2. SYNOPSIS

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Title of Study: Randomized, Controlled, Open-Labelled, Multi-Center Comparison of Thalidomide versus High-Dose Dexamethasone for the Treatment of Relapsed Refractory Multiple Myeloma

Principal Investigator:

Investigators: A total of 86 investigators had study initiation visits performed at their sites. Of these investigators, 68 enrolled and screened patients, and 67 of these randomized patients. (Please refer to Appendix 16.1.4 for a list of investigators).

Study Centers: A total of 67 sites in Bulgaria, Croatia, the Czech Republic, France, Germany, Hungary, India, Italy, the Philippines, Poland, Portugal, Serbia, Slovakia, South Africa, and the United Kingdom randomized patients into this study.

Publications (reference): None.

Studied Period (years): Date first patient enrolled: 30 Mar 2006 Date last patient completed: 28 Jan 2009	Phase of development: 3

Objectives:
Primary: The primary objective was to compare the time to progression (TTP) of 3 daily doses of thalidomide (100, 200, and 400 mg) with high-dose dexamethasone in relapsed refractory multiple myeloma (MM) patients and to subsequently select the optimum thalidomide dose in terms of median TTP and toxicity.
Secondary: The important secondary objectives were to compare each dose of thalidomide with high-dose dexamethasone for the following outcomes:

- Response rate
- Clinical benefit
- Survival (overall and progression free)
- Quality of life
- TTP in the subgroups defined by the number of therapeutic lines before randomization (1 line versus more than 1 line)

The safety of thalidomide compared with dexamethasone was also to be evaluated. In addition, population pharmacokinetics (PK)/pharmacodynamics were evaluated in thalidomide-treated patients who consented to participate in the PK part of the study.

Methodology: This was a randomized, open-label, parallel-group, active-controlled, 4-arm, multicenter, international, prospective phase 3 study with the following treatment groups:

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- Arm A: Thalidomide 100 mg/day
- Arm B: Thalidomide 200 mg/day
- Arm C: Thalidomide 400 mg/day
- Arm D: High-dose dexamethasone

Patients were randomized to the treatment groups equally in a 1:1:1:1 ratio and stratified at randomization by prognostic features known to be predictive of TTP and survival in patients with relapsed refractory MM: number of therapeutic lines before randomization (1 line versus more than 1 line), prior autologous stem cell transplantation (ASCT: yes or no), and International Staging System (ISS: Stage I+II versus III). All treatments consisted of capsules or tablets to be taken orally by patients at home. Patients were to be treated for a maximum of 12 cycles, each lasting 28 ± 3 days (a total of 336 ± 36 days). During the screening period, patients were to be screened for eligibility; screening procedures were to be performed no more than 28 days prior to the first day of treatment (Day 1) for invasive procedures (electrocardiogram [ECG], nerve conduction study [NCS], skeletal survey. and bone marrow collection) and 14 days for laboratory evaluations.

The treatment period consisted of a baseline visit on Day 1, Week 0, and then visits every 4 weeks until Week 48. A visit to confirm progressive disease (PD) was to be conducted within 1 to 4 weeks after the first evidence of PD. An end of treatment visit was to be conducted at 30 to 33 days after the last dose of study drug. The follow-up period began immediately following the end of treatment visit. During the follow-up period, patients were to attend visits every 6 weeks ± 2 weeks until PD, then every 12 weeks ± 2 weeks after PD. All patients who discontinued the treatment period of the study for any reason other than progression of disease, death, or withdrawal of consent including patients who completed treatment, were to continue to be followed for PD and/or survival until study closure. Study closure was triggered by the 2 requisites: 160 independent review committee (IRC)-documented progressions in the dexamethasone and thalidomide 400 mg groups; and the last patient's last end of treatment visit had occurred.

During the treatment period visits, one blood sample was to be collected from thalidomide-treated patients who agreed to participate in the PK portion of the study. Plasma was subsequently to be analysed for thalidomide (and possibly metabolite(s) concentrations), and the data were to be subjected to population PK modeling.

Number of Patients (planned and analyzed): A total of 496 patients (124 patients in each arm) were planned. A total of 499 patients were randomized (intent-to-treat [ITT] population): 373 in the thalidomide group (121 in the thalidomide 100 mg group; 122 in the thalidomide 200 mg group; 130 in the thalidomide 400 mg group) and 126 in the dexamethasone group. A total of 497 (99.6%) patients received study medication and were analyzed as the safety population; a total of 465 (93.2%) patients qualified for the per protocol (PP) population. Of the 499 randomized patients, 121 (24.2%) patients completed 12 cycles of treatment and discontinued at the planned end of treatment; the other primary reasons for discontinuation included confirmed progression of disease (263 [52.7%] patients) and adverse events (50 [10.0%] patients).

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Diagnosis and Main Criteria for Inclusion: Male or female patients who were at least 18 years of age with previously diagnosed MM and who had received between 1 and 3 prior lines of treatment for their disease, and who required therapy because of disease progression were eligible to enroll into the study. Patients with secretory MM with measurable levels of monoclonal protein (M-protein) in serum (> 10 g/L of Immunoglobulin G [IgG] M-protein and > 5 g/L of Immunoglobulin A [IgA] M-protein) or urine (≥ 200 mg/24 hours) were eligible. Patients with the rare subclasses of the Immunoglobulin D (IgD), Immunoglobulin E (IgE), or Immunoglobulin M (IgM) could be included in the study if the level of M-protein was > 5g/L in serum or ≥ 200 mg/24hours in urine. As IgM immunoglobulin isotype could be related to Waldenstrom's macroglobulinemia, it was important to distinguish and not to include in the study patients with Waldenstrom's macroglobulinemia. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 and life expectancy > 3 months were eligible to participate in the study. Patients able to adhere to the study visit schedule and other protocol requirements and willing to give written informed consent; women of child-bearing potential who had agreed to use 2 methods of contraception: 1 effective (i.e., hormonal or tubal ligation) and 1 barrier (i.e., latex condom, diaphragm) for at least 4 weeks before starting the therapy, during the treatment period, and for 4 weeks after the last dose; and males who agreed to use barrier contraception (latex condoms) when engaging in reproductive activity during the treatment period and for 4 weeks after the last dose were allowed to participate in the study.

Test Product, Dose and Mode of Administration, Batch Number: Thalidomide was to be taken orally once daily (before bedtime) as follows:

- Arm A: 100 mg/day
- Arm B: 200 mg/day
- Arm C: 400 mg/day

Batch numbers: 284A; 64B

Duration of Treatment: Thalidomide or high-dose dexamethasone was to be taken until progression of the disease for a maximum treatment period of 336 ± 36 days (12 cycles of 28 ± 3 days).

Reference Therapy, Dose and Mode of Administration, Batch Number:

Patients assigned to the high-dose dexamethasone arm were to receive oral dexamethasone at a dose of 40 mg daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for Cycles 1 to 4. Beginning with Cycle 5, the oral dexamethasone dosing schedule was to be reduced to 40 mg daily on Days 1 to 4 of each 28-day cycle.

Batch numbers: 7292804; 7492203

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the TTP, according to the European Bone Marrow Transplantation (EBMT) Group criteria, as determined by the IRC.

The key secondary efficacy variables were as follows:

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- Response rate (complete response [CR] + partial response [PR]), according to the EBMT criteria
- Clinical benefit as measured by:
  - ECOG performance status
  - Transfusion requirements (rate and timing of transfusions for each type of transfusion), from baseline until the end of the treatment period
  - Grade ≥ 3 infections (rate and timing of infections assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0), from baseline until the end of the treatment period
- Progression-free survival (PFS), defined as the time from randomization to the earliest of the dates of first documentation of disease progression or death (whichever occurs first)
- Overall survival (OS), defined as the time from randomization to date of death from any cause

Additional secondary efficacy variables were as follows:

- Duration of response
- Composite of disease progression and death (recurrent time(s) from randomization to disease progression and/or death)
- Skeletal survey data
- Quality of life was to be assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30).

Safety:

Safety parameters were defined as follows:

- Adverse events (AEs)
- Toxicity (proportion of patients with dose reduction, interruption, or discontinuation due to AE)
- Assessment of peripheral neuropathy, using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-Ntx) questionnaire and nerve conduction studies (NCS)
- Vital signs
- Physical examination

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- Clinical laboratory tests

Pharmacokinetic variables included:

- Plasma concentrations of thalidomide (and possibly metabolite(s))
- Derived PK parameters
- Population PK model

ECG and other data such as clinical laboratory values, creatinine clearance, or other appropriate parameters were explored in an attempt to model the pharmacodynamic relationship.

Statistical Methods:

The primary efficacy variable was TTP, defined as the time in days (analyzed and presented as time in months) from randomization to the first documentation of PD as determined by the IRC.

The confirmatory analysis was to be performed on the ITT population. Patients who did not experience progression during the treatment period or the follow-up period were to be considered a censored observation and were to be censored at the date of their last documented progression-free disease assessment.

The primary analysis was to be conducted after 160 IRC-documented progressions had occurred in the 2 treatment arms of 400 mg/day thalidomide and high-dose dexamethasone. The primary analysis consisted of 3 ordered comparisons of the TTP with a stratified log-rank test each conducted at the 2-sided 0.05 alpha level. Stratification was to be on the 3 factors used to stratify the randomization.

The first comparison was between the 400 mg/day thalidomide arm and the high-dose dexamethasone arm. If this comparison was not statistically significant, then the formal inference was to be stopped and the conclusion was that none of the 3 thalidomide doses demonstrated statistically significant TTP differences compared to high-dose dexamethasone at the overall 0.05 alpha level. If this first comparison was statistically significant, then the second comparison was conducted. The second comparison was between the 200 mg/day thalidomide arm and the high-dose dexamethasone arm. If this comparison was not statistically significant, then the formal inference was stopped, and the conclusion was that only the 400 mg/day thalidomide arm and the high-dose dexamethasone arm have statistically significantly different TTP at the overall 0.05 alpha level. If the second comparison was statistically significant, then the third comparison was conducted. The third comparison was between the 100 mg/day thalidomide arm and the high-dose dexamethasone arm. If this comparison was not statistically significant, then the formal inference was stopped, and the conclusion was that only the 400 mg/day and the 200 mg/day thalidomide doses demonstrated statistically significantly different TTP compared to high-dose dexamethasone at the overall 0.05 alpha level. If the third comparison was statistically significant, then the conclusion was that all 3 thalidomide doses demonstrated statistically significantly different TTP compared to high-dose dexamethasone at the overall 0.05 level. From the set of statistically significant thalidomide doses identified in the primary analysis, all thalidomide doses that had a median TTP within 6 weeks of the largest thalidomide median TTP were clinically considered equally efficacious. If there was only 1 thalidomide dose, then this dose was selected as the optimum thalidomide dose. If there were 2 or 3 doses considered equally efficacious, then all thalidomide doses

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that had a toxicity proportion (defined by the proportion of patients with a dose reduction, interruption or discontinuation) within 15% of the smallest toxicity proportion were clinically to be considered equally toxic. From among the doses considered equally toxic, the smallest thalidomide dose was to be selected as the optimum thalidomide dose.

Secondary Analyses: Data were to be summarized by treatment group using appropriate summary statistics. Time-to-event data (e.g., PFS; OS; composite of progression and death; time to Grade ≥ 3 infections) were to be analyzed using survival techniques and each dose of thalidomide was to be compared to dexamethasone using the stratified log-rank test. One-year survival rates with 95% confidence intervals (CI) and 95% CI for the difference in survival rates were to be constructed. The median time-to-event data were to be presented with 95% CI and the 95% CI for the difference in medians from Kaplan-Meier curves. Stratified Cox proportional hazard regression models were to be used to estimate the hazard ratio (HR) and associated 95% CIs for the HR. Categorical data (response rate and clinical benefit) were to be analysed using Cochran-Mantel-Haenszel and logistic regression techniques. The 9 QLQ-C30 domains (5 functional, 3 symptom, and 1 global health) were to be summarized and analyzed separately using analysis of variance techniques. As an additional secondary endpoint, the 3 thalidomide doses were be compared against each other in terms of the primary parameter – TTP.

PK and Pharmacodynamic Analyses: Plasma concentrations of the parent drug and possibly metabolite(s) were to be used to develop a population PK model. Covariates such as cancer status, demographics, and chemistry/hematology parameters were to be factored into the population model. ECG and other data such as clinical laboratory values were to be explored to further define the pharmacodynamic relationship.

Safety Variables: The incidences of AEs, drug-related AEs, serious adverse events (SAEs), and events that led to discontinuation from the study were summarized by treatment group for treatment-emergent AEs. Other safety data that were summarized include assessment of peripheral neuropathy, vital signs, physical examination, and clinical laboratory tests.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Overall, the ITT patient population was characterized by having mainly first and second relapse (approximately 86% of patients), above normal β2M (median of 3.7 mg/L), but with a majority (73%) being ISS I + II, approximately 1:1 male/female split, and with a median age of 64 years. Overall, 33.1% of all patients were pretreated with ASCT and 86.4% had an ECOG of 0 or 1.

Slight imbalances were observed in the use of concomitant medication between the thalidomide and dexamethasone groups. A higher percentage of patients in the thalidomide group than in the dexamethasone group used the following medications: laxatives (34% vs. 10.5%), antivirals (6.4% vs. 2.4%), immunostimulants (6.4% vs. 0%), antithrombotics (35.7% vs. 15.3%), blood substitutes (6.4% vs. 4%), angiotensin-converting enzyme inhibitors (33.5% vs. 25.8%), β-blockers (28.2% vs. 18.5%), cardiac therapy (11.8% vs.7.3%), and obstructive airway therapy (9.7% vs. 2.4%). However, the imbalances appeared to have no effect on study results.

The primary endpoint analysis revealed that in the ITT population of 499 patients, TTP was 3 months

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longer in patients receiving thalidomide 400 mg (9.1 months) than in patients receiving dexamethasone (6.1 months); however, the difference was not significant (stratified log-rank p-value = 0.055). In the PP population of 465 patients, the TTP was statistically significantly longer (3.1 months longer) in patients receiving thalidomide 400 mg (9.1 months) than in patients receiving dexamethasone (6.0 months; stratified log-rank p-value = 0.049). TTP in patients receiving thalidomide 100 and 200 mg was longer than in patients receiving dexamethasone, but the differences were not statistically significant in the ITT and PP populations.

The definition of TTP used in this study was different than that used in recent randomized phase 3 clinical trials in relapsed/refractory myeloma: patients who received subsequent therapy prior to an IRC-documented progression were followed to progression rather than being censored. Sensitivity analyses were conducted using modified definitions for TTP to investigate the effect of alternative definitions of TTP on the study outcome. TTP in the thalidomide 400 mg group was statistically significantly longer than in the dexamethasone group ($p < 0.05$) for all sensitivity analyses of TTP: when treating death and lost to follow-up as progression (Definition 1), when censoring patients who received new antimyeloma therapy prior to IRC-documented progression and adjusting TTP for those events that occurred during the follow-up period (Definition 2), when analyzed during the treatment period of the study only (Definition 3), and when analyzed for the planned duration of treatment as a fixed period of observation for assessing TTP and for censoring (Definition 4). None of the other thalidomide groups were significantly different from the dexamethasone group in any of the sensitivity analyses.

Based on the KM analysis of strata, the TTP was statistically significantly longer in the thalidomide 400 and 100 mg groups than in the dexamethasone group in patients with more than 1 treatment line and ISS stage I or II. Differences in TTP between the thalidomide and dexamethasone groups for all other strata were not significant; however, the results of the analysis of strata were questionable due to the low number of patients in each stratum.

Longer TTP was seen at all thalidomide dose levels in patients previously treated with more than 1 line of previous therapy. Forest plot analysis also revealed that TTP was longer for thalidomide-treated patients with ISS Stages I + II, lower β2M, age below 65 years, and a good cytogenetic profile (no translocation 4:14 and chromosome 17 deletion). Overall, thalidomide superiority over dexamethasone in TTP was evident for the myeloma group with better prognostic features, though benefit was also seen in patients with chromosome 13 deletion and in those patients previously treated with more than 1 line of previous therapy. Approximately 17% of patients of Asian ethnicity represented the second largest ethnic group in this study. In a post-hoc exploratory analysis, the median TTP for the Asian patients in the thalidomide 400 mg group was 12 months, in contrast to the 6.1 month median TTP for this patient group in the dexamethasone group. Although the study was not powered to detect a difference between the thalidomide and dexamethasone groups for this patient population, this exploratory analysis indicates that the study results can be extended to the Asian population.

In line with the results of the overall TTP, the proportion of ITT patients without disease progression at 1 year (estimated 1-year TTP) in the thalidomide 400 mg group (0.41) was almost double the proportion of patients in the dexamethasone group (0.23). Similar results were obtained for the PP population analysis. In both the ITT and PP populations, the proportion of patients with 1-year TTP was clearly

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higher in the thalidomide 100 and 200 mg groups than in the dexamethasone group, but the difference was not significant with overlapping confidence intervals.

In the ITT population, CR/PR response rate as assessed by an independent review committee was similar (approximately 20%) for all groups; this combined rate ranged from 18.0% in the thalidomide 200 mg group to 24.6% in the dexamethasone group. The higher PRs and overall response rates in the dexamethasone group were based on the faster and higher responses during the first 4 cycles when high-dose dexamethasone was given. The CR rate was low and comparable across all groups (between 1.6% and 2.5%). The median PFS was longer in the thalidomide 400 mg group (8.1 months) compared to the dexamethasone group (6 months). This difference was statistically significant for the PP population ($p = 0.039$) and reached borderline significance in the ITT population ($p = 0.051$). The study did not discriminate any OS advantage for any of the study groups.

Importantly, treatment with thalidomide 100, 200, and 400 mg significantly increased the duration of response in comparison with dexamethasone treatment ($p = 0.046$, $p = 0.005$, and $p = 0.016$, respectively). In the ITT population, the median duration of confirmed response in the thalidomide 200 mg group (13.1 months) was approximately double the duration in the dexamethasone group (6.5 months); median duration was 11.6 months in the thalidomide 400 mg group and 12.7 months in the thalidomide 100 mg group.

Patient questionnaires were used during the study to better capture patient-based assessments of changes in global health scores as well as in functional subscales (emotional, role, physical, cognitive, social functioning), symptoms subscales (fatigue, nausea/vomiting, pain), and other single-item measures (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). The EORTC QLQ-C30 questionnaire responses revealed that the global health score decreased slightly, but overall was stable over time and across all treatment groups.

SAFETY RESULTS:

A total of 373 patients in the thalidomide group and 124 patients in the dexamethasone group were part of the safety evaluation as they received at least 1 dose of study drug.

The mean duration of treatment was longer in the thalidomide groups compared with the dexamethasone group. The median number of cycles dosed was greater for the thalidomide group (7 cycles) compared with the dexamethasone group (6 cycles). Overall, 32.7% of patients in the thalidomide group and 13.7% of patients in the dexamethasone group completed 12 cycles of treatment in the safety population.

Overall, the number and percentage of patients reporting treatment-emergent adverse events (TEAEs) were comparable in both groups, with 92.2% of patients in the thalidomide group and 89.5% of patients in the dexamethasone group. A higher percentage of patients receiving thalidomide 400 mg (97.7%) reported TEAEs compared to patients receiving thalidomide 100 mg (90.2%) or thalidomide 200 mg (88.6%).

The treatment-related TEAEs in the thalidomide group that occurred with a frequency of more than 10% were constipation (38.6%), fatigue (20.4%), and dizziness (10.5%). Treatment-related TEAEs in the thalidomide group with a frequency of 5% to 10% were somnolence (9.4%); paresthesia (9.1%); asthenia (8.8%); polyneuropathy and neutropenia (7.2% each); headache and hypoesthesia (7% each); peripheral sensory neuropathy, nausea, and anemia (6.7% each); rash (6.4%); vertigo (5.6%); peripheral

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neuropathy (5.4%); and tremor (5.1%). The treatment-related TEAEs with a frequency of ≥ 5% in the dexamethasone group were insomnia (16.1%); asthenia and fatigue (9.7% each); constipation (8.9%); hyperglycemia (7.3%); arthralgia, diarrhea, and peripheral edema (6.5% each); and nausea (5.6%).

Thalidomide dose-dependent TEAEs included nervous disorders (dizziness and peripheral neuropathy); gastrointestinal disorders (constipation); hematological TEAEs (leucopenia and neutropenia); cardiac disorders (bradycardia); and cutaneous TEAEs.

The percentage of patients experiencing neuropathy TEAEs increased with the increase in the thalidomide dose; however, the difference between the dose groups was small. The percentage of patients experiencing neuropathy TEAEs in the total thalidomide group (36.5%) was more than twice the percentage of patients experiencing neuropathy TEAEs in the dexamethasone group (17.7%). In patients who had a preexisting neuropathy, it appeared to be a predisposing condition for either development or aggravation of neuropathy during thalidomide treatment. In contrast, dexamethasone did not increase severity or induce neuropathy in patients with history of neuropathy. Electrophysiological studies performed in this study confirmed the clinical evidence of peripheral neuropathy. This study confirmed that clinical evaluations of signs or history of peripheral polyneuropathy, as well as a continuous clinical monitoring of peripheral neuropathy, are key to patient management during thalidomide treatment.

The percentage of patients experiencing deep vein thrombosis/pulmonary embolism (DVT/PE) TEAEs was the same (3.2% each) in the overall thalidomide group and in the dexamethasone group. The DVT/PE TEAEs reported in the thalidomide group were DVT, thrombophlebitis, PE, thrombosis, and retinal vein thrombosis. The DVT/PE TEAEs reported in the dexamethasone group were DVT and PE. A history of DVT/PE did not predispose patients in any treatment group to experience DVT/PE events. A higher percentage of patients in the thalidomide group (35.7%) used antithrombotic agents (in particular, acetylsalicylic acid [20%]) than in the dexamethasone group (15.3%). We assume that a considerable group of investigators were concerned about a prothrombotic activity of thalidomide which has been demonstrated in combination therapy approaches and used acetylsalicylic acid or other antithrombotic agents as prophylactic treatment. The low number of DVT/PE events experienced occurred between Days 4 and 262. There was no evidence for a specific pattern regarding the time of the DVT/PE event (e.g., within initial 2 cycles vs. later cycles of therapy).

As expected, a higher percentage of patients experienced cardiac arrhythmias in the thalidomide group (8.3%) compared with the dexamethasone group (2.4%). The cardiac arrhythmias reported in the thalidomide group were bradycardia (2.9%); syncope (1.9%); arrhythmia, cardio-respiratory arrest, and palpitations (0.8% each); sick sinus syndrome (0.5%); Adams-Stokes syndrome, atrioventricular block, first degree bradyarrhythmia, sinus bradycardia, and tachycardia (0.3% each). The cardiac arrhythmias reported in the dexamethasone group were syncope, tachycardia, and sudden death (0.8% each). Supraventricular arrhythmias (0.8%) were reported predominantly in the thalidomide group. There was no evidence for an increase in torsade de pointes abnormalities in the thalidomide group, as events were very rare and similar in both treatment groups. The percentage of patients who had a medical history of cardiac arrhythmia and a cardiac arrhythmia event during the study was higher in the thalidomide group than in the dexamethasone group. Analysis of the prior medications in the thalidomide and dexamethasone groups indicated a higher percentage of patients receiving beta-blocking agents in the

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thalidomide group than in the dexamethasone group (26% vs. 16.9%). This class of medication might have contributed to some of the sinus bradycardia cases in the thalidomide group.

Thalidomide was associated with a higher percentage of patients with cutaneous TEAEs (27.3%) than dexamethasone was (18.5%). The severe cutaneous TEAEs reported in the thalidomide group were conjunctivitis (1.6%); exfoliative dermatitis and stomatitis (0.5% each); and drug eruption, exfoliative rash, skin exfoliation, and mouth ulceration (0.3% each). In the dexamethasone group, severe cutaneous events were stomatitis (1.6%) and conjunctivitis (0.8%).

A higher percentage (95.1%) of older (≥ 65 years of age) patients reported TEAEs compared with younger (< 65 years of age) patients (89.4%) in the thalidomide group. In the dexamethasone group, the percentages of patients with TEAEs were similar in the younger population (90.4%) and the older population (88.2%). In both treatment groups, a slightly higher percentage of female patients experienced TEAEs than male patients (female patients: 93% in the thalidomide group and 91% in the dexamethasone group; male patients: 91.4% in the thalidomide group and 87.7% in the dexamethasone group).

A total of 43.7% of patients reported Grade 3 or 4 events in the thalidomide group (thalidomide 100 mg: 32%, thalidomide 200 mg: 38.2%, and thalidomide 400 mg: 60.2%), and 37.9% of patients reported Grade 3 or Grade 4 events in the dexamethasone group.

The most commonly affected system organ class (SOC) with Grade 3 or 4 TEAEs in the thalidomide group was the blood and lymphatic system (12.1%). The most commonly affected SOC with Grade 3 or 4 TEAEs in the dexamethasone group was infections and infestations (10.5%); 8.3% of patients in the thalidomide group had events in this SOC. The most commonly reported Grade 3/4 TEAEs in either treatment group were neutropenia (thalidomide: 6.2%, dexamethasone: 0%), anemia (thalidomide: 5.9%, dexamethasone: 4%), fatigue (thalidomide: 5.1%, dexamethasone: 2.4%), and pneumonia (thalidomide: 3.8%, dexamethasone: 4%).

SAEs were reported by 27.1% patients in the thalidomide group and 30.6% patients in the dexamethasone group. The most commonly reported SAEs in the thalidomide group were pneumonia (4.8%); anemia (1.6%); bronchopneumonia (1.3%); and asthenia, pyrexia, back pain, and renal failure (1.1% each). The most commonly reported SAEs related to thalidomide were pneumonia (1.9%); syncope and asthenia (0.8% each); and herpes zoster, cerebrovascular accident, cardio-respiratory arrest, constipation, anorexia, pulmonary embolism, deep vein thrombosis, and hematoma (0.5% each). The most commonly reported SAEs in the dexamethasone group were pneumonia (4.8%); and DVT, pyrexia, and bronchopneumonia (2.4% each). The most commonly reported SAEs related to dexamethasone were pneumonia (3.2%), and DVT and gastrointestinal hemorrhage (1.6% each). These results are consistent with Grade 3 and 4 TEAEs.

The percentage of TEAEs with death as outcome was higher in the dexamethasone group (6.5%) compared with the thalidomide group (5.6%).

Due to a higher number of TEAEs in the higher dose groups of thalidomide, dose reductions and interruptions increased with dose. Average mean daily dose (with percentage of the expected dose) was 93.43 mg (93%) for the thalidomide 100 mg group, 176.59 mg (88%) for the thalidomide 200 mg group, 276.41 mg (69%) for the thalidomide 400 mg group, and 35.25 mg (87.5%) for the dexamethasone group. In addition, TEAEs were reported as the reason for dose modification or interruption in higher

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percentages in the higher dose groups: thalidomide 100 mg group, 34.4%, thalidomide 200 mg group, 41.5%, and thalidomide 400 mg group, 67.2%. A second dose reduction or interruption was dependent on the initial dose as well, with the highest percentage in thalidomide 400 mg group (43.0%), followed by the thalidomide 200 group (25.2%) and thalidomide 100 mg group (12.3%). In the dexamethasone group, 15.3% of patients required dose reduction or interruption.

Permanent discontinuations of treatment due to TEAEs were approximately equal in the thalidomide group and the dexamethasone group, with 15% and 16.9%, respectively. The most frequently reported TEAEs leading to permanent discontinuation of study drug were renal failure (1.3%), and pneumonia and polyneuropathy (0.8% each) in the thalidomide group; and pneumonia (1.6%) in the dexamethasone group.

FACT/GOG-Ntx scores as well as neurophysiologic measurements confirmed the clinical observation of an increase in peripheral neuropathy AEs in the thalidomide treatment groups. A clear differentiation between the thalidomide treatment groups was not apparent in the FACT GOG-Ntx questionnaire and the neurophysiologic measurements.

Population pharmacokinetics were performed utilizing patient data (N = 47) from this study as well as healthy volunteer data (N = 96) from phase 1 studies. The pharmacokinetics of thalidomide were similar in healthy subjects and patients with MM across all 4 dose levels (50, 100, 200, and 400 mg) evaluated in the PK analysis. Thalidomide pharmacokinetics were characterized using a 1-compartment model with first-order dose-dependent absorption and first-order elimination. Thalidomide clearance was found to be linearly correlated with body weight. The pharmacokinetics of thalidomide were not influenced to any significant level by age, gender, renal function (creatinine clearance), blood chemistry variables, and smoking history. In the 47 MM patients with PK samples collected, thalidomide exposure was not correlated with changes in QTcB, nor with selected general (weakness, fatigue, tiredness), GI (constipation), and CNS (neuropathy) adverse events, genomics variables (chromosome 13 or 17 deletion and 4:14 translocation), or neutrophil counts.

CONCLUSIONS:

- In the ITT analyses, no significant difference between the different thalidomide groups and the dexamethasone group could be found.
- Thalidomide 400 mg induced a significant increase in the TTP compared with dexamethasone for the PP analysis. Thalidomide 200 mg and 100 mg also showed a benefit for the TTP; however, the increase was not significantly different from dexamethasone.
- Consistent significant benefit in TTP over dexamethasone was seen with thalidomide at all dose levels in those patients who had received more than 1 prior line of therapy at entry into the study.
- Thalidomide 400 mg significantly improved 1-year TTP as well as PFS compared with dexamethasone. Thalidomide 200 mg and 100 mg also showed an advantage in the PFS in comparison to dexamethasone; however, the increase was not significantly different from

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dexamethasone.

- Thalidomide 100, 200, and 400 mg were similar to dexamethasone in inducing objective responses (PR/CR) in about 20% of patients.
- All doses of thalidomide significantly prolonged the duration of response in relapsed myeloma patients compared with dexamethasone.
- In a post-hoc exploratory analysis, the TTP for the Asian population in the thalidomide 400 mg group was almost twice as long as the TTP for this population in the dexamethasone group. The result was not significant as the study was not powered to address this question, but it does indicate that the study results can be extended to the Asian population.
- The safety profile of thalidomide in this study was as expected, with an increase in Grade 3 and 4 TEAEs associated with the thalidomide 400 mg dose as compared with the thalidomide 200 and 100 mg doses, where mainly Grade 1 and Grade 2 TEAEs were found.
- FACT/GOG-Ntx scores as well as neurophysiologic measurements confirmed the clinical observation of an increase in peripheral neuropathy AEs in the thalidomide treatment groups.
- The global health score in the EORTC QLQ C30 questionnaire for thalidomide and dexamethasone decreased slightly but overall was stable over time and across all thalidomide groups.
- The safety results suggest that dose reduction and, if necessary, drug discontinuation, associated with monitoring of patients with concomitant risk factors can be used to effectively manage the safety issues known to be associated with thalidomide, including neuropathy and events with potentially severe outcomes (e.g., thromboembolic and cardiac events).
- Due to TEAE-related dose reductions, the effective dose per day of thalidomide was 93% in the thalidomide 100 mg group, 88% in the thalidomide 200 mg group, and 69% in the thalidomide 400 mg group.
- Thalidomide pharmacokinetics were characterized using a 1-compartment model with first-order dose-dependent absorption and first-order elimination.
- The pharmacokinetics of thalidomide were similar in healthy subjects and patients with MM across all 4 dose levels (50, 100, 200, and 400 mg) evaluated in this analysis.
- Thalidomide clearance was found to be linearly correlated with body weight.
- The pharmacokinetics of thalidomide were not influenced to any significant level by age,

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gender, renal function (creatinine clearance), blood chemistry variables, and smoking history.

- In the 47 MM patients with PK samples collected, thalidomide exposure was not correlated with changes in QTcB, nor with selected general (weakness, fatigue, tiredness), gastrointestinal (constipation), and nervous system (neuropathy) AEs, genomics variables (chromosome 13 or 17 deletion and 4:14 translocation), or neutrophil counts.
- As TTP was longer in all thalidomide groups compared to dexamethasone and as the percentage of patients experiencing toxicity increased as the dose of thalidomide increased, the DSMB recommended 200 mg as the optimal dose for thalidomide monotherapy in relapsed/refractory MM patients.
- After conducting all of the various sensitivity analyses and considering that in this trial thalidomide was administered without dexamethasone, the recommended dose regimen in this patient population with thalidomide monotherapy would be a starting dose of 400 mg. Dose reductions should be considered if patients cannot tolerate thalidomide 400 mg.

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