A Phase II Randomized, Double-Blind, Placebo-Controlled Safety and Efficacy Study of Lenalidomide in Lumbar Radicular Pain with a Long-Term Open-Label Extension Phase.

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A Phase II Randomized, Double-Blind, Placebo-Controlled Safety and Efficacy Study of Lenalidomide in Lumbar Radicular Pain with a Long-Term Open-Label Extension Phase

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Conflicts of interest: Celgene Corporation developed the protocol in conjunction with the clinical investigators. Celgene Corporation was solely responsible for investigative site selection, data collection, storage methods, and technology, clinical monitoring of protocol and Good Clinical Practice guidelines compliance, statistical analysis plan and execution, provision of study drug and matching control, and reporting of efficacy and safety data to regulatory agencies.

Disclosures: Donald C. Manning was an employee of Celgene Corporation during the execution of the reported study and an owner of Celgene Corporation stock. Joseph Gimbel and Richard Rauck received standard compensation for participating as investigators in the study. Robert Wertz has no conflicts of interest to disclose; his institution received funds to conduct the study. Alyse Cooper and Jerome B. Zeldis are employees of Celgene Corporation and owners of Celgene Corporation stock. Dale M. Levinsky has no conflicts of interest to disclose; her institution received funds to conduct the study.

Abstract

Objective. This phase II study assessed lenalidomide efficacy and safety.

Design. Three-phase core study: 14-day prerandomization, 12-week treatment, and 52-week open-label extension.

Setting. Fourteen US centers from July 2005 to July 2007.

Subjects. Chronic lumbar radicular pain patients without history of nerve injury or deficit.

Methods. Subjects were randomized (1:1) to double-blind treatment with lenalidomide 10 mg or placebo once daily for 12 weeks, followed by a 52-week open-label extension. A 12-week, single-center, randomized-withdrawal (1:2, lenalidomide:placebo), exploratory study with open-label extension was undertaken in 12 subjects from the core extension who were naïve to neuropathic medications and with at least a two-point decrease from baseline average daily Pain Intensity–Numerical Rating Scale score.

Results. Of 180 subjects enrolled, 176 had at least one postbaseline measure; 132 completed the

12-week treatment phase. In the core study, no statistically significant difference in Pain Intensity–Numerical Rating Scale mean change (−0.02, $P = 0.958$) was observed at week 12 between lenalidomide and placebo; proportions achieving pain reduction at week 12 and other secondary measures were comparable between lenalidomide and placebo. In the exploratory study, week 12 mean changes in Pain Intensity–Numerical Rating Scale scores were −0.05 (lenalidomide: N = 3) and 2.11 (placebo: N = 8). Mean changes in Brief Pain Inventory–short form interference scores were −3.33 and 8.38, respectively; scores at six months were maintained or decreased in 10 of 12 subjects.

Conclusions. While this study does not support lenalidomide use in an unselected lumbar radicular pain population, an immunomodulating agent may relieve pain in select subjects naïve to neuropathic pain medications.

ClinicalTrials.gov identifier: NCT00120120.

Key Words. Lumbar Radicular Pain; Chronic Pain; Neuropathic Pain; Lenalidomide; Inflammation

Introduction

Lumbar radicular pain is part of a chronic pain syndrome typically characterized by unilateral, lancinating pain affecting the lower portion of the leg, ankle, and foot in a spinal nerve root pattern [1,2]. The syndrome is sometimes accompanied by neuropathic signs and symptoms such as numbness or paresthesia and/or abnormal motor function as a result of direct nerve compression and conduction block [1]. The estimated prevalence in the general population in studies using clinical criteria to establish a diagnosis of lumbar radicular pain is 4.8% [1,3].

Lumbar radicular pain is in part related to irritation and inflammation from ongoing production of pro-inflammatory cytokines, which lead to peripheral and central sensitization of pain responses [4]. Tumor necrosis factor-α (TNF-α), nitric oxide, and interleukin (IL)-1 and IL-6 have all been implicated in radicular pathophysiology [5]. No pharmacologic treatment has been approved specifically for lumbar radicular pain, and disc surgery is often recommended for patients who have failed treatment with oral analgesics, physiotherapy, or epidural steroid injections [6,7]. Because inflammatory signals may play a critical role in the etiology and maintenance of chronic lumbar radicular pain, a number of anti-inflammatory agents have been investigated as potential treatments. Biologic agents targeting TNF-α, such as infliximab and etanercept, have been used systemically and in targeted epidural injections, and have not demonstrated consistent efficacy for pain relief in patients with lumbar radicular pain [7–9].

Two small exploratory studies of thalidomide [10] and its analog lenalidomide (CC-5013) [11] reported pronounced reductions in pain intensity in patients with complex regional pain syndrome (CRPS), another pain condition with both inflammatory and neuropathic-proposed pathophysiologic mechanisms. These compounds inhibit the production of several pro-inflammatory mediators by monocytes, including TNF-α, IL-1β, IL-6, and IL-12 [12]. However, a phase II, randomized, double-blind, placebo-controlled study of lenalidomide in patients with CRPS conducted concurrently with the study described here failed to demonstrate significant pain relief compared with placebo [11].

The core study in lumbar radicular pain (CC-5013-RAD-001) was designed to provide preliminary efficacy and safety data for lenalidomide in this population and to serve as a pilot study for future development programs for related compounds. It was hypothesized that lenalidomide, acting as an immunomodulator, would reduce the inflammatory cytokine milieu contributing to the irritative radicular symptoms and thereby reduce lumbar radicular pain. In the absence of prior pharmacologic studies of lenalidomide in lumbar radicular pain, we sought input from the literature and a panel of experts. The current report describes the efficacy and safety results for lenalidomide in these subjects from the core study and the results of a small, exploratory, proof-of-concept study conducted based on the results of the core study.

Methods

Subjects

The intended population for the core and exploratory studies was subjects with lumbar radicular pain associated with irritative radiculitis, presumably due to spinal root exposure to extruded intervertebral disc material, producing pain in the distribution of the sciatic nerve. Pain, as defined in the current studies, should worsen while performing the straight leg raising maneuver and should not be associated with a history or evidence of nerve injury or deficit. To emulate real-world pain practice, and because of ethical considerations, subjects were allowed to remain on their concomitant pain medications as long as they were on stable doses before study enrollment. Lenalidomide (Revlimid) 10 mg once daily was chosen based on the safety profile in the CRPS and oncology studies.

Eligible subjects were 18 years of age or older with a clinical diagnosis of lumbar radicular pain for at least six months before screening, based on: 1) presence of pain in the distribution of the sciatic nerve and/or L4, L5, or S1 dermatomes, primarily in the lower leg, radiating to the ankle or foot, in one or both extremities; 2) positive straight leg raising test in the ipsilateral index leg (pain radiating below the knee at an elevation of less than 60°) [7]; 3) at least moderate pain, demonstrated by a score of at least 5 on the 11-point Pain Intensity–Numerical Rating Scale (PI-NRS; 0 = no pain, 10 = most severe pain imaginable); and 4) average lumbar radicular pain

PI-NRS score of at least 5 based on a combination of at least eight morning and evening assessments during the seven days before randomization. This score was considered the baseline score. Because lenalidomide is structurally similar to thalidomide, a human teratogen, men and women with reproductive potential were required to adhere to pregnancy prevention guidelines [13].

Subjects were excluded if pain was localized in areas other than the lower leg and comprised a majority of the total pain reported, including ankle or foot problems that could interfere with the assessment of radicular pain. Subjects also were excluded if they had an unstable lumbar spinal segment; acute operable lesion or tumor based on computed tomography or magnetic resonance imaging scan within two years of enrollment; a history of lumbar spine surgery within the past 12 months; a history of deep vein thrombosis within the past five years; signs or symptoms of any serious medical condition, laboratory abnormality, or psychiatric illness preventing informed consent; prior treatment with or allergy to lenalidomide; or pregnancy or lactation. Finally, subjects were excluded for active litigation (i.e., pending litigation or proceeding), disability compensation, or disability issues related to lumbar radicular pain. Subjects whose cases had been settled or finally decided were eligible for the study.

The protocol and informed consent were reviewed by each site's institutional review board, and written approval was obtained prior to study initiation. Subjects gave written informed consent prior to the initiation of any study procedures. A member of the staff explained to each subject the nature of the study (objectives, methods, potential benefits, and risks) and the procedures involved. Subjects were given sufficient time to review the consent form and to ask questions to ensure their understanding of the information provided. The forms were signed and dated by subjects, indicating their consent to participate in the study. Subjects received a copy of the form to retain for their files.

Study Design

The core phase II, randomized, double-blind, placebo-controlled study of lenalidomide treatment in subjects with lumbar radicular pain was conducted at 14 centers in the United States from July 2005 through July 2007 (ClinicalTrials.gov identifier: NCT00120120) (Figure 1A). The study consisted of a 14-day prerandomization phase, a 12-week treatment phase, and a 52-week open-label extension phase. Eligible subjects were randomized (1:1) to double-blind treatment with lenalidomide 10 mg or matching placebo once daily for 12 weeks. Randomization was performed centrally across all centers using blocked randomization with a block size of four. All subjects who completed the 12-week treatment phase were eligible to either initiate lenalidomide treatment, if they were initially randomized to placebo at baseline, or to continue receiving lenalidomide in the open-label extension phase, which continued for as long as a benefit was derived.

While the open-label extension phase of the core study was proceeding, we performed an interim analysis of the primary efficacy variable from the treatment phase, which did not show a significant separation of the lenalidomide treatment arm from placebo. Post hoc analyses of the core efficacy results suggested that subjects treated with fewer or no neuropathic pain therapies may have been more responsive to lenalidomide. Thus, the study protocol was amended to include a small convenience population exploratory investigation conducted at one participating center in which the continuing subjects were not taking any concomitant neuropathic medications. Given the convenience population, there was no sample size estimation used. For the other study centers, the open-label extension phase of the core study was terminated.

Because the standard parallel-group design is typically associated with larger placebo responses, the exploratory study was designed as a controlled withdrawal design, which has been shown to provide a better separation from placebo [14–17]. The objective of the exploratory study was to provide information relative to future study designs, such as crossover treatment vs withdrawal, allowing for drug response confirmation, determination of response duration, and information regarding possible carryover effects.

This single-center exploratory study, conducted between June 2007 and April 2009, consisted of a seven-day prerandomization phase during which subjects continued receiving lenalidomide and completed an average daily pain assessment at home, a 12-week randomized withdrawal phase with study visits every two weeks (subjects randomized 1:2 to double-blind treatment with lenalidomide 10 mg or placebo), and an open-label extension phase of lenalidomide that continued as long as subjects derived benefit from treatment (Figure 1B). Subjects were eligible to participate if they were in the core study open-label extension phase receiving lenalidomide and had at least a two-point decrease in their baseline average daily PI-NRS score on visit 1 of the exploratory study vs baseline of the core study, as determined by the average of at least five PI-NRS scores in the prerandomization week of the extension phase.

Concomitant Medication

For the core and exploratory studies, concomitant therapy for lumbar radicular pain, including opioid and nonopioid analgesics, nonsteroidal anti-inflammatory drugs, anticonvulsants, antidepressants, and other nondrug therapies, was permitted during the 12-week treatment phases if the dose/regimen had been stable for at least 28 days before randomization and remained stable throughout the treatment phase. Use of oral or injectable corticosteroids within 28 days of randomization and during the studies was not allowed, except for asthma inhalers and methylprednisolone in the core study. No new analgesic medications, nondrug therapies, or rescue medications were allowed except for

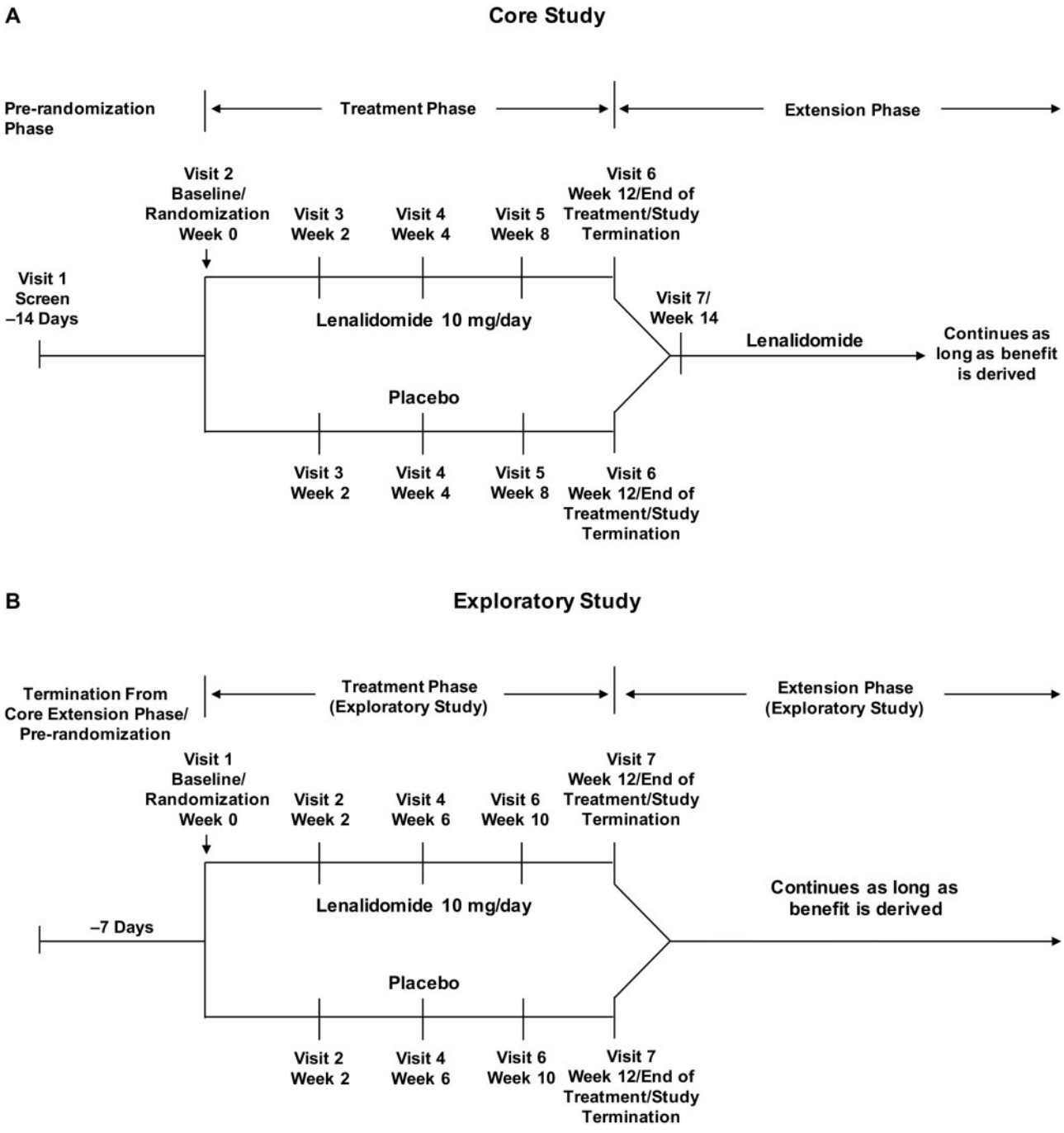

Figure 1 Design of the (A) core study and (B) exploratory study.

limited use of a rescue medication (acetaminophen 325 mg or short-acting opioid for no more than seven days) to treat pain flares, trauma, or procedural pain. During the open-label extension phases of both studies, subjects were permitted to initiate, reduce, increase, or withdraw from concomitant analgesic medications or nondrug therapies. Use of experimental therapies was not permitted.

Efficacy and Safety Assessments

Based on the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) Group [18], pain, disability, mood, function, and general symptoms were assessed at study visits. All subject-reported efficacy assessments were obtained and recorded using an electronic diary.

For the core and exploratory studies, the primary efficacy end point was the change from baseline in PI-NRS pain intensity ratings (combined morning/evening assessments for the core study; average daily pain assessment in the exploratory study) at week 12. Results of multiple daily assessments of pain were averaged over one week to minimize variability. Secondary efficacy end points in the core study included the change from baseline in morning and evening PI-NRS ratings at week 12, daily sleep assessment (an 11-point NRS), Short-Form McGill Pain Questionnaire (SF-MPQ) total score and subscale (sensory and affective) scores, and Brief Pain Inventory–short form (BPI-sf) interference scores (0–70) relative to baseline pain ratings. These scales are all standard, validated tools for assessing pain, related sleep problems, negative emotional state, and other quality-of-life factors. Concomitant analgesic medication usage was analyzed post hoc. The secondary end point in the exploratory study was the change from baseline in total BPI-sf interference score relative to baseline.

Safety was assessed throughout the studies and was based on collection of type, frequency, and severity of adverse events (AEs), physical examination findings, vital sign measurements at each visit, 12-lead electrocardiogram readings at screening and week 12, and clinical laboratory testing at each study visit except visit 2 (randomization) in the core study and at screening and week 12 in the exploratory study. During the core open-label extension phase, efficacy and safety assessments were performed at three-month intervals (after three two-week and two four-week visits following completion of the core treatment phase).

In the exploratory open-label extension phase, assessments were performed at three-month intervals.

Statistical Analysis

The change from baseline in the PI-NRS score at the end of the treatment phase was estimated to be −1.2 in the lenalidomide group (based on the results of a study conducted in patients with CRPS [CRPS-001]) and −0.3 in the placebo group, with a common standard deviation of 2.0. The sample size, based on these estimates, was that at least 90 subjects were needed in the intent-to-treat analysis set in each treatment group (N = 180) to provide 85% power to detect a significant difference between the two groups using a two-sided *t* test at the 0.05 significance level.

The primary analysis in the core and exploratory studies included all randomized subjects who took at least one dose of study drug and had at least one postbaseline PI-NRS electronic diary measurement. For the core study, the change from baseline in PI-NRS score at week 12 (primary end point) was compared between the groups using an analysis of covariance (ANCOVA) model, which included terms for treatment, center, baseline score, and treatment-by-baseline interaction; missing data were imputed using the last-observation-carried-forward methodology (LOCF). The same ANCOVA model was used for all secondary continuous efficacy end points. Proportions of subjects achieving pain relief, defined as at least a two-point reduction from baseline in the PI-NRS score at week 12, were compared between treatment groups using a continuity-corrected chi-square test and LOCF methodology for cases with missing data.

The primary end point for the exploratory study was the change from baseline in the average daily PI-NRS score at week 12, and the secondary end point was the change from baseline in the total BPI-sf interference score. Given the small, exploratory nature of this investigation, no between-group comparisons were planned; summary statistics were determined for the efficacy end points using observed cases data, with mean changes from baseline adjusted using ANCOVA, including terms for treatment as factor and baseline as covariate.

Results

Subjects

Subject disposition is shown in Figure 2. A total of 180 subjects were randomized in the core study and received at least one dose of study drug (safety population); 176 subjects had at least one postbaseline diary measurement and were included in the efficacy analyses. In all, 132 (75%) subjects completed the 12-week treatment phase and entered the open-label extension phase. Of the subjects discontinuing the treatment phase, 17 (19.1%) in the lenalidomide group and seven (7.7%) in the placebo group discontinued due to AEs. All subjects entering the open-label extension phase discontinued within 52 weeks, with 12 subjects entering the exploratory phase discussed below. Reasons included AEs (n = 35 [27.3%]) and lack of therapeutic effect (n = 24 [18.2%]). Baseline subject demographic and disease characteristic differences between the lenalidomide and placebo groups in the core study were not clinically meaningful (Table 1). At least one analgesic medication was given to 157 (87.2%) subjects at a stable dose for at least 28 days before randomization and was permitted as concomitant therapy during the treatment phase of the study.

Twelve subjects from a single site enrolled in the exploratory study. The subjects included seven males and five females, 75% of whom were Caucasian. The lenalidomide group included all males. In addition, the baseline BPI-sf interference score was higher in the placebo group than in the lenalidomide group (mean [SD] = 12.1 [12.9] and 4.5 [3.4], respectively) (Table 1). Among the 12 subjects enrolled, 11 (91.7%) subjects completed the 12-week randomized withdrawal treatment phase and all 12 originally enrolled subjects entered the subsequent open-label extension phase.

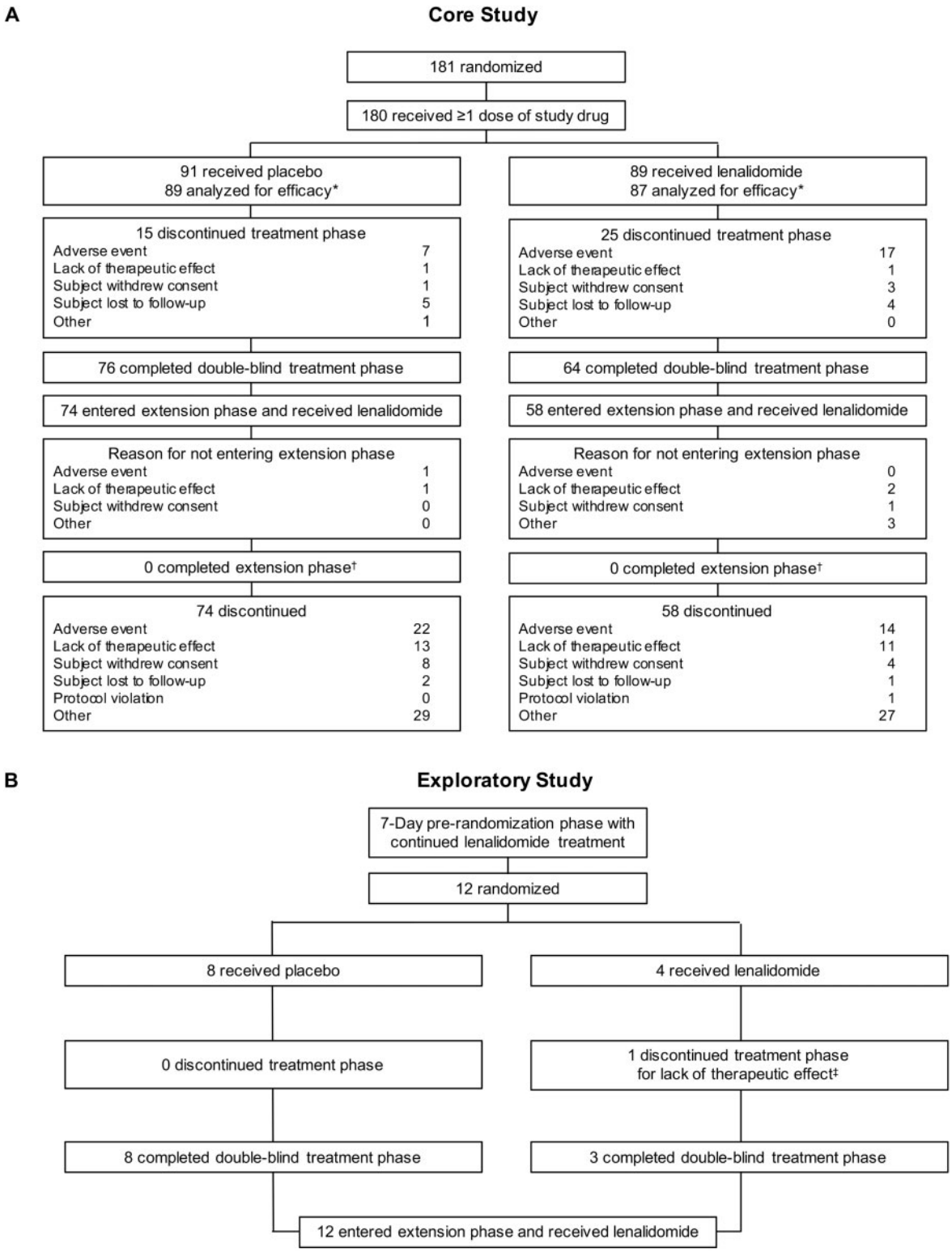

Figure 2 Subject disposition in the (A) core study and (B) exploratory study. *All patients who received at least one dose of study drug who had at least one postbaseline diary measurement. †Extension phase was terminated prematurely due to failure to meet the primary efficacy end point on interim analysis. ‡All 12 patients continued lenalidomide in the extension phase.

Table 1 Baseline subject demographics and clinical characteristics

Characteristic	Multicenter core study		Single-center exploratory study	
	Lenalidomide 10 mg once daily (N = 87)	Placebo Once daily (N = 89)	Lenalidomide 10 mg once daily (N = 4)	Placebo Once daily (N = 8)
Age, y, mean (SD)	54.0 (13.3)	55.4 (12.4)	64.8 (5.3)	57.8 (9.2)
Age distribution, y, N (%)				
≤65	69 (79)	73 (82)	1 (25)	5 (63)
>65	18 (21)	16 (18)	3 (75)	3 (38)
Sex, N (%)				
Male	37 (43)	39 (44)	4 (100)	3 (38)
Female	50 (58)	50 (56)	0 (0)	5 (63)
Race/ethnicity, N (%)				
White	72 (83)	74 (83)	3 (75)	6 (75)
Black	11 (13)	7 (8)	0 (0)	0 (0)
Hispanic	2 (2)	7 (8)	1 (25)	2 (25)
Asian/Pacific islander	1 (1)	1 (1)	0 (0)	0 (0)
Other	1 (1)	0 (0)	0 (0)	0 (0)
PI-NRS (0–10), mean (SD)*	6.9 (1.2)	6.8 (1.1)	1.8 (1.0)	1.7 (1.9)
SLR, degrees, mean (SD)	34.7 (14.1)	37.3 (12.8)	NA	NA
BPI-sf interference scores (0–70), mean (SD)	43.9 (12.7)	43.5 (12.9)	4.5 (3.4)	12.1 (12.9)
Prior analgesic†, N (%)				
Any	79 (91)	79 (89)	1 (25)	4 (50)
Opioids	44 (51)	50 (56)	0 (0)	0 (0)
NSAIDs	35 (40)	42 (47)	1 (25)	5 (63)
Centrally acting agents‡	12 (14)	14 (16)	0 (0)	0 (0)
Gabapentin	11 (13)	18 (20)	0 (0)	0 (0)
Pregabalin	6 (7)	2 (2)	0 (0)	0 (0)
MAOIs	4 (5)	4 (4)	0 (0)	0 (0)
SSRIs	0 (0)	1 (1)	0 (0)	0 (0)

BPI-sf = Brief Pain Inventory–short form; MAOIs = monoamine oxidase inhibitors; NA = not assessed; NSAIDs = nonsteroidal anti-inflammatory drugs; PI-NRS = Pain Intensity–Numerical Rating Scale; SLR = straight leg raise, angle of elevation without pain; SSRIs = selective serotonin reuptake inhibitors.

*Combined morning and evening assessments, based on a 0–10 scale, with higher ratings indicating more severe pain.

†Medications received for radicular pain at stable doses for at least 28 days before randomization and permitted as concomitant therapy during the treatment phase of the study.

‡Included cyclobenzaprine hydrochloride, tizanidine hydrochloride, baclofen, cyclobenzaprine, and tizanidine.

Efficacy

In the core study, no statistically significant difference in the mean change in PI-NRS ratings (−0.02; $P = 0.958$) was observed at week 12 between the lenalidomide and placebo groups (Table 2). The proportions of subjects who achieved a pain response at week 12 (e.g., at least a two-point improvement from baseline in the PI-NRS score) were also comparable between the lenalidomide and placebo groups (Table 2). Secondary measures also failed to show statistically significant or clinically important differences between lenalidomide and placebo (straight leg raising, SF-MPQ, and BPI-sf) (Table 2), and in the case of the SF-MPQ, the change in sensory subscore was favorable to placebo; no adjustments for multiplicity were made. In addition, no significant differences were observed at week 12 between treatment groups in the change from baseline in morning and evening PI-NRS ratings (not shown) or daily sleep assessments (Table 2). During the treatment phase, 18 of 180 (10.0%) subjects received rescue medication for pain; of these, 14 (77.7%) were in the placebo group. During the open-label extension phase, no differences between the lenalidomide-lenalidomide and placebo-lenalidomide groups were observed based on any efficacy end points.

Post hoc analyses from the treatment phase of the core study were designed to evaluate the impact of concomitant analgesic medication use on PI-NRS assessments to determine whether responses to lenalidomide varied within subpopulations of subjects and to assist in future

Table 2 Summary of selected efficacy assessments at week 12 in the core study (LOCF)

	Lenalidomide (N = 87)	Placebo (N = 89)	*P* values
PI-NRS (0–10), mean change (SD)	−1.29 (2.05)	−1.27 (2.23)	0.958
Pain response*, N (%)	27 (31.0)	31 (34.8)	0.592
Daily sleep assessment score (0–10)†			
Fall asleep, adjusted mean change (SE)	−1.48 (0.22)	−1.36 (0.22)	0.717
Stay asleep, adjusted mean change (SE)	−1.40 (0.22)	−1.47 (0.22)	0.819
SLR test (<60°), adjusted mean change (SE)‡	8.5 (1.8)	8.5 (1.7)	0.990
SF-MPQ total	−5.7 (1.05)	−5.5 (1.05)	0.863
Sensory	−4.4 (0.8)	−3.9 (0.8)	0.624
Affective	−1.4 (0.29)	−1.6 (0.29)	0.538
BPI-sf interference score (0–70), adjusted mean change (SE)§	−8.9 (1.5)	−9.4 (1.5)	0.811

Adjusted means were calculated using an analysis of covariance model, including term for treatment as factor and baseline as covariate.

BPI-sf = Brief Pain Inventory–short form; LOCF = last observation carried forward; PI-NRS = Pain Intensity–Numerical Rating Scale; SF-MPQ = Short-Form McGill Pain Questionnaire; SLR = straight leg raising, angle of elevation without pain.

*At least a two-point reduction from baseline in PI-NRS ratings.

†Placebo: N = 88.

‡Lenalidomide: N = 86; placebo: N = 86.

§Lenalidomide: N = 79; placebo: N = 79.

study design. For this analysis, concomitant medications were categorized into group 1 medications, which included various classes of agents used to treat neuropathic pain or related pain conditions (anticonvulsants/anti-epileptics, antidepressants, muscle relaxants, or benzodiazepines) and group 2 medications, which consisted of opioid agents. For post hoc analyses, subjects were included or excluded or placed into subgroups based on their concomitant use of group 1 or group 2 medications.

The first post hoc analysis re-examined the core study primary end point among subjects who did not receive a concomitant group 1 medication (lenalidomide: N = 82; placebo: N = 78). This revealed a small, nonsignificant improvement from baseline pain based on the mean change in PI-NRS at week 12 (difference in mean change: −0.15, $P = 0.665$). Further post hoc analysis of pain response rates showed that, on average, subjects who achieved a pain response in the lenalidomide and placebo groups had taken fewer types of group 1 medications than did nonresponders. Use of group 2 medications (i.e., opioids) was similar between responders and nonresponders.

In the exploratory study, pain returned between weeks 4 and 6 for subjects who were re-randomized to placebo from ongoing lenalidomide treatment. The mean change from baseline, week 0 in the single-center exploratory study to week 12 in PI-NRS scores, was −0.05 in subjects who continued lenalidomide treatment and 2.11 in subjects randomized to placebo ($P = 0.225$) (Table 3), suggesting a trend for an increase in lumbar radicular pain following withdrawal of open-label lenalidomide treatment that did not reach significance. The mean change in total BPI-sf ratings from baseline to week 12 decreased in the lenalidomide group (adjusted mean change = −1.11) and increased in the placebo group (adjusted mean change = 7.54), with a difference of −8.65 ($P = 0.236$) (Table 3). During the open-label extension phase, all 12 subjects were treated with lenalidomide. Pain assessments were based on the total BPI-sf interference score. Differences in baseline BPI-sf interference scores complicated the interpretation of results, as the mean score was 4.5 in the lenalidomide group vs 12.1 in the placebo group.

Safety

During the double-blind treatment phase of the core study, at least one AE was reported by 71 (79.8%) subjects receiving lenalidomide and 61 (67.0%) subjects receiving placebo. An overview of AEs in the treatment

Table 3 Summary of selected efficacy assessments at week 12 in the exploratory study.

	Lenalidomide (N = 3)	Placebo (N = 8)	*P* values
PI-NRS (0–10), adjusted mean change	−0.05	2.11	0.225
BPI-sf interference score (0–70), adjusted mean change	−1.11	7.54	0.236

BPI-sf = Brief Pain Inventory–short form; PI-NRS = Pain Intensity–Numerical Rating Scale.

Table 4 Overview of AEs in the core study

	Treatment phase		Open-label extension phase
	Lenalidomide (N = 89)	Placebo (N = 91)	Lenalidomide (N = 132)
Overview of AEs, N (%)			
Any AE	71 (80)	61 (67)	114 (86)
Any serious AE	6 (7)	1 (1)	13 (10)
Any AE leading to drug withdrawal	17 (19)	7 (8)	35 (27)
Death	0 (0)	0 (0)	0 (0)
AEs reported by ≥ 10% of patients in any treatment group, N (%)			
Diarrhea	8 (9)	3 (3)	22 (17)
Nausea	8 (9)	5 (5)	13 (10)
Constipation	10 (11)	5 (5)	7 (5)
Rash	23 (26)	6 (7)	22 (17)
Pruritus	13 (15)	4 (4)	9 (7)

AEs = adverse events.

and open-label extension phases of the core study is provided in Table 4. Most AEs in both phases were grade 1 (mild) or grade 2 (moderate). The most commonly reported AEs occurred with higher frequency in the lenalidomide group during the treatment phase, and these were considered related to study drug. During the 12-week treatment phase of the core study, one case of grade 1 anemia was reported. During the extension phase, three cases of grade 2 and one case of grade 3 neutropenia were reported, as well as six cases of thrombocytopenia (one of which was a grade 4 serious AE [SAE] and three of which occurred in the same subject), one case of anemia (grade 3), and one case of deep vein thrombosis. All cases were suspected to be related to the study drug except for deep vein thrombosis. The incidence of these known lenalidomide AEs tended to increase slightly (≈2–3%) with longer-term treatment in the open-label extension phase.

AEs leading to study discontinuation in the lenalidomide group during the treatment phase included rash (N = 3), pruritus (N = 2), dry eye (N = 2), and (in one subject each) increased alanine aminotransferase, increased aspartate aminotransferase, positive antinuclear factor, presence of protein in urine, increased weight, erythema multiforme, diverticulitis, oral hypoesthesia, dizziness, oral paresthesia, transient ischemic attack (TIA), depression, agitation, sleep disorder, fatigue, peripheral edema, myalgia, neck pain, blurred vision, cough, and throat tightness. In the placebo arm, AEs leading to discontinuation included rash (N = 2) and (in one subject each) increased alanine aminotransferase, increased aspartate aminotransferase, increased blood creatinine, constipation, dyspepsia, vomiting, headache, depression, fatigue, muscle spasms, and hepatic cirrhosis.

In the core study, seven (4%) subjects experienced SAEs during the treatment phase and 13 (10%) subjects experienced SAEs during the open-label extension phase. SAEs considered related to lenalidomide treatment in either phase were dizziness, TIA, anemia, thrombocytopenia, acute myocardial infarction, chest pain, pneumonia, and deep vein thrombosis occurring in one subject each. No notable drug-related shifts were observed in laboratory values or vital sign measurements from baseline in either phase of the core study, with a few exceptions that coincided with AE reports.

The safety profile of lenalidomide during the exploratory study was consistent with that observed in the core study. Two subjects each receiving lenalidomide and placebo had treatment-related AEs; these included leukopenia, decreased white blood cell count, muscle cramps, and pruritus in the lenalidomide group and leukopenia, decreased weight, and constipation in the placebo group. There were no SAEs, dose interruptions, or discontinuations due to AEs.

Discussion

Most widely used oral or epidural treatments have not provided consistent, adequate relief of lumbar radicular pain [6]. The chronic nature of lumbar radicular pain is believed to be initiated and maintained in part by the local and central effects of inflammatory cytokines, which sensitize the nociceptive system [4,5]. For the current investigation, it was hypothesized that lenalidomide might provide benefit in such patients owing to its broad inhibition of pro-inflammatory mediators, including TNF-α, IL-1β, IL-6, and IL-12 [12].

In the core study reported here, however, lenalidomide did not demonstrate significant pain relief compared with placebo in the overall population of subjects with lumbar radicular pain. Because the primary end point was not achieved, post hoc analyses of the core study treatment phase data were conducted to determine whether responses to lenalidomide varied within subpopulations of subjects and to assist in future study design. When subjects who had used anticonvulsants, antidepressants, anti-epileptics, muscle relaxants, or benzodiazepines (group 1 medications) were excluded, responders (defined as subjects with at least a two-point reduction in pain using PI-NRS) had, on average, taken fewer group 1 medications than did nonresponders; by contrast, use of concomitant opioids was similar between responders and nonresponders, although subjects using opioids comprised a much smaller group. These findings suggest that patients with lumbar radicular pain enrolled in the core study were a heterogeneous population.

In the single-center exploratory study of 12 subjects who participated in the core study, a suggestion of a pain relief response to lenalidomide treatment was detected based on findings during randomized withdrawal and the subsequent six months of open-label treatment. Some subjects achieving pain relief with lenalidomide treatment in the core study who were re-randomized to placebo experienced a slow re-emergence of pain, beginning at week 4 after withdrawal of active treatment, suggesting longer-than-expected effects following lenalidomide discontinuation. Moreover, 11 of the 12 subjects who received open-label, long-term lenalidomide treatment showed decreases in pain or maintained already low levels of pain for up to approximately seven months. However, these data are limited by the small sample size and are hypothesis generating only. In addition, they are complicated by the sex and baseline BPI-sf imbalance in the convenience population used. Larger randomized samples should address efficacy in this population.

These findings do not support the use of lenalidomide in the broad population of patients with lumbar radicular pain; however, they suggest that at least some of these patients may experience a clinical benefit with lenalidomide. For future clinical studies, it will be necessary to carefully select subgroups of patients most likely to benefit from a potential treatment, such as subjects naïve to neuropathic pain medications and subjects with variable levels of pain. As suggested by the single-center exploratory study reported here, it may also be valuable to employ alternative study designs, such as randomized withdrawal, in order to more effectively examine the effects of treatment on lumbar radicular pain. Selecting subjects who experience symptoms for at least six months is preferred, as in the current studies, because subjects with a shorter history of pain may experience spontaneous resolution of symptoms and potentially confounding analgesic assessments. Pain assessments may need to be more fine-tuned to examine intraday variation in pain, given that frequency of pain assessments may influence subject pain ratings. Using the straight leg raising test, as in the current study, is important for providing a true sciatic stretch to assess nerve irritation as opposed to pure muscular pain. Including assessments that evaluate production of lower leg or foot pain during sciatic nerve stretch may help investigators to determine the impact of treatment on underlying nerve root irritation [2].

Lenalidomide 10 mg once daily was generally well tolerated and had an acceptable safety profile in subjects who received treatment for up to a total of two years. Common AEs observed with the 10 mg dose (e.g., rash, diarrhea, nausea) were generally consistent with those observed in previous oncology studies. Hematologic toxicities were observed to a lesser degree than have been observed with higher doses in oncology studies [19]. No signs of neurotoxicity were observed, consistent with observations in a CRPS population [11] and in contrast to what has been seen with thalidomide [20]. With long-term treatment, aside from slight increases (≈2–3%) in the frequency of known lenalidomide AEs, including anemia, neutropenia, and thrombocytopenia, no clear or consistent signs of new AEs were observed.

In conclusion, the findings from the core study do not provide support for use of lenalidomide in an unselected population with lumbar radicular pain. The small exploratory study does suggest that an immunomodulating agent such as lenalidomide may provide pain relief in a subset of individuals from this population who are naïve to neuropathic pain medications and perhaps not resistant to treatment.

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