2. SYNOPSIS

Name of Sponsor/Company: Celgene International Sàrl Name of Finished Product: REVLIMID® Name of Active Ingredient: Lenalidomide (CC-5013)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: A Multicenter, Single-arm, Open-label Safety Study of Lenalidomide plus Dexamethasone in Previously Treated Subjects with Multiple Myeloma[†]		
Reviewing Principal Investigator:		
Study center(s): This study was conducted at 26 centers in Australia, 6 centers in Austria, 7 centers in Ireland, 22 centers in Spain, and 24 centers in the UK.		
Publications (reference): Yong K, Alegre Amor A, Browne P, Cavenagh J, Dodds T, Greil R, et al. A Multicenter, Single-arm, Open-label Safety and Quality of Life Study of Lenalidomide plus Dexamethasone in previously treated Patients with Multiple Myeloma. Haematologica 2010;95(suppl.2):392, abs. 0944.		
Studied period (years): Date first subject enrolled: 11 Nov 2006[‡] Date last subject completed: 13 Nov 2009		Phase of development: 3
Objectives: Primary: • To provide lenalidomide to subjects with a high likelihood of benefit. Secondary: • To obtain additional safety data • To assess the impact on quality of life (QoL).		

[†] Following Amendment # 1.1 (Spain only), the title of this study was changed to "A Multicenter, Single-arm, Open-label Safety and Efficacy Study of Lenalidomide plus Dexamethasone in Previously Treated Subjects with Multiple Myeloma" (Section 9.8.1.2.1). Following Amendment # 1.2 (United Kingdom and Ireland only), the title of this study was changed to "A Multicenter, Single-Arm, Open-label Expanded Access Study of Lenalidomide plus Dexamethasone in Previously Treated Subjects with Relapsed/Refractory Multiple Myeloma" (Section 9.8.1.3.1).

[‡] Two earlier dates of signed informed consent (study enrollment) are presented for all subjects in Listing 16.2.1: Subject and Subject ; however, these dates are incorrect. The dates of the Baseline visit and first dose of lenalidomide, respectively, were and for Subject , and and for Subject (Listing 16.2.1 and Listing 16.2.6.5.1). Hence, the date the first subject enrolled in the CC-5013-MM-018 study was (Subject ; Listing 16.2.1).

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Following country-specific Amendment # 1.1 (Spain only, see Section 9.8.1.2.1), the objectives of this study in Spain were as follows:

Primary:

- To obtain additional safety data.

Secondary:

- To obtain additional efficacy data
- To assess the impact on QoL.

Methodology: This was a multicenter, single-arm treatment study of the combination lenalidomide plus pulse high-dose dexamethasone. Screening procedures were to take place within 28 days prior to Cycle 1 Day 1. Subjects who were eligible for participation in the study were to receive lenalidomide plus high-dose dexamethasone in 4-week cycles. Following Amendment # 4.1 (Spain only), the dexamethasone dosing schedule beginning with Cycle 5 was either 40 mg QD on Days 1 to 4 of each 28-day cycle or 40 mg QD on Days 1, 8, 15, and 22 every 28-day cycle (Section 9.8.1.2.4). Subjects were to be seen (study visits) every 2 weeks for the first 3 cycles of therapy and then every 4 weeks after the third cycle. Treatment was to continue until disease progression was documented, study drug was discontinued for any reason, or lenalidomide became commercially available for this indication (see Duration of treatment for details of changes in the conduct of the study in the UK and Ireland [Section 9.8.1.4], in addition to details of relevant protocol amendments [Section 9.8.1.1.2, Section 9.8.1.2.1, Section 9.8.1.2.5, and Section 9.8.1.2.6]).

Number of subjects (planned and analyzed):

Planned: Up to 1400 subjects.

Analyzed: Enrollment into the study was stopped in the participating countries when lenalidomide became commercially available. Additionally, sample size was limited by site capacity and drug supply (Section 9.8.1.4). A total of 587 subjects signed the informed consent and received at least one dose of study drug; therefore all 587 subjects were included in the full analysis set (FAS) population and the Safety population.

Diagnosis and main criteria for inclusion: Subjects with a diagnosis of multiple myeloma (MM) that was progressing after at least 2 cycles of anti-myeloma treatment, or that had relapsed with progressive disease after treatment, were included in this study. Other inclusion criteria included: aged ≥ 18 years at the time of signing the informed consent form; the ability to understand and voluntarily sign the informed consent form; the ability to adhere to the study visit schedule and other protocol requirements; discontinuation of all anti-myeloma drug or non-drug therapy prior to the first dose of study drug with the exception of radiation therapy initiated prior to or at baseline (Day 1); measurable levels of myeloma paraprotein in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g excreted in a 24-hour collection sample); an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2; female subjects of childbearing potential (FCBP) had to agree to follow the contraceptive practices, restrictions in recommended oral contraception methods, and regular pregnancy testing assessments that were outlined in the clinical study protocol; male subjects had to agree to adhere to the contraceptive practices outlined

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in the clinical study protocol and abstain from donating semen or sperm during study participation and for at least 28 days after discontinuation from the study; all subjects were warned that sharing study drug was prohibited and were counseled about pregnancy precautions and potential risks of fetal exposure; all subjects had to agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study. Subjects could have been previously treated with thalidomide and/or radiation therapy. Additionally, radiation therapy initiated prior to or at baseline (Day 1) was permitted to be given concurrently with study therapy, provided that all other eligibility criteria were satisfied.

Following Amendment # 1 and Amendment # 2, the pregnancy language and permitted oral contraceptive concomitant medications described in the protocol were updated, including the inclusion criterion outlined above, to conform to the United States Food and Drug Administration (FDA) requirement for the RevAssist program as well as the requests made by the Irish Medicines Board (IMB) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) (Appendix 16.1.1 and Section 9.8.1.1).

Key exclusion criteria included the following: any serious medical condition, laboratory abnormality, or psychiatric illness that would have prevented the subject from signing the informed consent form; pregnant or lactating females; any condition, including the presence of laboratory abnormalities, which would have placed the subject at unacceptable risk if he/she had participated in the study or confounded the ability to interpret data from the study; absolute neutrophil count (ANC) < 1000 cells/mm^3 (1.0×10^9/L); platelet count < 75,000/mm^3 (75×10^9/L) for subjects in whom < 50% of the bone marrow nucleated cells were plasma cells; platelet count < 30,000/mm^3 (30×10^9/L) for subjects in whom ≥ 50% of the bone marrow nucleated cells were plasma cells; serum creatinine > 2.5 mg/dL (221 μmol/L); serum aspartate aminotransferase (AST/SGOT) or alanine aminotransferase (ALT/SGPT) > 3.0 × upper limit of normal (ULN), serum total bilirubin > 2.0 mg/dL (34 μmol/L); prior history of malignancies other than MM (except for basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or breast) unless the subject had been free of the disease for ≥ 1 year; known hypersensitivity to thalidomide or dexamethasone; prior history of uncontrollable side effects to dexamethasone therapy; the development of a desqamating rash while taking thalidomide; neuropathy ≥ grade 2.

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

Lenalidomide

Dose: 25 mg QD for the first 21 days of each 28-day cycle (supplied in bottles containing 21 capsules).

Dosage form: 25-mg and 5-mg capsules (no more than a 28-day supply of lenalidomide capsules was to be dispensed to a subject at any time).

Route of Administration: Oral.

Lot Numbers: 06F0010 (5 mg), 06F0130 (5 mg), 09F0142 (5 mg), 06F0011 (25 mg), 06F0131 (25 mg), 08F0016 (25 mg), and 08F0065 (25 mg).

Manufacturer:

Supplier:

Dexamethasone

Dose: pulse dexamethasone administered at a dose of 40 mg QD on Days 1 to 4, 9 to 12, and 17 to 20 for each 28-day cycle for Cycles 1 to 4. Beginning with Cycle 5, a reduced dose of dexamethasone (40 mg

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QD) was to be administered on Days 1 to 4 of each 28-day cycle. Following Amendment # 4.1 (Spain only), the dexamethasone dosing schedule beginning with Cycle 5 was either 40 mg QD on Days 1 to 4 of each 28-day cycle or 40 mg QD on Days 1, 8, 15, and 22 every 28-day cycle. The protocol was amended in Spain in order to allow the selection of the dexamethasone treatment regimen according to the investigator's medical judgment (Section 9.8.1.2.4).

Dosage form: tablets.

Route of Administration: Oral.

Batch/Lot Numbers: not applicable.

Supplier: locally available commercial supplies of dexamethasone tablets were to be used in this study.

Commercial supplies of 40 mg tablets of dexamethasone were not available in Spain. Amendment # 3.1 (Spain only) was implemented in Spain, and each site could prescribe pulse dexamethasone as per their normal clinical practice, either 40 mg intravenous (iv) solution ampoules or galenic tablets prepared by the Hospital Pharmacy or the subject's common pharmacy (Section 9.8.1.2.3).

Duration of treatment: Subjects were to remain in the study until disease progression was documented, study drug was discontinued for any reason, or lenalidomide became commercially available for this indication. The study was to be terminated in each participating country within 2 months of lenalidomide becoming commercially available for this indication in that country. Following Amendment # 2, the duration of treatment was to be up to the end of February 2008 (Section 9.8.1.1.2).

Following Amendment # 1.2 in the UK and Ireland, unless subjects were withdrawn by the clinician, the study period was to be a minimum of 6 months or until commercial drug became available, whichever was later. The combination of lenalidomide/dexamethasone was approved in EU member states on 14 Jun 2007 for the treatment of patients with relapsed or refractory MM. As a consequence of the approval of lenalidomide and implementation of Amendment # 1.2, treatment was stopped for all subjects in the UK and Ireland after 6 cycles of therapy had been completed (Section 9.8.1.3.1).

The provision of lenalidomide to subjects until lenalidomide became commercially available for relapsed or refractory MM was removed from the definition of study duration in Spain following Amendment # 1.1 (Spain only). In Spain, subjects could have remained on the study until disease progression was documented or the study drug was discontinued for any reason (Section 9.8.1.2.1). Following Amendment # 5.1 (Spain only), subjects in Spain could have remained on the study until disease progression was documented, or study drug was discontinued for any reason, or for a maximum of 2 years since the end of recruitment. The proposed termination date of this study in Spain was 31 Oct 2009. Upon termination of the study in Spain, the sponsor agreed to continue to provide lenalidomide free of charge to those subjects who continued on treatment and remained progression-free at the time of study closeout (Section 9.8.1.2.5). However, following Amendment # 6.1 (Spain only), it was clarified that lenalidomide was to be provided free of charge to subjects who, at study closure and to the knowledge of the main investigator of the site, were continuing to obtain benefit from treatment with lenalidomide (Section 9.8.1.2.6).

Reference therapy, dose and mode of administration, batch number: None.

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Criteria for evaluation:

Efficacy: The FAS population contained all subjects that signed the informed consent form and received at least one dose of study medication.

Safety: The Safety population included all subjects who received at least one dose of study drug.

Statistical methods:

Descriptive summary statistics (number of observations [n], mean, standard deviation [SD], median, minimum, and maximum) were presented for quantitative variables. Category frequencies and percentages were presented for qualitative variables. The disposition of subjects was summarized. All demographic and baseline characteristics, prior medications, and medical history were analyzed for the safety population. The safety analyses, including extent of exposure to study drug, study drug (lenalidomide) dose modification, and time to first dose reduction, were performed on the safety population. Analyses were performed for safety data obtained during the treatment phase. Treatment-emergent adverse events (TEAEs) were described in all relevant summaries. A TEAE was defined as any adverse event (AE) that started on or after the first dose of study drug. TEAEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 9.0 classification system. The severity of toxicities was graded according to the United States National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. Subject incidence rates of TEAEs were tabulated by system organ class and preferred term. Subsets of TEAEs were summarized as follows: suspected treatment-related TEAEs; suspected treatment-related TEAEs that led to discontinuation of study drug; TEAEs that led to discontinuation; TEAEs of all CTCAE grade severities; CTCAE grade 3/4 TEAEs; suspected treatment-related CTCAE grade 3/4 TEAEs; treatment-emergent serious adverse events (SAEs); suspected treatment-related SAEs; grade 5 SAEs; and TEAEs that led to dose reduction. All of these subsets of TEAEs were also summarized for TEAEs that started during the first 6 cycles as well as for those that started after Cycle 6. In the by-subject analysis, a subject who had the same TEAE more than once was counted only once in that particular category. The most severe grade of each preferred term for a subject was utilized for summaries of TEAEs by NCI CTCAE grade. Grade 5 TEAEs, or TEAEs that led to discontinuation from treatment, events classified as NCI CTCAE grade 3 or higher, suspected treatment-related events, and treatment-emergent SAEs were also displayed in separate by-subject listings. The following additional safety analyses were defined in the final Statistical Analysis Plan (SAP) dated 27 Nov 2009: TEAEs of special interest (peripheral neuropathy TEAEs and venous thromboembolic events [VTEs]); time to first peripheral neuropathy TEAE; and time to first VTE (Section 9.8.2). Laboratory data (immunoglobulin A [IgA], immunoglobulin G [IgG], immunoglobulin M [IgM], immunofixation studies, serum protein, electrophoresis, and urine protein) were captured only for subjects at centers in Spain and were listed. Laboratory abnormalities (hematology and serum chemistry), vital signs abnormalities, and electrocardiogram (ECG) abnormalities that were captured in the AEs section of the case report form (CRF) for all subjects were summarized by system organ class and preferred term. Vital signs and ECG assessments were captured in the AEs section of the CRF, but were not recorded in specific, dedicated sections of the CRF (Section 9.8.1.4). Additional safety assessments included serum thyroid-stimulating hormone and thyroid function assessments (T_3 and T_4) that were to be conducted at baseline and every 3 months thereafter starting at Cycle 4; abnormalities in thyroid function assessments were to be captured in the AEs section of the CRF. Pregnancy tests

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(serum/urine beta-human chorionic gonadotropin) for FCBP were to be conducted every 28 days if menstrual cycles were regular (every 14 days if menstrual cycles were irregular), at study discontinuation, and 28 days after study discontinuation (14 and 28 days for women with irregular menstrual cycles), or as required, eg if a FCBP missed her period or if there was any abnormality in her pregnancy test or in her menstrual bleeding. The following clarification was added in Amendment # 3.1 (Spain only): in both cases [FCBP with regular or irregular menstrual cycles], pregnancy tests had to be performed every 14 days during the first 28 days of study participation (Section 9.8.1.2.3).

Efficacy was assessed in an exploratory manner for subjects at centers in Spain only (Section 9.8.1.2.1). The efficacy analyses were performed on the FAS population (subjects at centers in Spain only, N = 63). The efficacy endpoints were: progression-free survival (PFS), overall survival (OS), time to progression (TTP), objective overall response rate, time to response, time to best response, and duration of response. The Kaplan-Meier product limit method was used to estimate the survivorship functions for time-to-event endpoints (PFS, OS, TTP, duration of response, time to first response, and time to best response). Summary statistics and 95% confidence intervals (CI) were provided for each of these assessments. The objective overall response rate was also assessed, and summarized as complete response, very good partial response, partial response, minimal response, no change, progressive disease, and response not evaluable.

The FAS population (all subjects, N = 587) was used for all QoL evaluations (baseline and post-baseline). The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Patients with Cancer (QLQ-C30) and validated EORTC Quality of Life Questionnaire for Patients with Multiple Myeloma (QLQ-MY20) were used for the QoL assessments. Changes from baseline in overall score and subscores were summarized by visit for both questionnaires. The number and percentage of subjects that improved in change from baseline of at least 5 points and at least 10 points were summarized. No subgroup analyses were defined. For further details regarding the statistical methods utilized in the analysis of the CC-5013-MM-018 study data, please refer to the final SAP (27 Nov 2009).

SUMMARY – CONCLUSIONS

The median age of subjects in the Safety population was 65 years (range: 36 to 89 years). The proportion of subjects aged ≤ 65 years (53.5%) was slightly larger than that of subjects aged > 65 years (46.5%). The majority of subjects were white (93.4%) and more than half were male (58.9%). Per the inclusion criteria, almost all subjects had a baseline ECOG score ≤ 2 (99.3%), and all subjects had previously undergone therapy for MM.

Slightly less than two-thirds of all subjects participated in the study for at least 6 cycles (61.2%), with a median duration of study participation of 23.7 weeks (range: 0.6 to 123.4 weeks). With regard to these data, it should be noted that subjects enrolled in the study in the UK and Ireland were treated for only 6 cycles. The median total number of days dosed was 126.0 days (range: 4.0 to 631.0 days) and the median number of days dosed per cycle was 20.9 days (range: 4.0 to 51.4 days). The mean (± SD) daily dose of lenalidomide was 23.2 ± 3.43 mg. The median duration of follow-up was 29.0 weeks (range: 1.1 to 128.7 weeks). A total of 173 (29.5%) subjects had at least one lenalidomide dose modification. In over two-thirds of cases (67.5%), the dose modification was due to an AE, whereas "other" was the reason for dose modification in 23.5% of cases. The median time to first dose reduction was 50.1 weeks

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(95% CI: 44.1 to 82.0 weeks; range: 0.1 to 123.4 weeks).

EFFICACY RESULTS:

Efficacy data were collected only at sites in Spain. The CC-5013-MM-018 study was set up and executed primarily as an expanded access program. The efficacy data collected in this study are not intended to contribute to the evaluation of the effectiveness of lenalidomide or provide definitive information on clinical pharmacology; therefore, an abbreviated clinical study report has been prepared for this study. Sufficient information to determine that the efficacy data collected during this study do not cast doubt on the effectiveness claims or the description of the clinical pharmacology is presented in Section 14.2. Efficacy data for all Spanish subjects in the FAS population (N = 63) are presented in Section 14.2 Table 14.2.1.1 to Table 14.2.1.7. QoL data for all subjects in the FAS population (N = 587) are presented in Section 14.2 Table 14.2.2.1 to Table 14.2.2.5, as well as Graph 14.2.2.6 and Graph 14.2.2.7.

SAFETY RESULTS:

The following summary describes the safety data observed in the overall Safety population. The safety data for subjects at sites in Australia and Austria, UK and Ireland, and Spain (grouped by amended clinical study protocol followed during the study) are summarized in Section 12.

Deaths, Serious Adverse Events, and Other Significant Treatment-emergent Adverse Events

A total of 88 (15.0%) subjects died: 54 (9.2%) subjects died during the study (≤ 30 days after last dose of lenalidomide) and 34 (5.8%) subjects died during follow-up (> 30 days after last dose of lenalidomide). Causes of death either during the study or during follow-up, reported in 2 or more subjects overall, were disease progression/MM (63 subjects; 10.7%), pneumonia (6 subjects; 1.0%), cardiac failure and sepsis (each in 5 subjects; 0.9%), neutropenic sepsis and renal failure (each in 3 subjects; 0.5%), and cardio-respiratory arrest, multi-organ failure, pleural effusion, renal failure acute, respiratory failure, and unknown (each in 2 subjects; 0.3%). Four subjects overall had suspected study-drug related TEAEs that led to death: MM (Subject); cardiac failure and acute pulmonary edema (Subject); cerebral hemorrhage (Subject); and hepatic failure (Subject).

Over half of all subjects (340 subjects; 57.9%) had at least one SAE, of which the most commonly reported (≥ 2% of subjects) were pneumonia (52 subjects; 8.9%), MM (39 subjects; 6.6%), lower respiratory tract infection (38 subjects; 6.5%), anemia (31 subjects; 5.3%), pyrexia (30 subjects; 5.1%), DVT (25 subjects; 4.3%), febrile neutropenia and pulmonary embolism (each in 22 subjects; 3.7%), sepsis (17 subjects; 2.9%), neutropenia and renal failure acute (each in 16 subjects; 2.7%), respiratory tract infection (15 subjects; 2.6%), cellulitis and dehydration (each in 14 subjects; 2.4%), confusional state (13 subjects; 2.2%), and atrial fibrillation (12 subjects; 2.0%).

One-quarter of all subjects (148 subjects; 25.2%) had at least one suspected study drug-related SAE, of which the most commonly reported (in 2 or more subjects) were DVT (24 subjects; 4.1%), pulmonary embolism (21 subjects; 3.6%), febrile neutropenia and neutropenia (each in 15 subjects; 2.6%), anemia (14 subjects; 2.4%), pneumonia (10 subjects; 1.7%), lower respiratory tract infection (9 subjects; 1.5%), thrombocytopenia (8 subjects; 1.4%), atrial fibrillation and pyrexia (each in 6 subjects; 1.0%), dehydration and respiratory tract infection (each in 5 subjects; 0.9%), fatigue and renal failure acute (each in 4 subjects; 0.7%), neutropenic sepsis and sepsis (each in 3 subjects; 0.5%), and abdominal pain,

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accidental overdose, acute pulmonary edema, angina unstable, cardiac failure, cellulitis, confusional state, hypocalcemia, infection, international normalized ratio increased, leukopenia, non-cardiac chest pain, and pneumocystis jiroveci pneumonia (each in 2 subjects; 0.3%).

Overall, the incidence of individual TEAEs that led to study discontinuation was low (115 subjects; 19.6%). The most frequently reported (in 2 or more subjects) TEAEs that led to discontinuation were thrombocytopenia (15 subjects; 2.6%), MM (13 subjects; 2.2%), neutropenia (12 subjects; 2.0%), fatigue and muscular weakness (each in 5 subjects; 0.9%), blood creatinine increased, lethargy, and neuropathy (each in 4 subjects; 0.7%), cardiac failure, confusional state, diarrhea, dizziness, dyspnea, general physical health deterioration, neutropenic sepsis, pneumonia, and sepsis (each in 3 subjects; 0.5%), and anemia, angina unstable, atrial fibrillation, blood bilirubin increased, dehydration, GGT increased, hyperglycemia, lower respiratory tract infection, nausea, neuropathy peripheral, pulmonary embolism, rash, renal impairment, and pancytopenia (each in 2 subjects; 0.3%).

The frequency of suspected study drug-related TEAEs that led to study drug discontinuation was lower still (67 subjects; 11.4%). The most frequently reported (in 2 or more subjects) suspected study drug-related TEAEs that led to study drug discontinuation were neutropenia and thrombocytopenia (each in 12 subjects; 2.0%), fatigue and muscular weakness (each in 4 subjects; 0.7%), neuropathy and blood creatinine increased (each in 3 subjects; 0.5%), and angina unstable, atrial fibrillation, blood bilirubin increased, cardiac failure, dizziness, dyspnea, general physical health deterioration, GGT increased, lethargy, neuropathy peripheral, neutropenic sepsis, pancytopenia, pulmonary embolism, and rash (each in 2 subjects; 0.3%).

A total of 118 (20.1%) subjects reported at least one TEAE that led to dose reduction, of which the most frequently reported (in 2 or more subjects) were neutropenia (36 subjects; 6.1%), thrombocytopenia (23 subjects; 3.9%), fatigue (12 subjects; 2.0%), neuropathy (10 subjects; 1.7%), neuropathy peripheral (7 subjects; 1.2%), anemia (4 subjects; 0.7%), blood creatinine increased, diarrhea, dizziness, peripheral sensory neuropathy, and rash (each in 3 subjects; 0.5%), and hypocalcemia, leukopenia, muscular weakness, pancytopenia, pyrexia, and tremor (each in 2 subjects; 0.3%).

Neutropenia and thrombocytopenia were the most commonly reported reasons for dose reductions in subjects treated with lenalidomide/dexamethasone, but the frequency of discontinuation of the study drug due to these TEAEs was low. Most cases of neutropenia and thrombocytopenia were suspected to be study drug-related and grade 3/4 in severity; however, the investigator considered few cases of neutropenia and thrombocytopenia to be serious in the context of the underlying pathology.

Treatment-emergent Adverse Events

Almost all subjects treated with lenalidomide and dexamethasone reported at least one TEAE (586 subjects; 99.8%), the most frequently reported (≥ 20% of subjects) of which were fatigue (255 subjects; 43.4%), neutropenia (249 subjects; 42.4%), muscle spasms (202 subjects; 34.4%), constipation (194 subjects; 33.0%), diarrhea (185 subjects; 31.5%), anemia (174 subjects; 29.6%), insomnia (173 subjects; 29.5%), and thrombocytopenia (132 subjects; 22.5%).

A total of 519 subjects (88.4%) had at least one suspected study drug-related TEAE, of which the most frequently reported (≥ 5% of subjects) were neutropenia (232 subjects; 39.5%), fatigue (128 subjects;

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21.8%), constipation and thrombocytopenia (each in 113 subjects; 19.3%), anemia (107 subjects; 18.2%), muscle spasms (105 subjects; 17.9%), diarrhea (58 subjects; 9.9%), dysgeusia (37 subjects; 6.3%), edema peripheral and neuropathy peripheral (each in 35 subjects; 6.0%), nausea and rash (each in 34 subjects; 5.8%), DVT (33 subjects; 5.6%), lethargy (32 subjects; 5.5%), and dizziness (30 subjects; 5.1%).

In total, 471 (80.2%) subjects had at least one grade 3/4 TEAE, of which the most frequently reported (≥ 2% of subjects) were neutropenia (208 subjects; 35.4%), thrombocytopenia (89 subjects; 15.2%), anemia (80 subjects; 13.6%), fatigue (50 subjects; 8.5%), pneumonia (47 subjects; 8.0%), hyperglycemia (34 subjects; 5.8%), DVT (31 subjects; 5.3%), lower respiratory tract infection (26 subjects; 4.4%), back pain (24 subjects; 4.1%), muscular weakness (23 subjects; 3.9%), pulmonary embolism (22 subjects; 3.7%), febrile neutropenia (21 subjects; 3.6%), confusional state and dyspnea (each in 18 subjects; 3.1%), leukopenia (16 subjects; 2.7%), hypokalemia (14 subjects; 2.4%), dehydration and sepsis (each in 13 subjects; 2.2%), cellulitis, insomnia, muscle spasms, and pyrexia (each in 12 subjects; 2.0%).

A total of 333 (56.7%) subjects had at least one TEAE that was suspected to be study drug-related, of which the most frequently reported (≥ 2% of subjects) were neutropenia (197 subjects; 33.6%), thrombocytopenia (72 subjects; 12.3%), anemia (45 subjects; 7.7%), fatigue (27 subjects; 4.6%), DVT (26 subjects; 4.4%), pulmonary embolism (21 subjects; 3.6%), leukopenia (16 subjects; 2.7%), and febrile neutropenia (14 subjects; 2.4%).

Treatment-emergent Adverse Events of Interest

At least one peripheral neuropathy TEAE was reported in 84 (14.3%) subjects: neuropathy peripheral (46 subjects; 7.8%), peripheral sensory neuropathy (33 subjects; 5.6%), neuralgia (5 subjects; 0.9%), peripheral motor neuropathy and polyneuropathy (each in 2 subjects; 0.3%), and sensory disturbance (1 subject; 0.2%). A medical history of neuropathy was reported in over half of all subjects (350 subjects; 59.6%). The mean (± SD) time to first TEAE of peripheral neuropathy was 25.6 ± 21.53 weeks (range: 0.1 to 123.4 weeks). Although the peripheral neuropathy TEAE was suspected to be study drug-related in majority of these subjects, most peripheral neuropathy TEAEs were grade 1 or 2 in severity, non-serious, and did not lead to a dose reduction or discontinuation. Treatment with lenalidomide and dexamethasone did not increase the incidence of peripheral neuropathy TEAEs (14.3%), despite approximately 60% of enrolled subjects having a medical history of neuropathy.

At least one VTE was reported in 60 (10.2%) subjects: DVT (38 subjects; 6.5%), pulmonary embolism (23 subjects; 3.9%), thrombophlebitis (7 subjects; 1.2%), and venous thrombosis limb (1 subject; 0.2%). A medical history of venous thromboembolic disease was reported in 77 subjects (13.1%). The mean (± SD) time to first VTE was 26.5 ± 21.51 weeks (range: 0.6 to 123.4 weeks). Although the majority of DVT and pulmonary embolism TEAEs were serious, suspected to be related to the study drug, and grade 3 or 4 in severity, these events rarely led to a dose reduction or discontinuation of the study drug (3 subjects; 0.5%). Treatment with lenalidomide and dexamethasone did not increase the incidence of VTEs (10.2%), despite approximately 13% of enrolled subjects having a medical history of venous thromboembolic disease.

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Clinical Laboratory, Electrocardiogram, and Vital Signs Treatment-emergent Adverse Events

Half of all subjects had at least one hematology laboratory abnormality that was reported as a TEAE (343 subjects; 58.4%). Of these, 49 (8.3%) subjects had at least one hematology laboratory abnormality that was reported as an SAE, which included anemia (31 subjects; 5.3%), neutropenia (16 subjects; 2.7%), thrombocytopenia (11 subjects; 1.9%), pancytopenia (3 subjects; 0.5%), leukopenia and international normalized ratio decreased (each in 2 subjects; 0.3%).

Slightly less than one-third of all subjects had at least one serum chemistry laboratory abnormality that was reported as a TEAE (173 subjects; 29.5%). Of these, 29 (4.9%) subjects had at least one serum chemistry laboratory abnormality that was reported as an SAE, which were as follows: hyperglycemia (8 subjects; 1.4%), blood creatinine increased (5 subjects; 0.9%), hypercalcemia and hypocalcemia (each in 4 subjects; 0.7%), and hypokalemia (2 subjects; 0.3%). All other hematology and serum chemistry laboratory abnormalities reported as SAEs were single cases.

Overall, 155 (26.4%) subjects had at least one vital signs abnormality that was reported as a TEAE: pyrexia (80 subjects; 13.6%), weight decreased (33 subjects; 5.6%), hypotension (32 subjects; 5.5%), hypertension (23 subjects; 3.9%), tachycardia (15 subjects; 2.6%), weight increased (8 subjects; 1.4%), bradycardia (3 subjects; 0.5%), and hypothermia (1 subject; 0.2%). An ECG TEAE (QT corrected interval) was reported in 1 (0.2%) subject only.

CONCLUSION:

The results of this open-label study demonstrate that lenalidomide, administered at a dose of 25 mg QD for 21 days of repeated 28-day cycles in combination with high-dose dexamethasone, shows an acceptable safety profile in subjects with relapsed or refractory MM. The safety profile for exposure to lenalidomide is well characterized and results of this study were consistent with the known safety profile of lenalidomide. Previously reported high tolerability and safety of the combination of lenalidomide and dexamethasone in subjects with relapsed or refractory MM was confirmed in this study. The safety data from this multicenter study are consistent with the data from two previous phase 3, randomized, multicenter studies (CC-5013-MM-009 and CC 5013 MM-010). In general, TEAEs were easily monitored and managed clinically. Of the grade 3/4 events in this study, neutropenia and thrombocytopenia were the most common; however, very few discontinuations occurred as a result of these TEAEs. No new safety concerns were identified.

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