2. SYNOPSIS

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Name of Active Ingredient:
Lenalidomide (CC-5013)

Title of Study:
A multicenter, open-label phase 2 study to determine the efficacy and safety of lenalidomide plus low-dose dexamethasone in Chinese subjects with relapsed/refractory multiple myeloma (RRMM).

Principal Investigator:

Investigators:

Study center(s): Subjects were enrolled in 13 centers in China.

Publications (reference): Not applicable

Studied period (years): **Phase of development:** 2

Date first subject enrolled: 12 Sep 2010
Data last subject completed: 04 Jan 2013

Objectives:

Primary: To determine the efficacy of lenalidomide plus low-dose dexamethasone in Chinese subjects with RRMM

Secondary: To determine the safety of lenalidomide plus low-dose dexamethasone in Chinese subjects with RRMM, and to determine the pharmacokinetics of lenalidomide when administered alone or in combination with dexamethasone in Chinese subjects with relapsed/refractory multiple myeloma (RRMM)

Methodology: CC-5013-MM-021 was a phase 2, multicenter, single-arm, open-label trial conducted in Chinese subjects in China to assess the efficacy and safety of a lenalidomide plus low-dose dexamethasone regimen (Rd) given until progressive disease (PD) or discontinuation of lenalidomide for any reason.

This study consisted of a screening period, a treatment phase, and a long-term follow-up phase. Pharmacokinetic (PK) assessments were performed on the first 10 subjects who were ≤ 75 years old and had a baseline creatinine clearance (CLcr) ≥ 60 mL/min.

Following full enrollment of the PK assessment treatment cohort, study treatment for all subjects consisted of Rd therapy in 28-day cycles (lenalidomide daily for Days 1 to 21 and dexamethasone on Days 1, 8, 15, and 22 [subjects in the PK assessment treatment cohort received dexamethasone on Days 8, 15, and 22 of Cycle 1]) until the documentation of PD or discontinuation of study therapy due to

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any reason. The initial dose of study treatment for each subject was determined by age (≤ 75 or > 75 years of age) and renal function.

Subjects who discontinued study treatment entered the long-term follow-up phase, unless they withdrew consent or were lost to follow-up. Subjects who entered the long-term follow-up phase were followed by clinic visit or documented telephone contact at a minimum of every 4 months (± 7 days) for at least 1 year from the start of study drug or until death. After all subjects in the study completed treatment for at least 1 year from start of study drug, all eligible subjects could be enrolled into the Extended Access Protocol.

Number of patients (planned and analyzed):

Planned:	194 subjects
Enrolled:	199 subjects
Analyzed:	199 subjects in the Intent-to-Treat (ITT) Population, 187 subjects in the Efficacy Evaluable (EE) Population, and 199 subjects in the Safety Population

Diagnosis and main criteria for inclusion: Prior or current diagnosis of Durie-Salmon Stage II or III MM and considered to have disease progression after at least 2 cycles of antimyeloma treatment or to have relapsed with PD after treatment; measurable levels of myeloma paraprotein in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g excreted in a 24-hour collection sample); and an ECOG performance status of 0, 1, or 2.

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

Lenalidomide oral capsules: 25 mg, 21-count packages (lot numbers 10F0353 and 11F0458); 15 mg, 21-count packages (10F0352 and 110457), 11-count packages (10F0356); 10 mg, 21-count packages (10F0351 and 11F0456), 11-count packages (10F0355); 5 mg, 21-count package (10F0350 and 11F0455).

Commercial supplies of dexamethasone (4-mg tablets; lot numbers 09F0633, 11F0173, and 11F0686) were centrally supplied by Celgene Corporation and were labeled appropriately as IP for the study.

The initial dose of study treatment for each subject was determined by age (≤ 75 or > 75 years of age) and renal function. The following were the starting doses of each study drug:

Lenalidomide: 25-, 15-, or 10 mg per day, given once daily on Days 1 – 21 of each 28-day cycle

Dexamethasone: 40- or 20 mg given once daily on Days 1, 8, 15, and 22 of each 28-day cycle. For subjects in the PK assessment cohort, the first dose of dexamethasone was given on Day 8 of Cycle 1; dosing was on Days 1, 8, 15, and 22 of each subsequent cycle.

Duration of treatment: Lenalidomide and dexamethasone were administered as scheduled until PD or discontinuation for any reason.

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

No reference therapy was used in this study.

Criteria for evaluation:

Efficacy: Efficacy was measured by the overall response rate [CR or PR per blinded IRAC review using the EBMT criteria and IMWG criteria for a very good partial response (VGPR)], by PFS (also per blinded IRAC review using the EBMT), by OS, and by response duration. Efficacy endpoints (ie, ORR, response duration, and PFS) were also assessed according to Investigator's assessment.

Safety: Safety was evaluated by incidence of treatment-emergent adverse events (TEAEs), second primary malignancies (SPMs), and changes from baseline in clinical laboratory assessments, electrocardiograms (ECGs), and vital signs.

Pharmacokinetics: The following plasma PK parameters were calculated for lenalidomide:

Parameter	Description
AUC_t	Area under the plasma concentration-time curve from Time 0 to the time of the last quantifiable concentration, calculated by the linear trapezoidal method.
AUC_τ	Area under the plasma concentration-time curve during a dosing interval (τ = 24 hours), calculated by the linear trapezoidal method.
AUC_∞	Area under the plasma concentration-time curve from Time 0 extrapolated to infinity, calculated as $[AUC_t + Ct/\lambda_z]$. C_t was the last quantifiable concentration. No AUC extrapolation was performed with an unreliable λ_z.
CL/F	Apparent total plasma clearance when dosed orally, calculated as $[Dose/AUC_\infty]$.
C_{max}	Maximum observed plasma concentration, obtained directly from the observed concentration versus time data.
Rac(AUC)	Accumulation ratio (Rac) between Days 1 and 7 based on AUC, calculated as $[AUC_{24(Day\ 7)}/AUC_{24(Day\ 1)}]$.
Rac(C_{max})	Accumulation ratio (Rac) between Days 1 and 7 based on C_{max}, calculated as $[C_{max(Day\ 7)}/C_{max(Day\ 1)}]$.
$t_{1/2},z$	Terminal phase half-life in plasma, calculated as $[(\ln 2)/\lambda_z]$; $t_{1/2},z$ would only be calculated when a reliable estimate for λ_z could be obtained.
t_{max}	Time to C_{max}, obtained directly from the observed concentration versus time data.
Vz/F	Apparent volume of distribution when dosed orally, calculated as $[(CL/F)/\lambda_z]$.

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Statistical methods:

For each quantitative variable, the following descriptive statistics were calculated: n, mean, median, standard deviation, minimum, and maximum. Qualitative variables were calculated as category frequencies and percentages. The denominator for calculating percentages was either the number of subjects in the analysis population or the number of non-missing observations for the particular variable presented. Visit windows were not used in the data analyses. The cycle number recorded on the case report form, if available, was used to mark the data collection time points. Actual visit or assessment dates were used to calculate intervals of time. No data were imputed in the efficacy analyses.

Demographics:

Age was summarized descriptively, and gender, race, ethnicity, treatment cohort, Durie-Salmon stage, ECOG performance status, baseline renal function, and prior antimyeloma therapies were summarized by frequency tabulation.

Efficacy:

The EE Population, defined as all enrolled subjects who took at least 1 dose of study drug and had at least 1 postbaseline myeloma response assessment, was used for the primary efficacy analyses. The ITT Population, defined as all subjects who enrolled, regardless of whether they received study treatment, was used for analysis of OS and sensitivity analyses of some other efficacy endpoints. The ORR was calculated as the number of confirmed responders (at least a partial response that was maintained for at least 6 weeks) divided by the total number of EE subjects. The ORR was examined together with the relative proportions in each response category (complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]).

Response duration, PFS, and OS are all time-to-event endpoints. The Kaplan-Meier product limit method was used to estimate the survival functions. Progression-free survival was calculated as the interval between study enrollment and the first date of PD as determined by the investigator or death, whichever occurred first. Subjects who withdrew for any reason were censored on the date of their last adequate response assessment, prior to receiving any other antimyeloma therapy. Subjects who were still on therapy without PD were censored on the date of their last adequate response assessment. Response duration was calculated as the time from the first response (CR or PR) to the first date the response criteria were met for PD or until date of death due to any cause, whichever occurred first. Response duration for subjects last known to be alive with no progression after a CR or PR were censored at the date of last adequate response assessment. Subjects who were nonresponders were excluded from this analysis. Overall survival was calculated s the time from enrollment to death.

Safety:

The Safety Population, defined as all enrolled subjects who took at least 1 dose of study drug (either lenalidomide or dexamethasone), was used for analysis of study drug exposure and all safety analyses.

Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system Version 14.0. The severity of the toxicities was graded according to the currently

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active minor Version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. Adverse event frequency was tabulated by body system organ class and preferred term. 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. Adverse events leading to death or discontinuation from treatment, events classified as NCI CTCAE grade 3 or grade 4, study drug related events, and serious adverse events (SAEs) 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.

All SPMs that occurred in any subject at any time were to be reported, including those subjects who discontinued the study for any reason, or who died. These cases were to be reported as SAEs, irrespective of whether seriousness criteria were met and irrespective of any causal relationship. A search for SPMs from the clinical and safety databases was to be performed by retrieving and manually reviewing all MedDRA preferred terms in the Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps) system organ class (SOC). Events deemed to not represent an SPM were excluded. Thus, the following were not included in the SPM terms: events in the high-level group terms of metastases and neoplasm-related morbidities (eg, tumor lysis syndrome, tumor flare, and cancer pain); reports of most neoplasms clearly identifiable as benign except for meningioma (considered as a solid tumor malignancy because the clinical course is not benign); events of disease progression of MM (eg, plasmacytoma); and reports of pre-existing SPMs.

Pharmacokinetics:

A full description of the PK analyses is contained in the CC-5013-MM-021-PK Report, finalized on 19 Sep 2011.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Overall, most subjects in the EE Population had very advanced disease, as indicated by the high number of subjects with Stage III disease (85.6%), subjects who had received >3 prior regimens of therapy (56.7%), and subjects having prior treatment with newer antimyeloma agents such as thalidomide (69.5%), bortezomib (63.1%), or both (44.9%).

The final efficacy results under the protocol-specified Rd regimen demonstrated the following:

As measured by IRAC-adjudicated response rates using EBMT criteria, 47.6% of EE subjects had a response (CR or PR), with one-third of the best responses being CR or VGPR (30 of 89 responders, 33.7%). Ten subjects (5.3%) had a best response of PD, and 88 subjects (47.1%) achieved a best response of SD. A total of 177 of 187 EE subjects had a best response of SD or better, constituting an overall disease control rate of 94.7%. Fewer than two-thirds of the subjects in the EE Population (64.2%) progressed, with median PFS of 36.1 weeks. More than one-third of subjects (35.5%) were event free at 52 weeks, and 26.1% remained event free at 78 weeks. Among the total of 89 responders, median time to response was 8.1 weeks, with a range from 3.9 to 44.4 weeks. The median duration of myeloma response

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among the 89 responders was 38.1 weeks, with a range from 1.9 to 81.6 weeks. The median OS was 93.0 weeks of the ITT population. Nearly three-quarters of all subjects (72.2%) were alive at 52 weeks, and 57.2% were alive at 78 weeks.

Based on the IRAC-adjudicated response assessments, the response rates among subjects previously treated with bortezomib, thalidomide, both bortezomib and thalidomide, or neither were similar to those in the overall EE Population (47.6%). This outcome is very encouraging as it shows lenalidomide is very effective in subjects even failed with bortezomib and thalidomide. As expected, the response rate for subjects with 1 or 2 prior antimyeloma therapies was higher (58.0% with CR or PR) than for subjects who had received more than 2 previous antimyeloma therapies (43.8%). These subgroup results are consistent with what was reported in the interim CSR.

Although the number of subjects with the IgD subtype of MM was small (n = 10), the response rate for these subjects was higher than what was reported in the literature for this myeloma subtype, with 7/10 IgD subjects (70.0%) experiencing a PR or CR and 3 IgD subjects (30.0%) experiencing SD. However, duration of response in this subgroup of subjects (28.7 weeks) fell shorter than the overall EE population (38.1 weeks), and that is expected and is consistent with the literature.

Among subjects with normal to moderately impaired renal function, best ORR (by IRAC-adjudicated assessment of response) was better among subjects with normal/mild renal impairment (50.4% of subjects with CR or PR) than among subjects with moderately impaired renal function (42.0% of subjects with CR or PR).

By the Investigator's assessment of best response, more than half of the subjects had a response (CR or PR; 53.5%), with most of these subjects experiencing a PR (83 of 100 responders) as best response; an additional 78 subjects (41.7%) had a best assessment of SD. Nine subjects (4.8%) had a best response of PD. The Investigator's assessment of response is better than that of IRAC's, especially for CR. This is because IRAC strictly followed EBMT criteria for CR assessment, which relies on bone marrow aspiration, thereby hindering CR confirmation in some cases. By contrast, many of the Investigator-assessed CRs did not involve bone marrow aspirate prior to CR assessment. Overall, 72.7% of EE subjects progressed or died, with a median PFS time of 32.7 weeks. Just under one-third of subjects (31.6%) had at least 52 event-free weeks, and 21.7% of subjects remained event free at 78 weeks. A total of 100 subjects responded, with a median time to response of 8.1 weeks. Among subjects who responded, the time to response ranged from 4.0 to 53.1 weeks. The median duration of response for all responders (as assessed by the Investigator) was 40.8 weeks, with a range from 0.1 to 94.0 weeks.

A clinically meaningful response was observed in all subgroups analyzed.

PHARMACOKINETICS RESULTS:

In Chinese MM subjects, lenalidomide was absorbed and eliminated rapidly with a median t_{max} of approximately 1 h and a mean $t_{1/2,z}$ of approximately 3 h after both single and multiple doses. In these subjects, lenalidomide did not accumulate in plasma with multiple doses. Consistent with the linear PK, lenalidomide did not show any time dependency in mean $t_{1/2,z}$, CL/F, and Vz/F.

Coadministration of lenalidomide with 40 mg dexamethasone had no effect on the multiple-dose PK

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profile of lenalidomide.

The lenalidomide PK in Chinese MM subjects was similar to the historical data obtained from Caucasian MM subjects (25 mg/day).

SAFETY RESULTS:

Overall, the Rd regimen of 25 mg oral lenalidomide once daily on Days 1 to 21 of each 28-day cycle and 40 mg oral dexamethasone daily on Days 1, 8, 15 and 22 of each 28-day cycle was well-tolerated and demonstrated a good safety profile among Chinese subjects with RRMM. The safety profile of lenalidomide in combination with low-dose dexamethasone remained relatively consistent with the known safety profile of this regimen and with the RRMM population.

Commonly reported AEs and SAEs are mostly consistent with the known safety profile of the Rd regimen. Treatment-emergent AEs were observed in most subjects who participated in this clinical trial, with the most frequently reported TEAEs being anemia, decreased neutrophil count, neutropenia, and decreased WBC count.

The most frequent Grade 3 or 4 AEs were anemia and neutropenia, followed by thrombocytopenia, pneumonia, leukopenia, and decreased neutrophil count. In general, the incidence of Grade 4 events was much lower than the incidence of Grade 3 events.

The most frequent SAE was pneumonia (23/199 subjects, 11.6%), including 2 subjects (1.0%) who discontinued study drug due to pneumonia. Thrombocytopenia (7/199 subjects, 3.5%); death (6/199 subjects, 3.0%); and cardiac failure, anemia, and multiple myeloma (each in 4/199 subjects, 2.0%); and acute renal failure (3/199 subjects, 1.5%) were reported as SAEs in a smaller number of subjects.

A total of 83 deaths were reported in the Safety Population (41.7%) over a period of approximately 2 years; of these, 25 subjects (25/83, 30.1%) died “on-treatment” (ie, within 28 days of the last study treatment). Except death NOS, the most common primary cause of death overall was multiple myeloma/disease progression (18/199 subjects, 9.0%). Death due to multiorgan failure occurred in 6 subjects in the Safety Population (3.0%). Four subjects each died from cardiac failure, lung infection, and respiratory failure in the Safety Population (2.0% each), 3 subjects each died from cerebral hemorrhage, intracranial hemorrhage, and renal failure (1.5% each), and 2 subjects each died from cardiopulmonary failure, pneumonia, and septic shock (1.0% each). All other causes of death occurred in only 1 subject each.

One subject (1/199; 0.5%) experienced a solid tumor SPM (duodenal neoplasm) during the post-treatment phase of the study (55 days after the last dose of study medication). One subject (1/199, 0.5%) experienced DVT. The event was serious and led to a dose interruption and a lenalidomide dose reduction; the subject subsequently recovered. No other subjects reported VTEs.

One subject (1/199, 0.5%) experienced tumor lysis syndrome with a fatal outcome. The event was considered by the Investigator to be related to lenalidomide. Of note, the subject also experienced the fatal SAEs of disseminated intravascular coagulation and septic shock, and had pneumonia immediately prior to screening. No other subjects were reported to have tumor lysis syndrome.

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Forty-two subjects (21.1%) experienced TEAEs of pneumonia, including bronchopneumonia, lobar pneumonia, pneumonia, and lung infection; of these, 7 subjects had a previous history of pneumonia. Twenty-three subjects (11.6%) experienced serious pneumonia. Two subjects (1.0%) discontinued lenalidomide due to pneumonia, and 2 subjects (1.0%) died from pneumonia. The overall incidence of pneumonia was somewhat higher than seen in study Report MM-010 (8.5%), but it was consistent with the incidence of pneumonia seen in Report MM-009 (24.9%). The incidence of pneumonia as an SAE (11.6%) was similar to that seen in previous studies (9.3% overall).

The cytopenias of anemia, neutropenia (neutropenia, decreased neutrophil count, and febrile neutropenia), and thrombocytopenia (thrombocytopenia and decreased platelet count) were frequently reported in this study. These AEs led to dose reductions or interruptions in some subjects, but anemia and neutropenia did not lead to dose discontinuation. Two subjects discontinued lenalidomide due to thrombocytopenia. Although Grade 3 or 4 anemia was common in this study, it was not unexpected given that 80.6% of subjects (154/191 subjects) had Grade 3 or 4 hemoglobin values at baseline.

CONCLUSIONS:

The overall best response rate as the primary efficacy endpoint demonstrated an excellent treatment effect of the combination therapy of lenalidomide plus low-dose dexamethasone (Rd) in RRMM subjects. The final efficacy data are consistent with those reported in previous interim and synoptic reports. These data demonstrate the robustness of this treatment regimen across various subgroups and over time.

On the safety side, lenalidomide administered as a part of the Rd regimen was well-tolerated among the Chinese RRMM subjects. There were no new safety signals among the trial subjects. Although TEAEs such as pneumonia, anemia, neutropenia, and thrombocytopenia were common and often led to dose reductions or interruptions in this study, these events rarely led to discontinuation of study treatment, suggesting that such AEs were manageable. These safety findings support the Rd safety profile acceptable for the target population.

The results in this final study report, together with data from the interim and synoptic reports, support the robustness and effectiveness of lenalidomide administered as a part of the Rd regimen at the doses used in this study and fulfills an unmet medical need for the RRMM population in China. Taken together, these efficacy and safety data provide a solid foundation for a favorable benefit to risk balance for the approved Revlimid indication in China.

Date of the report: 22 Aug 2013