1.   SYNOPSIS

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Lenalidomide		
Name of Active Ingredient: 3 [4'aminoisoindoline-1'-one]-1- piperidine-2, 6-dione		

Title of Study: A Phase III, Randomized, Open-Label, 3-Arm Study To Determine the Efficacy and Safety of Lenalidomide (Revlimid®) Plus Low-Dose Dexamethasone When Given Until Progressive Disease or for 18 Four-Week Cycles Versus the Combination of Melphalan, Prednisone, and Thalidomide Given for 12 Six-Week Cycles in Subjects with Previously Untreated Multiple Myeloma Who Are Either 65 Years of Age or Older or Not Candidates for Stem Cell Transplantation (IFM 07-01)
Principal Investigator: Dr. Thierry Facon, Centre Hospitalier, Régional Universitaire, Hôpital de Lille, Service des Maladies du Sang, Lille, France Investigators: A list of investigators is provided in Appendix 16.1.4.
Study center(s): 246 sites (165 in Europe [Austria, Belgium, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden, Switzerland], 23 in Asia [China, South Korea, Taiwan], 39 in North America [Canada, United States of America], and 19 in the Pacific [Australia, New Zealand])
Publications (reference): Not applicable.

Studied period (years): Date first subject enrolled: 29 Aug 2008 Date last subject completed: Ongoing study	Phase of development: Phase 3

Objectives: Primary: • To compare the efficacy of lenalidomide plus low-dose dexamethasone (Rd) given until progressive disease (PD) to that of melphalan, prednisone, and thalidomide (MPT) given for twelve 42-day cycles Secondary: • To compare the efficacy of Rd given for eighteen 28-day cycles (Rd18) to that of MPT given for twelve 42-day cycles • To assess the safety of Rd versus that of MPT • To assess the safety and efficacy of Rd therapy given until progressive disease versus the safety and efficacy of Rd given for eighteen 28-day cycles
Methodology: CC-5013-MM-020/IFM 07-01 is a Phase 3, multicenter, randomized, open-label, 3-arm study to compare the efficacy and safety of Rd given for 2 different durations of time (ie, until PD or for up to

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eighteen 28-day cycles [72 weeks]) to that of MPT given for a maximum of twelve 42-day cycles (72 weeks). The sponsor was blinded to the data until after the targeted number of events for the primary endpoint was met; the Celgene study team remained blinded to study results until the date of unblinding (09 Jul 2013). Key eligibility criteria included subjects with newly diagnosed symptomatic multiple myeloma (MM) who had measurable monoclonal protein (M-protein) by protein electrophoresis analyses (in serum [SPEP] and/or urine [UPEP]) and who were 65 years of age or older or who were not candidates for stem cell transplantation (SCT). Subjects who had nonsecretory MM by SPEP and UPEP analyses were not eligible for this study. For the purposes of this study, a subject who was < 65 years of age was not a candidate for SCT if the subject refused to undergo SCT therapy or the subject did not have access to SCT due to cost or other reasons. Subjects with poor performance status (Eastern Cooperative Oncology Group [ECOG} status of 3 or 4) or serious coexistent medical conditions, as judged by the investigational physician, were excluded from this study.

Screening

Potential study subjects were required to sign an informed consent document (ICD) before undergoing any study-related procedures. All subjects, despite age, had to be ineligible for SCT and not have had stem cell harvest. A standard-of-care bone marrow sample taken within 28 days of randomization was acceptable for use during screening (even if the sample was taken before the ICD was signed) but a bone marrow aspirate had to be repeated for cytogenetics. Subjects were screened for protocol eligibility. All females of childbearing potential (FCBP) had to use 2 forms of contraception, 1 highly effective method and 1 barrier method, during screening. The risks of both lenalidomide and thalidomide were explained to the subject during screening. At randomization, contraceptive methods and pregnancy and risk counseling could be modified to reflect the requirements of the study arm to which the subject was randomized.

Randomization

Eligible subjects were randomized (1:1:1) to 1 of 3 treatment arms: Treatment Arm A (Rd), Rd given in 28-day cycles until documentation of PD; Treatment Arm B (Rd18), Rd given in 28-day cycles for up to 18 cycles (72 weeks); and Treatment Arm C (MPT), MPT given in 42-day cycles for up to 12 cycles (72 weeks). The results of the skeletal survey, the bone marrow aspirate (percent plasma cells), and radiographic assessments of extramedullary plasmacytomas obtained during the screening period provided both eligibility and baseline information. If the subject's screening vital signs, complete blood count, serum chemistries, creatinine clearance (CrCL), and protein electrophoresis assessments were within 7 days of randomization, they did not need to be repeated at Cycle 1 Day 1 and were used as baseline results.

Randomization was performed by a validated interactive voice/web response system (IVRS/IWRS). Subjects were stratified at randomization by 1) age (≤ 75 versus > 75 years); 2)

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stage (International Staging System [ISS] Stages I or II versus Stage III); and 3) country.

Protocol Treatment

Study treatment began the same day the subject was randomized. Study visits and serial measurements of safety and efficacy were performed as outlined in the protocol. Subjects randomized to Rd continued Rd therapy until the documentation of PD or intolerable toxicity. Subjects randomized to Rd18 continued Rd therapy for up to eighteen 28-day cycles (72 weeks) and subjects randomized to MPT continued MPT therapy for up to twelve 42-day cycles (72 weeks), unless PD or intolerable toxicity developed before the completion of the maximum number of cycles. Efficacy assessments were performed at the start of each new cycle. If the start of a new cycle was delayed ≤ 7 days from the prescribed dosing cycle, efficacy assessments were not repeated before the start of the new cycle and Day 1 of the new cycle began when the next dose of Rd or MPT was given. If the new cycle was delayed > 7 days, efficacy assessments were performed before initiation of the next cycle or, if the delay was greater than a full cycle (28 or 42 days), efficacy assessments were performed every 28 (Arms Rd and Rd18) or 42 (Arm MPT) days until a new cycle began. Subsequent efficacy assessments were performed at the start of each new cycle. Regardless of study arm, efficacy assessments during the PFS follow-up phase were repeated every 28 days.

Response, including PD, was assessed according to the International Myeloma Working Group (IMWG) criteria (Durie, 2006) based on central laboratory values. The severity of AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. Guidelines for study drug dose reduction for dose-limiting toxicity (DLT) were followed.

In all 3 arms, screening assessments (eg, vital signs, complete blood count) performed ≤ 7 days before randomization were used as the baseline results and did not need to be repeated at Cycle 1 Day 1. Local laboratories performed bone marrow aspirate (cytology) procedures at screening and to confirm a CR, determination of percent plasma cells in the marrow, and complete blood counts (CBCs). Results of a bone marrow aspirate/biopsy performed within 28 days of randomization could be used to meet screening cytology requirements; a bone marrow aspirate for cytogenetics was still required at screening. Central laboratories performed the tests outlined in the protocol. Local laboratory specimens were drawn if immediate results were necessary for treatment-emergent adverse events (AEs).

Bisphosphonate therapy and hematopoietic growth factors could be used at the discretion of the treating physician. The use of myeloid growth factors was encouraged when the absolute neutrophil count (ANC) was < 1,000/μL.

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Careful consideration was to be given to avoiding the concomitant use of erythropoiesis-stimulating agents (ESA) known to potentially increase thrombotic risk.

Antithrombotic Prophylaxis

Subjects with a medical history of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 5 years of randomization received either a prophylactic dose of anticoagulation therapy with low molecular weight heparin (LMWH) or heparin (at a dose recommended for prophylaxis of DVT/PE per the package insert) or warfarin (Coumadin®; per the therapeutic index recommendations for DVT/PE to maintain an International Normalized Ratio [INR] of 2.0 to 3.0) for at least the first 4 months (16 weeks) of study participation. Then, at the discretion of the treating physician, oral low-dose aspirin (70 to 100 mg daily) or continued anticoagulation therapy was given to these subjects for the remainder of the study.

Subjects without a medical history of DVT or PE within 5 years of randomization were to receive, at the discretion of the treating physician, either oral low-dose aspirin or another prophylactic antithrombotic treatment during their participation in the study. The use of clopidogrel or ticolpidine was acceptable only in combination with oral low-dose aspirin or with another treatment for antithrombotic prophylaxis with lenalidomide or thalidomide.

Subjects unable or unwilling to undergo antithrombotic prophylactic treatment were not eligible to participate in this study.

Protocol-directed Follow-up for Progression-free Survival (PFS) and Censoring for PFS

Following screening and randomization, this study consisted of the following phases:

- An active treatment phase;
- A PFS follow-up phase; and
- A long-term follow-up phase

The active treatment phase was the period when a subject received study treatment. The active treatment phase ended when study treatment was discontinued permanently. Circumstances causing permanent discontinuation of study treatment included:

- The documented occurrence of PD (per investigator assessment)
- The completion of study treatment as per protocol (ie, the completion of 18 cycles of Rd for Arm Rd18 subjects and the completion of 12 cycles of MPT for Arm MPT subjects)
- Intolerable toxicity or any reason other than PD resulting in permanent

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discontinuation of study treatment before the protocol-designated duration of study therapy

Subjects in Arm Rd18 or MPT who completed 18 cycles entered the PFS follow-up phase to be followed until PD. Regularly scheduled response and PD assessments continued for these subjects after completion of protocol-designated duration of study treatment (every 28 days during PFS follow-up). No antimyeloma therapies (AMT) were to be started during the PFS follow-up phase until development of PD. Every attempt was made to keep subjects in the PFS follow-up phase until PD so that an accurate estimation of median PFS time for each treatment arm could be made.

Subjects in any treatment arm who permanently discontinued study treatment early, either due to toxicity or any reason other than PD, and who completed ≥ 6 cycles entered the PFS follow-up phase only if their treating physician determined that additional new AMT was not required before the development of PD. Generally, patients for whom study treatment is permanently discontinued before the completion of 6 cycles receive a new AMT to avoid a shortened duration of PFS.

The primary efficacy endpoint, PFS, was calculated as the time from randomization to the first documented PD (confirmed by the blinded Independent Response Adjudication Committee [IRAC}) or death due to any cause during the study, whichever occurs first. All subjects were followed for response and PD during the active treatment phase and the PFS follow-up phase. It should be noted that there might have been a slight bias against Arms Rd and Rd18 with regard to PFS. Subjects in those treatment arms were seen in the clinic on a more frequent basis (every 4 weeks versus every 6 weeks for Arm MPT) and, therefore, were more likely to have PD diagnosed earlier.

For the primary PFS analysis, PFS was censored at the date when the last response assessment determined lack of progression for those subjects who discontinued the active treatment phase or the PFS follow-up phase before documentation of PD. If a subject initiated a new AMT regimen following the withdrawal of study treatment but before documentation of PD in the PFS follow-up phase, then PFS was censored at the date of the last progression-free response assessment before the start date of the new regimen. Sensitivity analyses were performed using alternative censoring rules.

Long-Term Follow-up Phase

The following subjects entered the long-term follow-up phase:

- Subjects who developed PD in either the active treatment phase and/or the PFS

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follow-up phase

- Subjects who declined further participation in the active treatment phase or the PFS follow-up phases before documented occurrence of PD

- Subjects who did not complete 6 cycles of treatment and who discontinued for reasons other than PD

Subjects who entered the long-term follow-up phase initially had assessments every 4 months and then (from Amendment 3 onward) every 2 months. Subjects who progressed were assessed for subsequent antimyeloma therapies (best response to the first antimyeloma treatment regimen used after study discontinuation), potential development of second primary malignancies (SPMs), subsequent PD after second-line therapy, and overall survival. Per Amendment 3, subjects who had not progressed and entered the long-term follow-up phase (ie, subjects who discontinued from active treatment with < 6 cycles) also had ongoing response assessments (every 2 months) using local laboratory data (including SPEP/UPEP, serum and urine immunofixation analyses of M-proteins [IFE], serum chemistry if hypercalcemia confirmed PD or hematology if worsening anemia confirmed PD) and radiology scans (if increasing bone lesions or plasmacytoma confirmed PD) until the documented time of PD.

Contacts during the long-term follow-up phase were made by clinic visit or documented telephone contact. For subjects who had not reached PD before entering the long-term follow-up phase, every effort was made to obtain the required laboratory assessments (either at the study site or at the subject's local/primary oncologist office).

For subjects who declined further participation in the active treatment phase before documented occurrence of PD and who did not enter the long-term follow-up phase according to the criteria stated above (ie, subjects 'lost to follow up') the study site was to attempt to contact the subject and capture documentation of PD. This was done retrospectively if PD or death already occurred (including retrospective collection of local laboratory data) or prospectively by attempting to re-consent the subject in the long-term follow-up phase.

Number of subjects (planned and analyzed):

1590 (Planned enrollment 530 per treatment arm), 1623 (Analyzed)

Diagnosis and main criteria for inclusion:

Previously untreated, symptomatic multiple myeloma as defined by:

- MM diagnostic criteria (all 3 required):

  - Monoclonal plasma cells in the bone marrow ≥10% and/or presence of a

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       biopsy-proven plasmacytoma

- Monoclonal protein present in the serum and/or urine

- Myeloma-related organ dysfunction (at least one of the following)[a]

    [C] Calcium elevation in the blood (serum calcium > 10.5 mg/dL or upper limit of normal)

    [R] Renal insufficiency (serum creatinine > 2 mg/dL)

    [A] Anemia (hemoglobin < 10 g/dL or 2 g < laboratory normal)

    [B] Lytic bone lesions or osteoporosis

AND have measurable disease by protein electrophoresis analyses as defined by the following:

- Immunoglobulin (Ig) G multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours

- IgA multiple myeloma: Serum M-protein level ≥ 0.5 g/dL or urine M-protein level ≥ 200 mg/24 hours

- IgM multiple myeloma (IgM M-protein plus lytic bone disease documented by skeletal survey plain films): Serum M-protein level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24hours

- IgD multiple myeloma: Serum M-protein level ≥ 0.05 g/dL or urine M-protein level ≥ 200 mg/24 hours

- Light chain multiple myeloma: Serum M-protein level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours

AND are at least 65 years of age or older or, if younger than 65 years of age, are not candidates for stem cell transplantation because:

- The subject declines to undergo stem cell transplantation, or

- Stem cell transplantation is not available to the subject due to cost or other reasons

[a] A variety of other types of end organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma-related.

Test product, dose and mode of administration, batch number:

A list of batch numbers is provided in Appendix 16.1.6.

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Duration of treatment:

- Arm Rd: treatment until disease progression

- Arm Rd18: treatment for eighteen 4-week cycles (72 weeks)

- Arm MPT: treatment for twelve 6-week cycles (72 weeks)

Reference therapy, dose and mode of administration, batch number:

A list of batch numbers is provided in Appendix 16.1.6.

Criteria for evaluation:

Efficacy:

- Date of documentation of disease progression

- Myeloma paraprotein

- Serum immunoglobulin

- Bone marrow aspiration or biopsy

- Radiographic assessments of lytic bone lesions

- Overall survival (date of death or last date known to be alive)

- Cytogenetic findings in malignant myeloma clone

Safety:

- Complete physical examination including vital signs and clinical neurological examination

- Clinical laboratory evaluations

- Serum thyroid-stimulating hormone (TSH), Tri-iodothyronine (T_3), and thyroxine (T_4) levels

- Serum or urine beta-human chorionic gonadotropin (ß-HCG; FCBP only) levels

- Electrocardiogram (ECG)

- Concomitant medications and procedures

- Adverse events (AEs)

- Second Primary Malignancies

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Statistical methods:

Sample Size:

The primary analysis for the study is to compare PFS between Arm Rd (lenalidomide plus dexamethasone until PD) and Arm MPT (MPT for 12 cycles). For the primary efficacy variable, PFS, an improvement in median PFS from 24 months for Arm MPT to 30 months for Arm Rd is considered clinically relevant. It is assumed that the overall PFS distribution is exponential with a constant failure (hazard) rate and that accrual is uniform during the accrual period. It is also assumed that the annual dropout rate is about 10% and that the dropout rate is exponentially distributed. With a 24-month accrual period and 36-month follow-up after the study closes to accrual, 530 subjects in each treatment group would have 80% power to detect a hazard rate ratio of 1.25 using a 2-sided log-rank test with overall significance level of 0.05 and significance level of 0.049 for the final analysis (adjusted for one interim analysis at 50% information). A third treatment group (Arm Rd18, lenalidomide plus dexamethasone for 18 cycles) was added for the secondary analysis to compare efficacy between Arms Rd and Rd18 as well as between Arms Rd18 and MPT. Therefore a total of approximately 1590 subjects (530 in each arm) were enrolled, with accrual of about 67 subjects per month for 24 months. Full information necessary for a log-rank test to have 80% power was achieved when approximately 950 subjects across all treatment arms have progressed or died (PFS).

Overall survival (OS) will be compared after all subjects have been followed for at least 5 years from randomization, or have died or been lost to follow-up before 5 years. With an estimate of a median survival of 56 months in Arm Rd and 45 months in Arm MPT, assuming the survival distribution is exponential, for 530 subjects in each treatment arm, a total of 597 deaths would be expected in the 2 arms at 5 years. In a test of survival curves reflective of a 25% improvement in median OS, a 2-sided log-rank test at the 0.05 significance level performed when there are 597 deaths in the 2 arms (a total of 896 deaths across all 3 arms) would have a power of 78%.

Efficacy Analysis:

Primary efficacy analyses was based on the intent-to-treat principle. The primary efficacy endpoint is the PFS, calculated as the time from randomization to the first documented progression confirmed by a blinded, IRAC or death due to any cause up to the end of the PFS follow-up phase, whichever occurs first. The primary comparison was made between Arms Rd and MPT, and secondary comparisons were made between Arms Rd and Rd18 and between Arms Rd18 and MPT.

Primary analyses for PFS, response rate, time to response, duration of response, time to treatment failure, and time to the next anti-myeloma therapy will be performed after at least 950 subjects across all 3 treatment arms have developed disease progression or died due to any cause up to the end of the PFS follow-up phase (ie, PFS).

Sensitivity analysis of PFS was performed using different censoring rules.

Final analyses to compare OS will be performed after all subjects have followed for at least 5 years after the date of randomization or have died.

The Kaplan-Meier (KM) product limit method was used to estimate the survivorship functions for time-

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to-event endpoints with censoring (eg, PFS, duration of response, time to treatment failure, time to second-line anti-myeloma treatment, and overall survival). An unstratified log-rank test was used to compare treatment arms for time-to-event variables. The Cox proportional hazards regression model was used to assess the significance of demographic and prognostic variables on relative treatment differences.

Exact tests for proportions were used to compare objective overall response rates.

Repeated measures analysis of variance (ANOVA) was used to analyze the quality of life (QoL) data.

In addition, an analysis will be performed on pharmacoeconomic and clinical benefit data.

Summary statistics (mean, standard deviation, median, minimum and maximum) were provided for all the other relevant variables.

Safety Analysis:

Data from all subjects who receive any study drug were included in the safety analyses.

Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities were graded according to the NCI CTCAE whenever possible.

Adverse event frequency was tabulated by body system, MedDRA term, and treatment arm. In the by-subject analysis, a subject having the same event more than once was counted only once.

Adverse events were summarized by worst NCI CTCAE grade. In the case that the adverse events or event frequencies were judged to be clinically important, an exact test was used to analyze the difference between the treatment groups.

Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE Grade 3 or higher, study-drug-related events, serious adverse events, and events of interest (including second primary malignancies) were summarized separately.

Laboratory data were graded according to NCI CTCAE severity grade. Cross tabulations were provided to summarize frequencies of abnormalities.

For vital sign and body weight data, means, medians, standard deviations, minimum and maximum values were provided.

Graphical displays were provided where useful to assist in the interpretation of results.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The results of this randomized, open-label Phase 3 study in subjects with NDMM who were deemed ineligible for SCT showed statistically significant and clinically meaningful improvement in PFS with Rd (a doublet regimen) administered until PD compared with MPT (an established triplet regimen), with results of interim OS analysis also favoring Rd. Treatment with both continued Rd and Rd18 produced a higher overall response rate versus treatment with MPT, with improved rates of complete response (CR)

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and very good partial response (VGPR) suggesting a deeper quality of response. Furthermore, a significant improvement in PFS2 indicated that continued Rd treatment does not impact negatively on the efficacy of second-line therapy. Results for the other secondary endpoints (including OS, response rate [RR], duration of response [DOR]) and for PFS after next-line therapy (PFS2) were consistent with results for the primary endpoint.

The age-adjusted MPT regimens used as the control in this study are consistent with the regimens evaluated previously by the Intergroupe Francophone du Myélome (IFM) cooperative group (Facon, 2007; Hulin, 2009). This study was conducted in accordance with Good Clinical Practice (GCP) guidelines. A safety monitoring committee (DMC) reviewed the safety of the study at regular time intervals. An IRAC reviewed the response assessments, including PD, according to IMWG criteria and adjudicated the date of PD in a blinded fashion.

Subject Disposition, Demographics, and Baseline Disease Characteristics

- The study randomized 1623 subjects from Europe (69%), North America and Pacific regions (24%), and Asia (7%) from 29 Aug 2008 to 10 Mar 2011.

- At the time of the 24 May 2013 data cutoff, the median follow-up for surviving subjects is 37.0 months and 121 (23%) subjects in Arm Rd remain on treatment, while all subjects in Arm Rd18 and Arm MPT have discontinued study treatment per study design.

- The median duration of treatment was 80.2 weeks in Arm Rd, longer than the 72.0 weeks for Arm Rd18 (per study design) and 67.1 weeks for Arm MPT. In Arm Rd, 39% of subjects have continued treatment for longer than 2 years.

- Overall, the median age was 73.0 years, approximately one-third of the population was > 75 years and 5.7% of the subjects were < 65 years but deemed ineligible for SCT, per study entry criteria.

- Baseline disease-related characteristics were well balanced across the treatment arms. Forty-one percent of all subjects had ISS Stage III MM. Albumin at study entry was ≤ 35 g/L in 35.9% of subjects in Arm Rd, 38.6% in Arm Rd18, and 40.8% in Arm MPT. Approximately 21% to 23% of subjects had an ECOG performance status (PS) ≥ Grade 2; 31% to 33% had CrCl < 50 mL/min; 32% to 35 % had an adverse cytogenetic risk profile.

- As expected, a number of subjects had comorbidities including prior history of cardiac disorders, vascular disorders, and metabolic disorders.

Progression-free Survival

- The final analysis of PFS was based on IRAC assessments and conducted on a total of 960 (of 950 preplanned) events, corresponding to 59% of the intent-to-treat (ITT) population.

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- The study met its primary endpoint. The probability of remaining free from progression or death was significantly better in Arm Rd compared with Arm MPT (hazard ratio [HR]=0.72; p-value=0.00006) with a 28% decrease in the risk of progression or death.

- Sensitivity analyses for PFS using different criteria for censoring, including criteria as per the European Medicines Agency (EMA) guidelines, confirm the robustness of the PFS results.

- At 3 years, 42% of the subjects in Arm Rd and 23% of the subjects in Arm MPT remained event-free; at 4 years, 35% of the subjects in Arm Rd and 15% of the subjects in Arm MPT remained event-free.

- The results for the control Arm MPT in this study are similar to the efficacy results previously published for the MPT regimen including a meta-analysis that analyzed 6 studies comparing MPT versus melphalan and prednisone (MP) (Fayers, 2011), which have shown MPT to be superior to MP for OS and PFS.

- The comparison of Arm Rd with Arm Rd18 also shows a significant reduction in the risk of progression or death (HR=0.70; p-value=0.00001), indicating that continued treatment with Rd is beneficial for disease control.

- Multivariate analysis identified treatment with Rd until progression, non-adverse cytogenetic risk profile, ECOG PS score of 0 compared with 1 or 2, $CrCl \geq 80$ compared with < 30 mL/min, lactate dehydrogenase (LDH) < 200 U/L, and ISS Stage I or II to be independent predictive factors for a PFS advantage. After the correction for prognostic factors, the Rd treatment effect remained clinically meaningful (HR=0.75; 95% confidence interval (CI): 0.6593-0.8842) for the primary comparison Arm Rd versus Arm MPT.

- A PFS benefit in favor of Arm Rd versus MPT was observed in most subgroups analyzed, including those of age (≤ 75 years and > 75 years), gender, race (White or Caucasian and Asian), ISS stage, creatinine clearance category, baseline albumin level, ECOG performance status, and cytogenetic profile category.

Overall Survival

- For the comparison of Arm Rd versus Arm MPT, the planned interim OS analysis conducted at the time of final PFS analysis was based on 382 death events (35.3% [382/1082] of the ITT population in these 2 arms), which represented 64% information (382 of the prespecified 597 events for the final OS analysis for 2 arms).

- Treatment with continued Rd clearly did not have an adverse effect on survival compared with treatment with MPT. A 22% reduction in risk of death in favor of Arm Rd versus Arm MPT (HR=0.78; 95% CI: 0.64-0.96) was observed. The nominal p-value is p=0.01685 (log-rank test).

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The estimated 3-year survival rates were 70% for Arm Rd, 66% for Arm Rd18, and 62% for Arm MPT.

- The prespecified boundary for superiority (p < 0.0096) was not crossed and the results are included to support the other efficacy endpoints and the overall clinical benefit of the treatment. As the prespecified boundary was not crossed, these OS results have to be interpreted with caution.

Time to Event Endpoints

The table below summarizes results for time to event endpoints, which were consistent with the primary endpoint and show the robustness of these data.

Summary of Time to Event Endpoints

Endpoint	Rd versus MPT		Rd versus Rd18		Rd18 versus MPT	
	HR	p-value	**HR**	p-value	**HR**	p-value
PFS (primary)	**0.72**	0.00006	**0.70**	0.00001	**1.03**	0.70349
OS	**0.78**	0.01685	**0.90**	0.30743	**0.88**	0.18433
TTP	**0.68**	0.00001	**0.62**	<0.00001	**1.11**	0.21718
TTF	**0.77**	0.00012	**0.81**	0.00187	**0.95**	0.45973
TT 2nd AMT	**0.66**	<0.00001	**0.74**	0.00067	**0.88**	0.12333
PFS2	**0.78**	0.00508	**0.92**	0.37177	**0.85**	0.05472

d = low-dose dexamethasone; M = melphalan; P = prednisone; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival on next-line therapy; R = lenalidomide; T = thalidomide; TT 2nd AMT = time to second-line anti-myeloma therapy; TTF = time to treatment failure; TTP = time to progression.
Data cutoff date = 24 May 2013.

Types of Second-line Treatment, Time to Second-line Treatment, and Progression-free Survival on Next-Line Therapy

- A lower proportion of subjects in Arm Rd (43.2%) received any second-line therapy compared with Arms Rd18 (55.3%) and MPT (56.5%). Most subjects who had second-line therapy received a bortezomib-based regimen (61.9% in Arm Rd, 56.2% in Arm Rd18, and 48.5% in Arm MPT). An alkylating agent was part of the second-line therapy in 54.1% of subjects in Arm Rd, 44.5 % in Arm Rd18, and only 24.6% in Arm MPT.

- Time to second-line therapy was longer in Arm Rd (39.1 months) compared with Arm Rd18 (28.5 months) and Arm MPT (26.7 months).

- Time from second-line to third-line therapy (by type of therapy) was analyzed in order to examine the impact of continued first-line treatment in Arm Rd on the efficacy of second-line therapy. For

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subjects who received a bortezomib-based regimen, the median time from second-line to third-line therapy was 17.1 months in Arm Rd, 13.5 months in Arm Rd18, and 10.8 months in Arm MPT.

- PFS2 was longer in Arm Rd (42.9 months) compared with Arm Rd18 (39.4 months; p=0.37177), and compared with Arm MPT (36.3 months; p=0.00508).

- The PFS2 benefit in Arm Rd was observed in all subgroups evaluated except for subjects with severe renal function insufficiency (CrCl < 30 mL/min) and subjects with high tumor burden (LDH ≥ 200 g/L).

Response Rate

- Response rates (CR+VGPR+ partial response [PR]) as determined by IRAC were also significantly higher in Arm Rd and Arm Rd18 (75% and 73%, respectively) compared with Arm MPT (62%) (p < 0.00001 for Arm Rd versus Arm MPT; and p=0.00010 for Arm Rd18 versus Arm MPT).

- The rate of CR+VGPR, indicating a deeper quality of response, was higher in Arm Rd compared with Arm MPT (44% versus 28%, respectively), and also in Arm Rd18 compared with Arm MPT (43% versus 28%, respectively).

- Regardless of cytogenetic risk, subjects treated with Rd or Rd18 had better response rates than subjects treated with MPT; approximately 70% achieved PR in the Rd and Rd18 arms compared with 58% in the MPT arm.

- Among the responders, the median duration of response was longer for subjects in Arm Rd (35.0 months) compared with those in Arm MPT (22.3 months) (p < 0.00001; HR=0.63; 95% CI: 0.51-0.76).   Based on the KM estimates, 39% of the responders in Arm Rd had responses lasting at least 4 years compared with 11% of subjects in Arm MPT.

Quality of Life

- Analysis with data collected up to 18 months showed that QoL improves after treatment initiation and was generally maintained while subjects are progression free, but deteriorates with PD. Such findings are made clinically meaningful by the parallel statistically significant increase in PFS for Arm Rd versus Arm MPT.

- Treatment with MPT was associated with a significant worsening of treatment side effects as compared with treatment with Rd or Rd18.

Efficacy Conclusions

In summary, the study has met its objective for the primary analysis. Analyses of the secondary efficacy endpoints are consistent with the primary endpoint. Treatment with Rd has shown superiority in terms

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of PFS, PFS2, RR, time to progression (TTP), and time to treatment failure (TTF) compared with MPT. The current OS data favor Rd, suggesting that treatment with Rd has no adverse impact on survival. The MPT regimen is a standard control treatment that has previously shown a statistically significant OS and PFS advantage over MP. The results of Arm MPT in this study are similar to the efficacy results previously published for MPT (Fayers, 2011).

SAFETY RESULTS:

Subjects assigned to the Rd regimen received a larger proportion of their planned dose compared with subjects in Arm MPT, with fewer dose reductions and more subjects completing their treatment as planned.

- Arm Rd18 and Arm MPT had the same maximum length of treatment (up to 18 or 12 cycles, respectively, for a scheduled treatment duration of 72 weeks) allowed by the protocol. Subjects in Arm Rd were to be treated until disease progression. The median duration of treatment in Arm Rd, Arm Rd18, and Arm MPT was 80 weeks, 72 weeks, and 67 weeks, respectively, with 39.1% of subjects in Arm Rd still on treatment after 2 years (104 weeks). A total of 121 subjects (23%) in Arm Rd were still receiving treatment as of the data cutoff date for this report.

- Time to first dose reduction was shorter with the MPT arm compared with the Rd-containing arms (median of 12 weeks for melphalan and 14 weeks for thalidomide versus 14 to 16 weeks for lenalidomide and 18 to 29 weeks for dexamethasone).

- The total person-years of study treatment exposure was 921 for Arm Rd, 587 for Arm Rd18, and 549 for Arm MPT, representing the observation period for which treatment-emergent adverse events were collected in each study arm.

The safety data observed in this study for the Rd regimen is consistent with the known safety profile of lenalidomide plus dexamethasone in the MM population.

- In this study, the starting dose for lenalidomide was adjusted by baseline renal function and the dose of dexamethasone was adjusted by age. Treatment adherence and tolerance were similar between the older and younger age groups.

- In general, the most frequently reported adverse events (ie, individual preferred terms in at least 25% of subjects overall in the 2 Rd-containing arms) were observed at comparable frequencies in Arm Rd and Arm Rd18, and included diarrhea, anemia, constipation, peripheral edema, neutropenia, fatigue, back pain, nausea, asthenia, and insomnia. The most frequently reported Grade 3 or 4 events (ie, individual PTs in at least 5% of subjects in either Arm Rd or Rd18) included neutropenia, anemia, thrombocytopenia, pneumonia, asthenia, fatigue, back pain, hypokalemia, rash, cataract, lymphopenia, dyspnea, DVT, hyperglycemia, and leukopenia. No particular adverse event led to discontinuation of any study drug in more than 2% of subjects in

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either arm.

- Differences in frequencies of some adverse events were noted between Arms Rd and Rd18.

    - A slightly increased frequency of infections, an underlying characteristic of the disease, was observed in Arm Rd (75%) versus Arm Rd18 (70%), likely influenced by the increased exposure to dexamethasone in Arm Rd. During active treatment, deaths due to infection were reported at a higher frequency in Arm Rd (3.8%) versus Arm Rd18 (2.0%), which was similar to the frequency in Arm MPT (1.8%). Overall, when considering the entire study (active treatment and follow-up), deaths due to infection were reported at generally comparable frequencies across all treatment arms (6.2% in Arm Rd; 4.6% in Arm Rd18, and 5.7% in Arm MPT). Infection is the leading cause of death in patients with myeloma (Nucci, 2009).

    - A higher frequency of myocardial infarction/ischemic heart disease events was observed in Arm Rd (8.1%) versus Arm Rd18 (3.1%). This observed imbalance largely reflected an increased frequency of events that occurred during the first 6 months in Arm Rd versus Arm Rd18, and thus, did not appear to be related to the longer treatment duration in Arm Rd.

        - Given that assigned treatments were identical during these first 6 months, and baseline characteristics were similar between Arm Rd and Arm Rd18, the higher frequency of events during the first 6 months may be due to chance or to underlying differences (despite randomization) in other baseline patient characteristics that were not collected in the study data.

    - The IRs of cataract in both Arm Rd18 and Arm Rd increased during each subsequent 6-month interval, up to 18 months in Arm Rd18 (when treatment was stopped per protocol), and up to 24 months in Arm Rd, likely associated with increased exposure to dexamethasone. Routine collection of treatment-emergent cataract events did not continue in Arm Rd18 after 18 months so it is not possible to determine if the frequency of cataract continued to increase in Arm Rd18 after discontinuation of treatment.

    - There was no apparent increased risk of SPM with continued treatment of Rd until progression versus a fixed duration of Rd; in fact, there were fewer subjects with solid tumors in Arm Rd (2.8%) than in Arm Rd18 (5.4%). As of the 24 May 2013 data cutoff date, there were few subjects with hematologic SPMs (2 subjects in each arm).

The safety results observed in Arm MPT were consistent with the known safety profile of MPT.

- In this study, the initial dose of thalidomide was adjusted by age and the initial dose of

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melphalan was adjusted by both age and bone marrow reserve at baseline. Treatment adherence and tolerance were similar between the older and younger age groups.

- The most frequently reported adverse events observed in Arm MPT (occurring in ≥ 25% of subjects) included neutropenia, constipation, anemia, peripheral edema, peripheral sensory neuropathy, nausea, fatigue, and thrombocytopenia. The most frequently reported Grade 3 or 4 events (occurring in ≥ 5% of subjects) included neutropenia, anemia, thrombocytopenia, leucopenia, peripheral sensory neuropathy, lymphopenia, asthenia, pneumonia, fatigue, constipation, back pain, and rash. As expected, the most frequent adverse events leading to discontinuation of thalidomide were in the group of Nervous System Disorders (peripheral sensory neuropathy, neuropathy peripheral, paraesthesias, etc) occurring in 12.6% of subjects.

- As of the 24 May 2013 data cutoff date, the frequency of solid tumor SPM in Arm MPT was similar to that in Arm Rd; however, significantly more hematologic SPMs were observed in Arm MPT than Arm Rd.

Overall, the safety profiles of the Rd and MPT regimens differ. Over time, the Rd regimen was generally better tolerated than MPT. Subjects in Arm MPT discontinued treatment sooner and more frequently prior to disease progression than subjects receiving Rd. Subjects in Arm MPT also more frequently experienced adverse events leading to study drug discontinuation.

- Diarrhea, back pain, insomnia, and rash were reported more frequently (difference of ≥ 5%) in Arm Rd18 compared with Arm MPT. Constipation, peripheral sensory neuropathy, neutropenia, thrombocytopenia, and nausea on the other hand, were reported more frequently in Arm MPT than in Arms Rd or Rd18.

- The most frequently reported Grade 3 or 4 AEs in each arm pertained to the Blood and Lymphatic System Disorders system organ class (SOC). Grade 3 or 4 neutropenia was notably more frequent in Arm MPT compared with Arm Rd18 and Arm Rd. Grade 3 or 4 thrombocytopenia and leukopenia were also more frequent in Arm MPT (difference of ≥ 2%) compared with Arm Rd and Arm Rd18.

- The frequency of SAEs was higher in Arm Rd18 (57.0%) versus Arm MPT (49.9%). Few SAE preferred terms were reported in ≥ 2% of subjects in any treatment arm. The most frequently reported SAE in each of the 3 arms was pneumonia.

- Adverse events leading to permanent discontinuation of study drug were reported more frequently for discontinuation of thalidomide than discontinuation of lenalidomide and melphalan, but more subjects had AEs leading to discontinuation of the entire Rd regimen (potentially related to the longer duration of treatment on this study arm with almost twice the treatment exposure time) than discontinuation of the entire MPT regimen. No specific AEs led

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to discontinuation of any study drug in more than 2% of subjects in any arm, with the exception of peripheral sensory neuropathy which lead to discontinuation of thalidomide in 6.7% of subjects in Arm MPT.

- The frequency of invasive SPMs in Arm MPT was similar to the frequencies observed for the combined Arms Rd and Arm Rd18; however, more hematologic SPMs were observed in Arm MPT.

Deaths:

- The most common primary cause of death over the entire course of the study in all 3 arms was multiple myeloma.

- There were more deaths due to cardiac events in Arm Rd and Arm Rd18; deaths due to infections occurred at a similar frequency across all 3 arms over the entire course of the study. Deaths due to general disorders were more common in Arm MPT.

- A total of 126 (7.8%) subjects died during active treatment. The percentage of subjects who died while in the active treatment phase was comparable between Arm Rd18 (6.9%) and Arm MPT (7.0%), and was 9.6% in Arm Rd, likely influenced by the prolonged observation/treatment period for subjects in Arm Rd (921 person-years of time on active treatment for subjects in Arm Rd, compared with 587 person-years for Arm Rd18 and 549 person-years for Arm MPT). The most common primary causes of death during active treatment were infections followed by cardiac disorders.

  – Deaths due to infections during active treatment were reported at similar frequencies in Arm Rd18 (2.0%) versus Arm MPT (1.8%), and were reported more frequently in Arm Rd (3.8%).

  – Deaths due to cardiac disorders during active treatment were reported in 1.7% of subjects in Arm Rd18, 0.7% of subjects in Arm MPT, and 1.9% of subjects in Arm Rd. Of the 23 deaths due to cardiac disorders in all treatment arms, 21 of the subjects were > 70 years old; each of these 23 subjects had a history of cardiac disorders, comorbidities or conditions associated with increased risk of cardiovascular disease (obesity, hypertension, hypercholesterolemia, etc), or they experienced other (noncardiac) events leading to cardiac arrest. (eg, postsurgical complication).

Overall Safety Summary:

- In general, the safety profile of the Rd regimen in Study MM-020 was consistent with the known safety profile of lenalidomide with low-dose dexamethasone.

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- Extended treatment in the Rd arm beyond 18 months generally resulted in a limited increase in adverse events compared with the frequency of adverse events observed with Rd18 or MPT.

  - The occurrence of TEAEs in the Infections and Infestations SOC and in the Cardiac Disorders SOC appeared to be higher in the Rd-containing arms, with more events in Arm Rd compared with Rd18. The difference in infections TEAEs between Arm Rd and Rd18 may have correlated with the longer duration of treatment for Rd.

  - Cataracts were observed more frequently with prolonged Rd treatment.

  - AEs in the nervous system disorders SOC were more frequent in Arm MPT.

Considering data for dose reductions and for AEs leading to withdrawal of lenalidomide or thalidomide, as well as cumulative doses of study drugs administered, treatment tolerance tended to be better in Arm Rd and Arm Rd18 compared with Arm MPT.

CONCLUSION:

Study MM-020 comparing continuous treatment with Rd with MPT (as the primary comparison) has met its primary endpoint, supported by consistent findings for key secondary endpoints. The safety profile of Rd was generally well tolerated. These findings support the role of first-line therapy with Rd until disease progression in transplant non-eligible patients with multiple myeloma.

Date of the report: 13 Dec 2013