 38% had ISS Stage III disease at screening. Of the 616 subjects who had baseline cytogenetic data reported, 98 subjects (16%) had at least one high-risk abnormality. The median time from diagnosis of multiple myeloma to randomization was 0.76 and 0.82 months in the D-VMP and VMP groups, respectively.

Eighty percent (80%) of subjects in the D-VMP group and 62% of subjects in the VMP group completed 9 cycles of VMP treatment. The median duration of treatment was 14.7 months for the D-VMP group and 12.0 months for the VMP group. During the first 9 cycles, 19% of subjects in the D-VMP group and 33% of subjects in the VMP group discontinued treatment; a lower percentage of subjects in the D-VMP group versus VMP group discontinued treatment due to disease progression (7% vs. 13%), and adverse events (5% and 9%), and a similar percentage discontinued due to death (3% vs. 2%).

EFFICACY RESULTS: The combination of daratumumab with VMP resulted in highly compelling and clinically meaningful outcomes with a statistically significant 50% reduction in the risk of disease progression or death compared with VMP alone (HR=0.50; 95% confidence interval [CI]: 0.38, 0.65; p<0.0001). As of the clinical cut-off date of 12 June 2017, median PFS was not reached for the D-VMP group and was 18.1 months for the VMP group. The PFS results were robust and consistent across multiple sensitivity analyses and across all predefined, clinically relevant subgroups including subjects 75 years of age or older, and those with renal impairment, high risk disease by ISS staging or cytogenetics, or poor ECOG performance status.

The superiority in PFS for D-VMP was further supported by statistically significant improvements in key secondary endpoints based on the pre-specified hierarchical testing procedure. The combination of daratumumab with VMP resulted in significantly higher ORR (91% versus 74%; odds ratio=3.55; p<0.0001), rate of VGPR or better (71% vs 50%; odds ratio=2.50; p<0.0001), and rate of CR of better (43% versus 24%; odds ratio=2.31; p<0.0001). The MRD negativity rate at the sensitivity threshold of 10^{-5} was more than tripled in subjects treated with D-VMP (22%) compared with subjects treated with VMP (6%) (odds ratio=4.36; p<0.0001). The improvement in ORR and depths of the responses in the D-VMP group compared to the VMP group were consistent across all prespecified subgroups. With a median follow-up of 16.5 months, OS data were not yet mature, as only 13% of subjects had died at the time of the data cutoff for this interim analysis.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS: The pharmacokinetic profile for daratumumab was comparable to that observed in other daratumumab studies. Daratumumab accumulated after multiple doses; at the beginning of the second every-3-week-dosing cycle (Cycle 3 Day 1), the mean daratumumab C_{max} (595.9 µg/mL) was approximately 2.2-fold greater than the C_{max} following the first dose (266.7 µg/mL). Daratumumab concentrations observed after 3 additional cycles of every-3-week-dosing (Cycle 6 Day 1) were similar to the Cycle 3 Day 1 values, with a mean C_{max} of 636.4 µg/mL. Inter-subject variability for daratumumab exposure appeared moderate, with a 33-34% CV for post-infusion concentrations.

No subjects were positive for anti-daratumumab antibodies, indicating a low risk of immunogenicity to daratumumab with this combination.

PATIENT-REPORTED OUTCOMES RESULTS AND MEDICAL RESOURCE UTILIZATION RESULTS: The functional status and well-being results from patient reported outcome (PRO) endpoints, including the cancer-specific EORTC-QLQ-C30 and the general health EQ-5D-5L, indicated that improvements in health-related quality of life (HRQOL) were maintained in both treatment groups for subjects who remained in the study.

Fifty-nine percent (59%) of subjects in the D-VMP group and 51% of subjects in the VMP group had a hospitalization or an outpatient visit. A similar proportion of subjects from the D-VMP group (45%) and VMP group (50%) were hospitalized or had an outpatient visit due to adverse events.

SAFETY RESULTS: Daratumumab in combination with VMP was well-tolerated, and overall, the safety profile was consistent with the known toxicity of daratumumab and the VMP regimen. Combining daratumumab with VMP did not result in additional toxicity except for IRRs and higher rates of infection. The rate of treatment-emergent adverse events (TEAEs) was similar between treatment groups, with the exception of a higher frequency of upper respiratory tract infection in the D-VMP group (D-VMP: 26%; VMP: 14%), and a lower frequency of peripheral sensory neuropathy (D-VMP: 28%; VMP: 34%), and anemia (D-VMP: 28%; VMP: 38%) in the D-VMP group. The tolerability of this combination is highlighted by the lower frequency of treatment discontinuations due to TEAEs in the D-VMP group (5%) compared with the VMP group (9%). The frequency of Grade 3 or 4 TEAEs was similar between treatment groups (D-VMP: 78% and vs VMP: 77%). The most common Grade 3 or 4 TEAEs were balanced between the

2 study groups, except for pneumonia (D-VMP: 11%; VMP: 4%). Deaths within 30 days of last dose were low and balanced between treatment groups (D-VMP: 4% vs VMP: 5%).

Infusion-related reactions (IRR) associated with daratumumab administration were reported in 28% of subjects; 26% of subjects experienced the IRR during the first infusion of daratumumab. The preferred terms, severity, and onset of IRRs are consistent with those previously reported following daratumumab monotherapy and combination therapy. Most treatment-emergent IRRs (95%) were mild (Grade 1 or 2). Only 5 subjects (1.4%) discontinued daratumumab due to IRRs. There were no IRRs with the outcome of death.

The incidence of infections (all grades and Grade 3 or 4) was higher in the D-VMP group compared with the VMP group. The most common Grade 3 or 4 infection was pneumonia (11% for D-VMP vs 4% for VMP). The majority of infections were mild (Grade 1 or 2) and did not require hospitalization. Most infections, including pneumonia, resolved over time and did not result in increased rates of discontinuation of study treatments (D-VMP: 3 subjects [0.9%]; VMP: 5 subjects [1.4%]). Pneumonia (any grade) resulted in discontinuation of study treatments in 1 subject (0.3%) in each treatment group. Deaths due to infection were infrequent and balanced between groups (5 subjects [1.4%] in the D-VMP group and 4 subjects [1.1%] in the VMP group).

The frequency of second primary malignancies (SPMs) was low and balanced in the D-VMP and VMP groups (2% versus 3%, respectively). Tumor lysis syndrome (TLS) was rare and balanced between the 2 groups (<1%; 2 subjects in each treatment group).

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

CONCLUSION(S): Daratumumab in combination with VMP resulted in a compelling clinical benefit that was both statistically significant and clinically meaningful when compared to VMP alone. Specifically, the combination of daratumumab with VMP resulted in a significant improvement in PFS, with a 50% reduction in the risk of disease progression or death, compared with VMP. The superiority in PFS is further supported by consistent and highly statistically significant improvement in overall response rate (ORR) and depths of response, which include a near doubling of the CR or better rate and a more than three-fold increase in the MRD negativity rate for subjects in the D-VMP group. Daratumumab in combination with VMP was well-tolerated, and did not result in any new safety signals. Collectively, the data demonstrate a favorable benefit/risk profile for the use of daratumumab in combination with VMP for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT).

Note:
Name of Investigational Product: DARZALEX®
Name of Active Ingredient: daratumumab

Protocol ID	Country	Investigator Site
54767414MMY3007	Argentina	Hospital Italiano de Buenos Aires Juan Domingo Peron 4190 Buenos Aires Ciudad Autonoma de Buenos Aires, C1181ACH Argentina
54767414MMY3007	Argentina	Hospital Iturraspe Bv Pellegrini 3551 Santa Fe, Santa Fe, 3000 Argentina
54767414MMY3007	Argentina	Fundaleu J. E. Uriburu 1520 Buenos Aires, C1114AAP Argentina
54767414MMY3007	Australia	Calvary North Adelaide Hospital 89 Strangways Terrace North Adelaide, SA, 5006 Australia
54767414MMY3007	Australia	Gosford Hospital Holden Street Gosford, NSW, 2250 Australia
54767414MMY3007	Australia	Royal Prince Alfred Hospital Missenden Rd Camperdown, 2050 Australia
54767414MMY3007	Australia	Gallipoli Medical Research Centre 121 Newdegate Street Greenslopes, Queensland, 4120 Australia
54767414MMY3007	Australia	Andrew Love Cancer Centre Po Box 281 Geelong, VIC, 3220 Australia
54767414MMY3007	Australia	Royal Adelaide Hospital Adelaide, SA 5000 Australia
54767414MMY3007	Belgium	Cliniques Universitaires-UCL De Mont Godinne Avenue du Dr Therasse 1 Yvoir, 5530 Belgium

54767414MMY3007	Belgium	ZNA Stuivenberg Lange Beeldekensstraat 267 Antwerpen, 2060 Belgium
54767414MMY3007	Belgium	Centre Hospitalier Regional La Citadelle Boulevard Du Xii De Ligne 1 Liege, 4000 Belgium
54767414MMY3007	Belgium	Universitair Ziekenhuis Gent-UZ Gent De Pintelaan 185 Gent, 9000 Belgium
54767414MMY3007	Belgium	Grand Hopital de Charlero Site Notre Dame Grand Rue 3 Charleroi, 6000 Belgium
54767414MMY3007	Belgium	UZ Brussel 101 Laarbeeklaan Brussel, 1090 Belgium
54767414MMY3007	Brazil	Irmandade Da Santa Casa De Misericordia De Sao Paulo Rua Marques De Itu 579 3 Andar Vila Buarque Sao Paulo, SP, 01223001 Brazil
54767414MMY3007	Brazil	Liga Norte Riograndense Contra O Cancer Av Miguel Castro, 1355 Natal, RN, 59075-740 Brazil
54767414MMY3007	Brazil	Hospital Santa Marcelina R Sta Marcelina 177 Sao Paulo Brazil
54767414MMY3007	Brazil	Clinica De Tratamento E Pesquisa em Hematologia Cuiaba - MT, 78055-000 Brazil
54767414MMY3007	Brazil	Hospital De Clinicas De Porto Alegre Av Ramiro Barcelos 2350 Porto Alegre, RS, 00000 Brazil
54767414MMY3007	Brazil	Hospital Universitario Walter Cantidio Rua Capitao Francisco Pedro 1290 Fortaleza Ceara, CE, 60430-370 Brazil

54767414MMY3007	Bulgaria	University Multiprofile Hospital for Active Treatment-UMHAT 8A Georgi Kochev Str. Pleven, 5800 Bulgaria
54767414MMY3007	Bulgaria	Mhat St Marina 1 Hristo Smirnenski str Varna, 9010 Bulgaria
54767414MMY3007	Bulgaria	National Center of Oncology 6, Plovdivsko Pole Str. Sofia, 1756 Bulgaria
54767414MMY3007	Bulgaria	Multriprofile Hospital for Active Treatment Hristo Botev 66 Vtori Yuni Blvd Vratsa, 3000 Bulgaria
54767414MMY3007	Bulgaria	University Multiprofile Hospital For Active Treatment St George 15A, Vasil Aprilov Blvd Plovdiv, 4002 Bulgaria
54767414MMY3007	Bulgaria	St Ivan Rilski University Multiprofile Hospital For Active Treatment 15 Ivan Geshov Blvd Sofia, 1431 Bulgaria
54767414MMY3007	Croatia	University Hospital Merkur Dpt of Internal Medicine-Hematology Zajceva 19 Zagreb, 10000 Croatia
54767414MMY3007	Croatia	KBC Zagreb-Hematology Kispaticeva 12 Zagreb 10000 Croatia
54767414MMY3007	Croatia	Klinicka Bolnica Dubrava Avenija Gojka Shushka 6 Zagreb, 10000 Croatia
54767414MMY3007	Czech Republic	Vseobecna Fakultni Nemocnice v Praze-I. Interni Klinika-Klinika Hematologie U Nemocnice 2 Praha 2, 128 08 Czech Republic

54767414MMY3007	Czech Republic	Fakultni Nemocnice Brno Jihlavska 20 Brno, 625 00 Czech Republic
54767414MMY3007	Czech Republic	Fakultni Nemocnice Olomouc I. P. Pavlova 6 Olomouc, 775 20 Czech Republic
54767414MMY3007	Czech Republic	Fakultni Nemocnice Hradec Kralove Hradec Kralove 50005 Czech Republic
54767414MMY3007	Czech Republic	University Hospital 17 listopadu Ostrava-Poruba, 70852 Czech Republic
54767414MMY3007	Georgia	LTD Oncohematology and Chemoth 13 Tevdore Mgvdeli Str Tbilisi, 0112 Georgia
54767414MMY3007	Georgia	LTD Medinvent Institute of H Kavtaradze Str 21a Tbilisi, 0186 Georgia
54767414MMY3007	Georgia	5 K Chachaava Str Tbilisi 0159 Georgia
54767414MMY3007	Germany	Universitätsklinikum Würzburg Med. Klinik U. Poliklinik Ii Josef-Schneider-Str. 2 97080 Würzburg Germany
54767414MMY3007	Germany	Schwerpunktpraxis für Hämatologie und Onkologie Europaallee 5 66113 Saarbrücken Germany
54767414MMY3007	Great Britain	Leicester Royal Infirmary-Haematology Infirmary Square Leicester, LE1 5WW Great Britain

54767414MMY3007	Great Britain	Imperial College Healthcare St Mary's Hospital London, W2 1NY Great Britain
54767414MMY3007	Great Britain	University Hospitals Birmingham NHS Trust, Queen Elizabeth Hospital Birmingham, B15 2TH Great Britain
54767414MMY3007	Great Britain	Cambridge University Hospitals NHS Foundation Trust Addenbrookes Hospital Cambridge, CB2 2QQ Great Britain
54767414MMY3007	Great Britain	Princess Alexandra Hospital NHS Trust Hamstel Road Harlow, Essex, CM20 1QX Great Britain
54767414MMY3007	Great Britain	Lewisham & Greenwich NHS Trust-Oncology Lewisham High Street Woolwich, SE13 6LH Great Britain
54767414MMY3007	Great Britain	Colchester Hospital University NHS Turner Road Colchester, Essex, CO4 5JL Great Britain
54767414MMY3007	Great Britain	North Manchester General Hospital Delaunays Road Manchester, M8 6RL Great Britain
54767414MMY3007	Greece	University General Hospital of Rio Panepistimio Rio Patra, Achaia, 265 00 Greece
54767414MMY3007	Greece	General Hospital "George Papanikolaou" Exohi Thessaloniki, 57010 Greece
54767414MMY3007	Greece	Alexandra General Hospital of Athens 80 Vass Sofias & K Lourou Athens Attica, 115 28 Greece
54767414MMY3007	Greece	251 Airforces Hospital Kanellakopoulou 3 Street Athens, 115 25 Greece

54767414MMY3007	Greece	Agios Andreas General Hospital of Patra 1 Tsertidou Street Patra, Achaia, 263 35 Greece
54767414MMY3007	Hungary	Debreceni Egyetem Orvos Es Egeszsegtudomanyi Centrum Ii Sz Belgyogyaszati Klinika Nagyerdei Krt. 98 Debrecen, 4032 Hungary
54767414MMY3007	Hungary	Semmelweis Medical University Cardiovascular Center Semmelwies Egyetem Varosmajor Utca 68 Budapest, 1122 Hungary
54767414MMY3007	Hungary	Egyesitett Szent Istvan Es Szent Laszlo Korhaz-Rendelointezet Gyali Ut 5-7 Budapest, 1097 Hungary
54767414MMY3007	Hungary	Somogy Megyei Kaposi Mor Oktato Korhaz Tallian Gyula u 20-32 Kaposvar, Somogy, 7400 Hungary
54767414MMY3007	Hungary	Semmelweis Orvostudomanyi Egye Kutvolgyi Ut 4 Budapest, 1125 Hungary
54767414MMY3007	Italy	Azienda Ospedaliera Papa Giovanni XXIII A.O. Papa Giovanni XXIII Bergamo, Bergamo, 24127 Italy
54767414MMY3007	Italy	Dipartimento Di Oncologia Medica -Oncology Via Cavour 31 Torino, 10123 Italy
54767414MMY3007	Italy	Ospedali Riuniti Di Ancona Comitato Etico Regionale delle Marche A.O.U. Ospedali Riuniti Ancona, AN, 60020 Italy
54767414MMY3007	Italy	Dipartimento Di Biotecnologie Cellulari Ed Ematologia-Universita La Sapienza Via Benevento 6 Roma, RM, 00161 Italy

54767414MMY3007	Italy	Azienda Ospedaliera Santa Maria Viale Tristano Di Joannuccio Terni 05100 Italy
54767414MMY3007	Italy	Azienda Ospedaliera Spedali Civili Di Brescia Piazza Spedali Civili, 1 Brescia, 25123 Italy
54767414MMY3007	Italy	Ospedale Ca Granda-Niguarda P.Zza Ospedale Maggiore, 3 Milano, 20162 Italy
54767414MMY3007	Italy	IRCCS CROB Rionero in Vulture 85028 Italy
54767414MMY3007	Italy	General Hospital Via Trabucco, 180 Palermo, 90146 Italy
54767414MMY3007	Italy	IRCCS Policlinico San Matteo, Universita Degli Studi Di Pavi Via le Golgi 19 Pavia, Pavia, 27100 Italy
54767414MMY3007	Italy	Divisione Si Ematologia 2 Azienda Ospedaliera Universitaria San Martino Genova Largo R. Benzi nr. 10 Genova, 16132 Italy
54767414MMY3007	Italy	Azienda Ospedaliera Policlinico S. Orsola-Malpighi via Massarenti, 9 Bologna, 40138 Italy
54767414MMY3007	Japan	Kurume University Hospital 67 Asahi-Machi, Kurume-City, Fukuoka Kurume, 830-0011 Japan
54767414MMY3007	Japan	Nagoya City University Graduate School of Medical Sciences Kawasumi 1, Mizuho-cho, Mizuho-ku Nagoya, Aiti, 467-8601 Japan
54767414MMY3007	Japan	Japanese Red Cross Central Medical Center 4-1-22 Hiroo, Shibuya-Ku, Tokyo Tokyo, 150-8935 Japan

54767414MMY3007	Japan	NHO Shibukawa Medical Center 383 Shirai Shibukawa, 377-0280 Japan
54767414MMY3007	Japan	National Disaster Medical Center 3256 Midorimachi, Tachikawa-City, Tokyo Tachikawa, 190-0014 Japan
54767414MMY3007	Japan	National Hospital Organization Okayama Medical Center 1711-1 Tamasu, Kita-ku, Okayama-City, Okayama Okayama, 701-1192 Japan
54767414MMY3007	Japan	Ohgaki Municipal Hospital 4-86 Minaminokawa-Cho Ohgaki-City, Gifu Ohgaki, 503-8502 Japan
54767414MMY3007	Japan	Kobe City Medical Center General Hospital 2-1-1 Minatojimaminami-Machi, Chuo-ku, Kobe-City, Hyogo Kobe, 650-0047 Japan
54767414MMY3007	Japan	Osaka Red Cross Hospital 5-30 Fudegasaki-Cho, Tennohji-ku, Osaka-City, Osaka Osaka, 543-8555 Japan
54767414MMY3007	Japan	Toyohashi Municipal Hospital 50 Hachiken-Nishi, Aotake-Cho, Toyohashi-City, Aichi Toyohashi, 441-8570 Japan
54767414MMY3007	Japan	Hitachi General Hospital 2-1-1 Jonan-Cho, Hitachi-City, Ibaraki Hitachi, 317-0077 Japan
54767414MMY3007	Japan	Tohoku University Hospital 1-1 Seiryo-cho, Aoba-ku Sendai, 980-8574 Japan
54767414MMY3007	Japan	Kanazawa University Hospital 13-1 Takara-Machi, Kanazawa-City, Ishikawa Kanazawa, 920-8641 Japan

54767414MMY3007	Japan	Japenese Red Cross Nagoya 2nd Hospital 2-9 Myoken-Cho, Showa-ku, Nagoya-City, Aichi Nagoya, 466-8650 Japan
54767414MMY3007	Japan	Kameda General Hospital 929 Higashi-Cho Chiba, 2968602 Japan
54767414MMY3007	Japan	Matsuyama Red Cross Hospital 1 Bunkyo-Cho, Matsuyama-City, Ehime Matsuyama, 790-8524 Japan
54767414MMY3007	Japan	Japanese Red Cross Narita Hospital 90-1 Iida-Cho Narita-City, Chiba Narita, 286-8523 Japan
54767414MMY3007	Korea	Inje University Busan Paik Hospital 75 Bokji-ro Busanjin-gu Busan, 614-735 Korea
54767414MMY3007	Korea	National Cancer Center 323 Ilsan-ro, Ilsandong-gu, Goyang-si Gyeonggi-do, 10408 Korea
54767414MMY3007	Korea	Seoul National University Bundang Hospital 82 Gumi-ro 173 Beon-gil, Bundang-gu Seongnam, Gyeonggi-do, 463-707 Korea
54767414MMY3007	Korea	Gachon University Gil Medical Center 21, Namdong-daero 774beon-gil, Namdong-gu Incheon, Incheon Gwang'yeogsi Inch'n-K, 21565 Korea
54767414MMY3007	Korea	Catholic University of Korea Seoul St. Mary's Hospital Seoul, 06591 Korea
54767414MMY3007	Korea	Chonnam National University Hwasun Hospital 322 Seoyang-ro Hwasun-eup. Hwasun-gun Jeonnam, 58128 Korea
54767414MMY3007	Korea	Seoul National University Hospital 101 Daehak-Ro Seoul, 03080 Korea

54767414MMY3007	Macedonia	University Clinic for Heamatology 17 Vodnjanska St 1000 Skopje, 1000 Macedonia
54767414MMY3007	Macedonia	University Clinic for Heamatology 17 Vodnjanska St 1000 Skopje, 1000 Macedonia
54767414MMY3007	Macedonia	University Clinic for Heamatology 17 Vodnjanska St 1000 Skopje, 1000 Macedonia
54767414MMY3007	Poland	Zespol Szpitali Miejskich Oddzial Hematologiczny Chorzow, 41-500 Poland
54767414MMY3007	Poland	Szpital Uniwersytecki Nr 2 Im. Jana Biziela W Bydgoszczy Ujejskiego 75 Bydgoszcz, 85-168 Poland
54767414MMY3007	Poland	Klinika Hematologii AM Ul M Sklodowskiej-Curie 24A Bialystok, 15-276 Poland
54767414MMY3007	Poland	MTZ Clinical Research Sp. z o.o.ul. Pawinskiego 5 Warszawa, 02-106 Poland
54767414MMY3007	Poland	Wojewodzki Szpital Specjalistyczny Im. Janusza Korczaka Hubalczykow 1 Slupsk , 76-200 Poland
54767414MMY3007	Poland	Oddzial Hematologii Szpital Wojewodzki w Opolu Opole, 45-061 Poland
54767414MMY3007	Poland	Samodzielny Publiczny Szpital Kliniczny nr 1 w Lublinie ul. Staszica 11 Lublin, 20-081 Poland

54767414MMY3007	Poland	Klinika Hematologii I Transplantologii UCK U Gdansk, 80-952 Poland
54767414MMY3007	Poland	Klinika Hematologii A.M. We Wroclawiu Ul Pasteura 4 Wroclaw, 50-367 Poland
54767414MMY3007	Poland	Centrum Onkologii-Instytut im. Marii Sklodowskiej-Curie Klinika Nowotworow Ukladu Chlonnego Warszawa ul, 02-781 Poland
54767414MMY3007	Portugal	Instituto Portugues De Oncologia R Dr Antonio Bernardino Almeida Porto, 4200072 Portugal
54767414MMY3007	Portugal	Champalimaud Foundation Champalimaud Centre Avenida Brasilia Lisbon, 1400-038 Portugal
54767414MMY3007	Romania	Spitalul Clinic Coltea, Clinica Hematologie Bdul I C Bratianu Nr 1 Bucharest Romania
54767414MMY3007	Romania	Comisia Nationala De Bioetica A Medicamentului Si A Sos Stefan cel Mare Nr.19-21 Bucharest, 020125 Romania
54767414MMY3007	Romania	Clinica De Hematologie, Institutul Regional De Oncologie Str. G-ral Berthelot nr 2-4 Lasi, 700483 Romania
54767414MMY3007	Romania	Policlinica de Diagnostic Rapid Str. Livada Vulturului nr. 10 Brasov Romania
54767414MMY3007	Russia	N.N. Petrov Research Institute Of Oncology St Petersburg, 189646 Russia
54767414MMY3007	Russia	Nizhny Novgorod Regional Oncology Dispensary Rodionova Str 190, build. 5 Nizhny Novgorod, 603126 Russia

54767414MMY3007	Russia	Ryazan Regional Clinical Hospital 3A, Internacionalaya str. Ryazan, Ryazanskaya oblast, 390039 Russia
54767414MMY3007	Russia	State Medical Institution Oncological Center #2 of Healthcare Department at Krasnodar Regio 38, Dagomysskaya ul. Sochi, 354057 Russia
54767414MMY3007	Russia	Saint-Petersburg State Pavlov University 6/8 Lva Tolstogo Str Saint-Petersburg, 197022 Russia
54767414MMY3007	Russia	Sverdlovsk Regional Clinical Hospital N. 1 Volgogradskaya Street 185 Ekaterinbourg, 620102 Russia
54767414MMY3007	Russia	Emergency Hospital of Dzerzhinsk Pirogova str, 8 Dzerzhinsk, 606019 Russia
54767414MMY3007	Russia	Clinic of Professional Pathology 53-Strelkovoy Divisii Str Bld 6/9 Saratov Russia 4 Saratov, 410028 Russia
54767414MMY3007	Russia	Arkhangelsk Regional Clinical Hospital Lomonosova pr.292 Arkhangelsk, 163045 Russia
54767414MMY3007	Russia	Volgograd Region Oncology Dispensary Zemliachki str. 76 Volgograd, 400138 Russia
54767414MMY3007	Serbia	Institute for Oncology Pasterova 14 Belgrade, 11000 Serbia
54767414MMY3007	Serbia	Clinical Center Of Nis Bulevar Zorana Djindjica 48 Nis, 18000 Serbia

54767414MMY3007	Serbia	Institute for Oncology Institutski put 4 Sremska Kamenica, 21204 Serbia
54767414MMY3007	Serbia	Clinical Hospital Center Zvezdara Presevska 31 Belgrade, 11000 Serbia
54767414MMY3007	Spain	Complejo Hospitalario Universitario de Canarias Ctra. Ofra S/N La Cuesta La Laguna Santa Cruz de Tenerife, 38320 Spain
54767414MMY3007	Spain	Hospital Universitario Dr. Peset Avda Gaspar Aguilar 90 Valencia, 46017 Spain
54767414MMY3007	Spain	Hospital Universitario De Valme 4 Planta Izq Habitacion 433 Sevilla, 41014 Spain
54767414MMY3007	Spain	Centro Integral Oncologico Clara Campal Ona 10 Madrid, 28050 Spain
54767414MMY3007	Spain	Hospital Clinic de Barcelona Calle Villarroel 170 Barcelona, Cataluna, 08036 Spain
54767414MMY3007	Spain	Hospital Universitario De Girona Dr. Josep Trueta Avenida De Francia Girona, 17007 Spain
54767414MMY3007	Spain	Hospital Universitari Germans Trias i Pujol Hospital Germans Trias I Pujol Badalona, Barcelona, 08916 Spain
54767414MMY3007	Spain	Clinica Universitaria De Navarra Avenida Pio XII 36 Pamplona, Navarra, 31008 Spain
54767414MMY3007	Spain	Hospital Universitario Virgen Del Rocio Avda Manuel Siurot Andalucia, Sevilla, 41013 Spain

54767414MMY3007	Spain	Hospital Universitario De Salamanca Paseo De San Vincente Salamanca, 37007 Spain
54767414MMY3007	Spain	Hospital General Universitario-J.M. Morales Meseguer Marques De Los Velez s/n Murcia, 30008 Spain
54767414MMY3007	Spain	ICO L'Hospitalet-Hospital Duran I Reynals Adva. Gran Via 199-203 Barcelona, 08908 Spain
54767414MMY3007	Spain	Hospital Universitario 12 De Octubre Avenida de Cordoba, s/n Madrid, 28041 Spain
54767414MMY3007	Spain	Hospital Universitario Vall D´Hebron-Barcelona Paseo Vall D'hebron 119-129 Planta 8 Barcelona, 08035 Spain
54767414MMY3007	Spain	H.Virgen De La Salud Avda. Barber 30 Toledo, 45004 Spain
54767414MMY3007	Spain	H. Gregorio Maranon Calle Doctor Esquerdo 46 Maranon, 28007 Spain
54767414MMY3007	Spain	Hospital Clinico Universitario Lozano Blesa Avenida San Juan Bosco, 15 Zaragoza, 50009 Spain
54767414MMY3007	Spain	Complejo Hospitalario De Orense Calle Ramon Puga 52-54 Ourense, 32005 Spain
54767414MMY3007	Turkey	Gazi University Faculty of Medicine Hematology Department Gazi Universitesi Tip Fakultesi Ic Hastaliklari Ab Ankara, 06500 Turkey

54767414MMY3007	Turkey	Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Hematology Unit Demetevler, Yenimahalle-Ankara Ankara, 06200 Turkey
54767414MMY3007	Turkey	Dokuz Eylül Üniversitesi Tip Fakultesi Izmir, 35340 Turkey
54767414MMY3007	Turkey	Ondokuz Mayis Universitesi Tip Fakultesi Kardiyoloji Abd Samsun, 55139 Turkey
54767414MMY3007	Turkey	Adnan Menderes University Aydin, 09100 Turkey
54767414MMY3007	Turkey	Erciyes University Medical Faculty Dept. of Hematology Kayseri, 38039 Turkey
54767414MMY3007	Turkey	Ankara Universitesi Tip Fakultesi İbn-I Sina Hastanesi Cebeci Kampusu ıc Hastaliklari Anabilim Dali Hematoloji Bilim Dalı, Cebeci Ankara, 06590 Turkey
54767414MMY3007	Ukraine	Cherkassy Regional Oncology Dispensary, Department of Hematology 7 Mendeleeva Str Cherkassy, 18009 Ukraine
54767414MMY3007	Ukraine	Zaporizhzhya Regional Clinical Hospital Orikhivske Shose, 10 Zaporizhzhia, Zaporiz'ka Oblast, 69600 Ukraine
54767414MMY3007	Ukraine	Kharkov Regional Clinical Oncology Center, Dept. of Hematology 2 Lesoparkovaya Str Kharkov, 61070 Ukraine
54767414MMY3007	Ukraine	Institute of Blood Pathology and Transfusion Medicine, Lviv Clinical Hospital 5, Hematology Dept. 45 Generala Chuprinky Str Lviv 79044 Ukraine
54767414MMY3007	Ukraine	Ivano-Frankivsk Regional Clinical Hospital 91 Fedkovycha str. Ivano-Frankivsk, 76008 Ukraine

54767414MMY3007	Ukraine	Dnepropetrovsk City Clinical Hospital #4, Regional Hematology Center 31 Blizhnya Str Dnepropetrovsk, 49102 Ukraine
54767414MMY3007	Ukraine	Khmelnitskiy Regional Hospital, Hematology Department 1 Pilotskaya Str Khmelnitskiy, 29000 Ukraine
54767414MMY3007	USA	Cancer Specialists of North Florida-Florida Oncology Associates 1715 Eagle Harbor Pkwy Ste C Orange Park, FL, 32003 USA
54767414MMY3007	USA	University Hospital of Cleveland 11100 Euclid Ave Cleveland, OH, 44106 USA
54767414MMY3007	USA	Virginia Commonwealth University-Massey Cancer Center 4501 Empire Ct Fredericksburg Virginia, 22408 USA

Note: There is discrepancy in 1 site of Bulgaria and 1 site of Croatia.

In Bulgaria there are 7 Sites as per CSR Synopsis and 6 sites as per investigator site list. Reason for discrepancy is that 7 sites received drug (criteria for CSR listing) and 6 sites randomised (enrolled) a patient. Therefore, 7 sites are showing for Bulgaria in CSR Synopsis and 6 sites as per investigator site list.

In Croatia there are 2 Sites as per CSR Synopsis and 3 sites as per investigator site list. Reason for discrepancy is that there was an error in the CSR. Therefore, 2 sites are showing for Croatia in CSR Synopsis and 3 sites as per investigator site list.

Changes in Conduct:

The original protocol, dated 26 June 2014, was amended 5 times on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Amendment INT-1, 24 November 2014 was considered as substantial amendment

Amendment INT-2, 05 November 2015 was considered as substantial amendment

Amendment INT-3, 25 July 2016 was considered as non-substantial amendment

Amendment INT-4, 11 November 2016 was considered as substantial amendment and

Amendment INT-5, 14 February 2018 was considered as substantial amendment

General Amendments

The first general Protocol Amendment 1, dated 24 November 2014 was incorporate investigator feedback into the protocol, to further clarify minimal residual disease (MRD) monitoring, to clarify safety reporting requirements for sites in Japan, to incorporate updated international myeloma working group (IMWG) criteria; To align the definition of multiple myeloma with the updated IMWG criteria; Provided instructions for preventing interference of daratumumab in determining blood type for future transfusions; To clarify details of bone marrow collection for MRD monitoring; To clarify that the secondary objective and secondary endpoint was to assess the MRD negative rate; To clarify product quality complaint (PRO) and eastern cooperative oncology group (ECOG) collection procedures. Removed 2-hour post infusion collection of vital signs on Cycle 1 Day 1, in absence of safety signal and in response to investigator request; Align inclusion criteria and exclusion criteria with other daratumumab protocols; Improved instructions for pre-infusion medications; Provided examples of subjects at higher risk of respiratory complications for post-infusion medications; Improved guidelines for delay of daratumumab infusions; Clarify criteria for discontinuation of treatment after Cycle 9 due to dose delays; To allow prednisolone to substitute for prednisone in countries where prednisone was not available; Updated investigational product characteristics and handling according to new guidelines; Revisions to improved accuracy and consistency; In response to PMDA comments, additional safety monitoring for Japanese subjects was added. Minor errors were noted.

The second general Protocol Amendment 2, dated 05 November 2015 was released to provide updated guidance with respect to VELCADE dose modifications (per summary of product characteristics [SmPC] and united sates package insert [USPI]) and to add a window for within-cycle VELCADE and daratumumab treatments for site and subject convenience; To allow flexibility in the administration of pre-infusion medications, to clarify allowable pre-infusion medications, and to be consistent with other daratumumab protocols; Provided additional guidance as to acceptable methods of bone marrow preparation and indicate that flow cytometry was also an acceptable method of confirming multiple myeloma diagnosis; To clarify assessments and procedures, and timing thereof, and allow flexibility, as applicable, for some assessments and procedures, in relation to screening. Modified language and guidance pertaining to the indirect antiglobulin test (IAT); To clarify inclusion and exclusion criteria; To align with updated investigator's brochure (IB) and risk language wording, updated the timeframe associated with birth control use; To clarify if assessments were to be analyzed by the local or central laboratory and provided the reference for determination of international staging system (ISS) stage; To update recommended and prohibited therapies; To update serum chemistry panel assessments to allow urea to be performed instead of blood urea nitrogen (BUN) as some centers do not assess BUN; to add sodium and potassium to the chemistry panel; and to clarify that direct bilirubin assessment was only necessary if total bilirubin was greater than 1.5x upper limit of

normal (ULN); Clarify procedure for management of infusion-related reactions; To align with updated protocol template language; Miscellaneous updates and clarifications made throughout the protocol; Minor errors were noted.

The third general Protocol Amendment 3 (Amendment INT-3), dated 25 July 2016 was considered as non-substantial.

The fourth general Protocol Amendment 4, dated 11 November 2016 was considered as substantial. Addition of Kumar 2016 reference to support IMWG recommendations for multiple myeloma treatment response criteria; Clarification of the MRD secondary objective for cross protocol consistency; Inclusion of objective "time to response" for cross-protocol consistency; New objective added to provide cross protocol consistency and to explore durability of MRD negativity; Whole blood samples for MRD assessment obtained with bone marrow aspirates was no longer collected; Revision of endpoint presentation for protocol consistency; Revision of the definition of MRD negativity required to align with IMWG; Text correction to include exploratory endpoints to align with exploratory endpoints; Text correction to include a time to response secondary efficacy endpoint to align with secondary objectives; Clarification of use for collected whole blood samples; Modification of disease evaluation prior to disease progression (PD) time points in the follow-up phase to align with evaluation time points in the treatment phase; Addition of ± 2 weeks window to allow for flexible scheduling for follow-up visits after PD; Clarification of visit time points to ensure consistent timing of assessments for both ECOG and ePRO; Reinstatement of the 2-hour collection window for the pre-infusion daratumumab pharmacokinetics (PK) sample for subjects in Arm B; Align bone marrow aspirate/biopsy collection time points in the time and events schedule with new MRD guidelines and across daratumumab protocols; Inclusion of antihistamine medication listing to align with daratumumab protocols; Clarification that order of combination drug administration applies to subjects in Arm B only; Clarification that criteria required for VELCADE-melphalan-prednisone (VMP) administration are applicable for Cycles 2-9 only; Minor text modifications to align with VELCADE SmPC; Clarification that text within Table 4 was applicable to "within cycle" administration only; Clarification of VELCADE dose reduction; Clarification of text regarding re-escalation of melphalan after dose reduction post toxicity to align with melphalan dose-modification guidelines; Clarification of toxicity guidelines provided for the administration of VELCADE, melphalan, and prednisone; Clarification of dose modification category for Grade 3 or Grade 4 neutropenia; Dose modification for melphalan in the event of Grade 3 thrombocytopenia should be implemented in the subsequent treatment cycle; Prophylaxis text revision to align with daratumumab label; Clarification of the use of study drug during or after emergency orthopedic surgery or radiotherapy; Clarification to provide additional scheduling flexibility for subject follow-up visits after PD and to clarify follow-up intervals for subjects not continuing disease evaluations after PD; Highlight that increases in serum free light chains or the free light chain (FLC) ratio alone do not meet IMWG criteria for progressive disease in patients with measurable disease by serum M-protein quantitation by electrophoresis (SPEP) and/or urine M-protein quantitation by electrophoresis (UPEP) at baseline; Bone marrow examination table modified to align with new MRD guidelines and daratumumab protocols; Revision of time points for bone marrow collection for MRD assessment; Clarification of collection points for the serum chemistry panel; Addition of Chapuy 2016 reference to support processes to eliminate daratumumab IAT interference; Although vital signs were performed at multiple time points as specified in the time and events schedule, only vital signs obtained at screening or associated with an adverse event are captured in the electronic case report form (eCRFs); Clarification that subjects do not have to discontinue all components of the VMP regimen if only one component requires a third dose reduction for toxicity; Realignment of the testing order of the major secondary endpoints for the control of familywise type 1 error during the second interim analysis; Changes from baseline could not be summarized since vital signs were only captured in the eCRF at screening and when associated with an adverse event; Inclusion of anticipated adverse events guidelines to align daratumumab protocols; Alignment of text with

recent protocol template changes; Alignment of text with recent protocol template changes; Minor errors were noted.

The fifth general Protocol Amendment 5, dated 14 February 2018 was considered to be substantial. Subjects randomized to Arm A (VMP) who have sponsor-confirmed disease progression may have the option to receive daratumumab provided by the sponsor (in any subsequent line of therapy) if recommended by the investigator; Eligibility for and administration of daratumumab must be in accordance with local prescribing information and local regulations; To update statistical text following positive findings for the second interim analysis; To clarify/emphasize the requirement to wait until confirmed PD prior to starting subsequent anti-myeloma therapy; Clarification of the independent data monitoring committee (IDMC's) role in data review following database lock for the primary analysis; To clarify the daratumumab PK and immunogenicity assessments specific to Arm B daratumumab plus VELCADE-melphalan-prednisone (D-VMP); To clarify quantitative immunoglobulin (Ig) assessments; To clarify that eastern cooperative oncology group (ECOG) and patient-reported outcomes (PRO) assessments that occur at Week 8 and Week 16 post-PD was scheduled relative to the date of confirmation of disease progression; Replaced time qualifier of '1-3 weeks later' because in urgent situations, a repeat investigation may be needed sooner; 'At least 1 day later' was used to make clear that the confirmatory test cannot happen on the same day as the initial test; To clarify that sites should continue to monitor extramedullary plasmacytomas for PD following complete response (CR); To clarify required chemistry assessments at End-of-Treatment; Minor errors were noted.

Publications:

Mateos M.V, Dimopoulos M.A, Cavo M, Suzuki K et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. The new england journal of medicine 2017;1-11: DOI:10.1056/NEJMoa1714678

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