American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 15, No 12 (December), 2014: pp 1366-1376
Available online at www.jpain.org and www.sciencedirect.com

Lenalidomide for Complex Regional Pain Syndrome Type 1: Lack of Efficacy in a Phase II Randomized Study

Donald C. Manning,[*,†] Guillermo Alexander,[‡] Joseph C. Arezzo,[§] Alyse Cooper,[¶] R. Norman Harden,[||] Anne Louise Oaklander,[**,††] Srinivasa N. Raja,[‡‡] Richard Rauck,[§§] and Robert Schwartzman[‡]

[*]Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia.
[†]Adynxx Inc, San Francisco, California.
[‡]Department of Neurology, Drexel University, Philadelphia, Pennsylvania.
[§]Department of Neuroscience and Neurology, Albert Einstein College of Medicine, Bronx, New York.
[¶]Celgene Corporation, Summit, New Jersey.
[||]Center for Pain Studies, Rehabilitation Institute of Chicago, Chicago, Illinois.
[**]Departments of Neurology and [††]Pathology (Neuropathology), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.
[‡‡]Division of Pain Medicine, Johns Hopkins University, Baltimore, Maryland.
[§§]Center for Clinical Research, Salem, North Carolina.

Abstract: **Complex regional pain syndrome (CRPS) is a potentially debilitating chronic pain syndrome with a poorly understood but likely neuroimmune/multifactorial pathophysiology associated with axonal injury. Based on the potential contribution of proinflammatory cytokines to CRPS pathogenesis and prior research with thalidomide, we investigated lenalidomide, a thalidomide derivative, for CRPS treatment. We conducted a phase II, randomized, double-blind, placebo-controlled study to evaluate the efficacy of oral lenalidomide 10 mg once daily in consenting patients with unilateral or bilateral CRPS type 1. The study comprised 12 weeks of treatment followed by a long-term extension. The primary efficacy outcome was reduced pain in the index limb, defined as ≥30% improvement from baseline using an 11-point numeric rating scale. One hundred eighty-four subjects enrolled. The primary endpoint was not met because equal proportions of treated (16.1%) and control (16.1%) subjects achieved the outcome; however, lenalidomide was well tolerated, with no evidence of neuropathy or major adverse effects. This study is the largest controlled, blinded clinical trial in subjects with chronic CRPS using the Budapest research criteria. It demonstrates the feasibility of conducting high-quality clinical trials in CRPS type 1 and provides considerations for designing future trials.**

Perspective: ***This article reports an adequately powered, controlled clinical trial in subjects with CRPS. Treatment and placebo were equally effective, but the study demonstrated that lenalidomide treatment is feasible in this population. The study provides examples to consider in designing future CRPS trials.***

Received February 19, 2014; Revised September 10, 2014; Accepted September 22, 2014.

This study was sponsored by Celgene Corporation. Celgene developed the protocol in conjunction with the clinical investigators. Celgene was solely responsible for investigative site selection, data collection and storage methods and technology, clinical monitoring of protocol and Good Clinical Practice guidelines compliance, statistical analysis plan and execution, reporting of safety data to regulatory agencies, and the provision of study drug and matching control. The authors received editorial support for manuscript preparation from Amy Zannikos, PharmD, of Peloton Advantage, LLC, funded by Celgene Corporation. The authors, however, directed and are fully responsible for all content and editorial decisions for this manuscript. D.C.M. was an employee of Celgene Corporation during the execution of the reported study, an owner of Celgene stock, and a former member of the Board of Directors for Reflex Sympathetic Dystrophy Syndrome Association-USA. G.A. received standard compensation for participating as an investigator in this study. J.C.A. received standard compensation for assisting with the design and analysis of the electrophysiology data from this study. A.C. is an employee of Celgene Corporation. R.N.H. received standard compensation for participating as an investigator in this study and also had an unrestricted grant from Celgene at the time of this study. He also has received research support from the Reflex Sympathetic Dystrophy Syndrome Association. A.L.O. reports no conflicts of interest. S.N.R. received standard compensation for participating as an investigator in this study and reports a research grant from Medtronic Inc for studies on the mechanisms of spinal cord stimulation–induced analgesia. R.R. received standard compensation for participating as an investigator in this study. R.S. received standard compensation for participating as an investigator in this study.

Trial registration: clinicaltrials.gov #NCT00109772.

Address reprint requests to Donald C. Manning, MD, PhD, 16 Johnston Drive, Bloomsbury, NJ 08804. E-mail: donaldcmanning@gmail.com

1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2014.09.013

Key words: *Complex regional pain syndrome, cytokines, immunomodulation, lenalidomide, thalidomide, clinical trial.*

Complex regional pain syndrome (CRPS) is an often debilitating neuropathic/neuroimmune syndrome usually triggered by injury to a limb.[7,13,34,42] Its clinical features can include pain symptoms such as allodynia and hyperalgesia; difficulty moving, including reduced range of motion; changes in limb color, temperature, appearance, and sweating; edema; and bone changes.[15,17,25,38,40] CRPS affects more females than males (relative risk 2:1–4:1) and has an average age of onset of 37 to 60 years.[3,8,33] Its pathophysiology is likely multifactorial,[13] and far more patients have type 1, which often involves soft-tissue and small-fiber axonal injury,[24] than type 2, which requires injury to a major nerve.[15,22,24] Treatment guidelines based on limited available data and expert opinion recommend physical and occupational therapy, analgesic and other medications, interventional procedures, and psychological therapy and support.[15,27] Proposed mechanisms include peripheral afferent and efferent as well as central neural involvement; clinical presentation suggests a neurogenic inflammation and/or activation of the immune system leading to an exaggerated inflammatory process. Regardless, there is increasing consensus that inflammation plays an important role in CRPS type 1.

Increased levels of proinflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin [IL]-1β, IL-2, and IL-6) and anti-inflammatory cytokines (IL-4 and IL-10) have been identified in plasma and cerebrospinal fluid and within the affected limbs of CRPS patients compared with nonaffected controls.[1,20,26,39] Increased levels of TNF-α and IL-6 have been identified in blister fluid from the skin of the affected limb when compared with the unaffected limb.[16] The elevated levels of proinflammatory and anti-inflammatory cytokines found in CRPS suggest that immunomodulating agents might be useful because of their anti-inflammatory effects. Few well-controlled and adequately powered clinical treatment studies of anti-inflammatory agents have been performed, and existing study designs vary.[9,14] Small pilot studies have also suggested possible therapeutic avenues, including a report of observable but variable resolution of CRPS in 2 patients treated with the TNF-α antagonist infliximab.[21] Thalidomide is a relatively selective inhibitor of TNF-α production by human monocytes, both in vitro and in vivo, and it exerts costimulatory effects on T-cell responses, including inhibiting proinflammatory cytokines and stimulating anti-inflammatory cytokines.[6] Following demonstration of near resolution of CRPS symptoms after thalidomide treatment in a woman with CRPS for 3 years,[28] thalidomide was studied in 42 patients with long-standing, previously treated CRPS. Objective and subjective improvement was observed in 17% of patients, with 14% experiencing at least modest pain relief.[36] However, use of thalidomide is limited by its well-known neurotoxicity and teratogenicity. Teratogenicity is a particular concern in CRPS, because most patients are female.

Lenalidomide is a thalidomide derivative created in a program to enhance the anti-inflammatory and immunomodulatory properties of thalidomide while reducing its toxicity. It is approved in the United States and Europe for treating multiple myeloma and anemia in some patients with myelodysplastic syndromes[12,30] and in several other countries (eg, China, Japan) for treating multiple myeloma.[4,37] Lenalidomide has approximately 1,000 times more anti-inflammatory activity in vitro than thalidomide.[6] Its pharmacologic activities include inhibiting secretion of the proinflammatory cytokines TNF-α, IL-1β, and IL-6, and increasing secretion of the anti-inflammatory cytokine IL-10 from stimulated monocytes.[6,19] Lenalidomide's safety and effect on reported pain in CRPS type 1 were studied in a preliminary phase IIa, multicenter, single-arm, open-label, 40-patient pilot study initiated in 2003.[35] The good response rates ($\geq$2-point improvement from baseline on an 11-point numeric rating scale [NRS]) were 28.9% at week 12 and 52.0% at week 52, and patient-rated pain and sleep scores also improved ($P < .05$).[35] In addition, lenalidomide was well tolerated, with few treatment-related serious adverse events (AEs) and no evidence of neurologic toxicity. These findings provided the rationale for the current phase IIb, multicenter, double-blind, placebo-controlled study.

Methods

Subjects

The inclusion criteria were age $\geq$18 years and CRPS type 1 (as per Budapest research criteria[17]) for $\geq$1 year with unilateral or bilateral involvement of a distal hand or foot, with or without proximal spread, plus a CRPS-related pain intensity score of $\geq$4 in the index limb. In cases where both limbs were affected, subjects selected their limb to be assessed (designated as the index limb). For subjects with single-limb involvement, that limb was the index limb. Because lenalidomide is structurally similar to thalidomide, a human teratogen, men and women with reproductive potential had to follow pregnancy prevention requirements, including counseling about preventing pregnancy. Subjects had to agree to use reliable forms of contraception, and women had to agree to periodic pregnancy testing. Potentially fertile women had to submit 2 negative pregnancy tests before randomization.

Subjects were excluded for history of stroke or deep vein thrombosis in the past 5 years (based on experience with lenalidomide in the oncology program); peripheral neuropathy; severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, or cerebral disease; any serious medical diagnoses or abnormal laboratory test results; or psychiatric illness that could prevent informed consent. Additional exclusions were prior treatment with lenalidomide or allergy to thalidomide;

pregnancy or lactation; or use of concomitant medications that increase the risk of deep vein thrombosis. Low-dose aspirin (81 mg) was required for subjects receiving sex hormones in any form for contraception or treatment of menopausal symptoms.

Study Design

This multicenter, phase IIb study was conducted from February 2005 to April 2008 at 24 study sites in the United States. It included a 2-week screening phase and a 12-week double-blind treatment phase, followed by an optional extension phase that allowed treatment to continue as long as benefit was maintained (Fig 1). All subjects meeting CRPS-related morning and evening pain intensity numerical rating scale (PI-NRS) score requirements averaged over the 7-day period before randomization (≥8 recorded scores, average score ≥4 in affected limb) were randomized 1:1 to receive lenalidomide 10 mg orally once daily or placebo for up to 12 weeks in the treatment phase. Concomitant therapy for CRPS pain (opioid and nonopioid analgesics, nonsteroidal anti-inflammatory drugs, anticonvulsants, antidepressants, and other nondrug therapies) was permitted if the dose/regimen had been stable for ≥4 weeks before randomization and remained stable throughout the study. No new CRPS medications or nondrug therapies were allowed except for limited use of a rescue medication (short-acting opioid for no more than 7 days) to treat pain flare, trauma, or invasive procedure. During the extension phase, subjects were permitted to initiate, reduce, increase, or withdraw from concomitant CRPS pain medications/nondrug therapies except for initiating experimental therapies.

Randomization codes were generated by a Celgene statistician not involved in the study using a randomization program in the Statistical Analysis Software system. Randomization was performed centrally across all centers using blocked randomization with a block size of 4. Eligible patients were randomized in a 1:1 ratio to 1 of the 2 treatment groups. Sites were provided with drug for 4 subjects at a time, and additional shipments were sent as required. Each qualifying subject was assigned the next sequential number in the series of numbers assigned to the site. Code-break envelopes were provided in the boxes containing the drug, and site personnel were instructed to contact the Celgene Medical Monitor before breaking the code. The Celgene Clinical Supplies group worked with Xeremis, which packaged the drugs. All subjects completing the entire 12-week double-blind phase were eligible for the extension phase. Subjects first randomized to placebo were allowed to cross over to lenalidomide 10 mg/d and continue treatment in the extension phase.

The study protocol, amendments, and informed consent form were approved by the institutional review board at each site, and the study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. All subjects provided written informed consent before initiating study procedures.

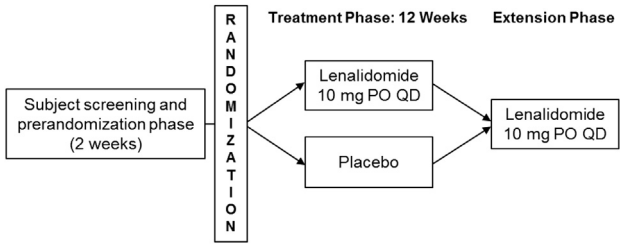

Figure 1. Study design.

Dose Selection

The lenalidomide dose for continuous dosing in myelodysplastic syndrome starts at 10 mg/d and can be adjusted downward for renal function. For intermittent dosing, such as for multiple myeloma, the dose can start at 25 mg/d for a defined portion of the chemotherapeutic cycle. AEs in general were dose related. Preliminary data from the open-label study in CRPS showed lenalidomide to be well tolerated with an expected AE profile. Subjects who responded to lenalidomide 10 mg/d reported return of their CRPS if their dose was reduced to 5 mg/d because of AEs, and most chose to resume 10 mg/d to complete the study. On the basis of the requirement for continuous dosing as well as experience in other patient populations, lenalidomide 10 mg/d was selected as the study dose.

Efficacy and Safety Assessments and Endpoints

Subjects used an electronic diary to collect daily morning and evening efficacy assessment data, including the PI-NRS. The PI-NRS was presented twice per day at set consistent times (morning and evening) as a discrete 11-box Likert scale from 0 (no pain) to 10 (worst pain imaginable) with the instructions "Please rate your pain due to CRPS right now." The primary efficacy endpoint was the PI-NRS responder rate, with response defined as completion of the treatment phase with a ≥30% reduction from baseline (ie, improvement) in the 7-day averaged morning and evening PI-NRS score for the week before the week 12 assessment as compared with the 7-day averaged morning and evening PI-NRS scores during the baseline period. The secondary efficacy endpoints included change from baseline in the Short-Form McGill Pain Questionnaire total score and sensory and affective subscale scores, pain intensity ratings (combined morning and evening assessments) using PI-NRS in the index limb, sleep rating (NRS), activity level rating (NRS), subject's assessment of CRPS signs and symptoms in the index limb, allodynia NRS score, allodynia rating between the index limb and the normal limb at the end of week 12 (unilateral CRPS subjects only), and concomitant use of pain medications.

Safety assessments included type, frequency, and severity of AEs; physical examination; vital signs; and laboratory test results. A battery of noninvasive nerve conduction studies were included as a safety measure to explore the possibility of lenalidomide-induced

peripheral neuropathy, and to evaluate whether the anti-inflammatory effects of lenalidomide could improve nerve conduction. The principal electrophysiologic outcome was maximal nerve conduction velocity. Responses were recorded from sural sensory, median sensory, peroneal motor, and median motor nerves on 2 occasions before the onset of dosing and 2 occasions at the end of the initial 12-week dosing period.

Statistical Analysis

When the responder definition of this study was applied to the data from the pilot study,[35] the response rate was calculated to be 34%. Based on this, plus the 19% response rate in patients with postherpetic neuralgia who received placebo in a published study,[32] response rates for the current study were hypothesized to be 15% for placebo and 35% for lenalidomide. Using these assumptions, a sample size of 83 subjects per group would have 80% power to detect a significant difference in PI-NRS score between groups using a 2-sided, continuity-corrected χ^2 test at the .05 significance level.

The primary analysis used the modified intent-to-treat population (subjects who received at least 1 dose of study medication and had at least 1 postdose measurement). Differences in responder rates between groups were assessed using the Cochran-Mantel-Haenszel test. Subjects who discontinued the treatment phase prematurely, regardless of reason, were considered nonresponders. All comparisons used 2-tailed tests at the .05 level of significance. Summary statistics were provided for continuous outcome measures. Secondary endpoints were evaluated with an analysis of covariance model, which included terms of treatment, center, baseline score, concomitant CRPS medication change status, and treatment-by-baseline score. Analysis of covariance results presented here are for the observed cases subpopulation of the modified intent-to-treat population with no imputation for missing data, thus giving varying sample sizes, because not all data were available for all subjects.

Results

Among the 184 subjects randomized, 180 received ≥1 dose of study medication (97.8%; the safety population) and had ≥1 postdose diary measurement (the modified intent-to-treat population). The 12-week, double-blind treatment phase was completed by 68 subjects who received lenalidomide (78.2%) and 79 who received placebo (84.9%; Fig 2). The primary reason for discontinuation during this phase was AEs. These affected 14 subjects who received lenalidomide (16.1%) and 5 subjects who received placebo (5.4%). The mean duration of treatment in the double-blind treatment phase was similar between groups: 10.6 weeks with lenalidomide and 11.4 weeks with placebo. During the 12-week double-blind treatment phase, small numbers of subjects receiving lenalidomide (11; 12.6%) and receiving placebo (7; 7.5%) altered their concomitant CRPS medication (including addition, discontinuation, or dosage change).

One hundred forty-two subjects entered the extension phase (lenalidomide, n = 64; placebo, n = 78). Ninety-four subjects discontinued—among them, 45 receiving only lenalidomide (70.3%) and 49 receiving lenalidomide (62.8%) after crossing over from placebo. The primary reason for discontinuation among subjects receiving lenalidomide was lack of therapeutic effect (29.7%). Among placebo subjects who crossed over to lenalidomide, it was AEs (24.4%). The mean duration of treatment in the extension phase was 43.8 weeks for subjects receiving lenalidomide and 46.2 weeks for placebo subjects who crossed over to lenalidomide. The cumulative durations of treatment were 41.1 weeks and 49.9 weeks, respectively. The baseline demographics and characteristics of subjects are summarized in Table 1.

The study was discontinued prematurely during the extension phase because unblinding of the data from the double-blind treatment phase revealed that the primary efficacy endpoint had not been met. At week 12, 16.1% of subjects receiving lenalidomide and 16.1% receiving placebo were considered responders based on changes in PI-NRS scores. Changes (morning assessments, evening assessments, and combined morning and evening assessments) from baseline to week 12 (7-day averaged scores) did not differ between groups (Table 2). In addition, there were no significant differences between groups in change from baseline in the daily sleep assessment, Short-Form McGill Pain Questionnaire, activity level rating, and allodynia NRS score at week 12 (Table 3; no adjustment for multiplicity was made, so *P* values are for reference only).

To better understand the types of subjects in the responder and nonresponder categories, use of concomitant drugs (Table 4), nondrug therapies (Table 5), and rescue medications (Table 6) was analyzed in relation to responder status for the lenalidomide and placebo treatment groups. There were no significant differences in these outcomes between the lenalidomide and placebo groups, with responders using only slightly fewer concomitant treatments, but this did not determine responder status. The vast majority of subjects either took no rescue medication or used the described opioid-rescue protocol. More subjects in the placebo group (n = 15) than lenalidomide-treated subjects (n = 3) used nonallowed rescue therapies.

Given lenalidomide's mechanism of action, we evaluated whether subjects with higher baseline scores for potential markers of inflammation or microvasculopathy (changes in skin temperature, color, or swelling) on the subject's assessment of CRPS symptoms (Table 7) were more likely to respond. The placebo group had slightly lower assessment ratings for these symptom categories compared to the lenalidomide-treated group, but there were no appreciable differences between responders and nonresponders.

Safety Outcomes

During the double-blind treatment phase, at least 1 AE was reported by 81 subjects receiving lenalidomide (93.1%) and 76 subjects receiving placebo (81.7%).

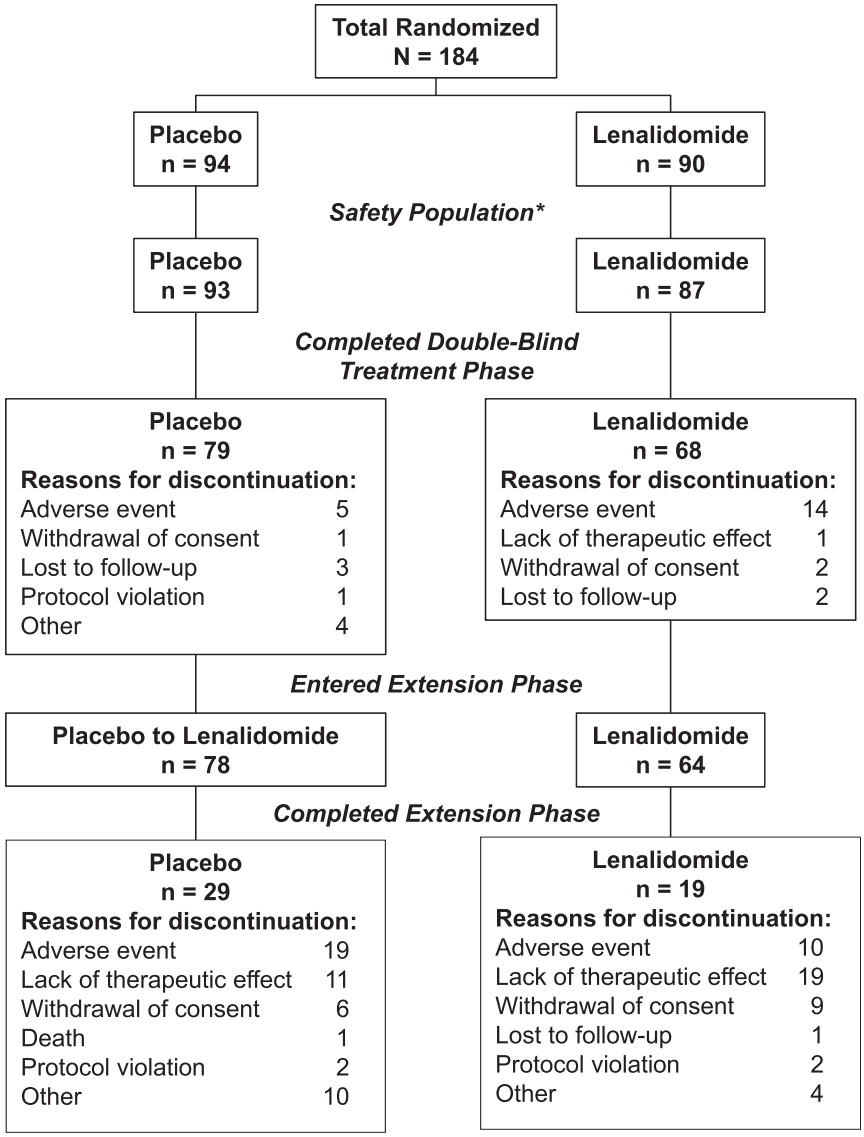

Figure 2. Subject disposition. *Defined as all subjects who took at least 1 dose of study drug.

Cumulative data for the double-blind plus open-label treatment phases indicated that at least 1 AE was reported by 83 subjects receiving lenalidomide (95.4%) and 85 placebo subjects who crossed over to lenalidomide (91.4%). The most common AEs are summarized in Table 8. In the double-blind phase, at least 1 serious AE was reported by 4 subjects receiving lenalidomide (4.6%) (ie, decreased potassium, pain, joint sprain, angioneurotic edema) and 6 receiving placebo (6.5%) (ie, increased blood pressure, neuropathic pain, vomiting, tremor, clostridium colitis, and respiratory failure); cumulative data indicated that ≥1 serious AE was reported in 12 subjects receiving lenalidomide (13.8%). This included, in addition to the above, joint sprain (n = 2), foot fracture, deep vein thrombosis, positive human chorionic gonadotropin, false-positive pregnancy test, sick sinus syndrome, pregnancy (n = 2), neuropathic pain, spontaneous abortion, and arthritis. Sixteen placebo subjects who crossed over to lenalidomide (17.2%) also reported accidental overdose, hip fracture, deep vein thrombosis (n = 2), bradycardia, thyroiditis, adrenal insufficiency, cholecystitis, gallbladder obstruction, allergic alveolitis, hemolytic anemia, thrombotic thrombocytopenic purpura, upper abdominal pain, vomiting, or endometriosis. Treatment-related AEs led to discontinuation in 18 subjects receiving lenalidomide (20.7%) and 5 receiving placebo (5.4%); cumulative data showed that treatment-related AEs led to discontinuation in 29 subjects receiving lenalidomide (33.3%) and 29 placebo subjects who crossed over to lenalidomide (31.2%). Most AEs leading to discontinuation were grade 1 (mild) or 2 (moderate). AEs led to dose reduction in 11 subjects receiving lenalidomide (12.6%) and 2 receiving placebo (2.2%) during the double-blind phase. The most common AE leading to reduction of lenalidomide was rash (3.4% of subjects), and the 2 AEs in the placebo group were clostridium colitis and conjunctivitis. Few shifts in laboratory values from baseline were noted in the double-blind treatment phase and the extension phase; of those that were different, few were reported

Table 1. Subject Demographic and Baseline Characteristics

Characteristic	Lenalidomide (N = 87)	Placebo (N = 93)	Total (N = 180)
Age, y, M (SD)	43.9 (11.4)	45.1 (11.1)	44.5 (11.2)
Age distribution, n (%)			
≤65 y	83 (95)	89 (96)	172 (96)
>65 y	4 (5)	4 (4)	8 (4)
Sex, n (%)			
Male	22 (25)	14 (15)	36 (20)
Female	65 (75)	79 (85)	144 (80)
Race/ethnicity, n (%)			
White	81 (93)	86 (93)	167 (93)
Black	3 (3)	4 (4)	7 (4)
Hispanic	1 (1)	3 (3)	4 (2)
Asian/Pacific Islander	2 (2)	0 (0)	2 (1)
Baseline CRPS PI-NRS score, M (SD)*	7.2 (1.4) (n = 85)	7.0 (1.7) (n = 92)	–
Daily sleep assessment average score, M (SD)	5.4 (1.1) (n = 85)	5.5 (1.3) (n = 92)	–

Abbreviations: M, mean; SD, standard deviation.
*Combined morning and evening assessments, based on a 0–10 scale, with higher ratings indicating more severe pain.

as AEs. Likewise, no notable shifts in thyroid function or vital sign parameters (diastolic and systolic blood pressure, pulse, temperature) were reported.

The pattern and variance of the electrophysiologic measures in the current study were consistent with previous reports for multicenter clinical trials of pain.[2] There were no significant differences in mean changes from baseline to study termination for the 2 sensory or the 2 motor nerve velocities. Lenalidomide, at the doses and for the duration tested, was not associated with slowing of velocity, reduction in amplitude, or exacerbation of peripheral neuropathy.

Discussion

This phase IIb study evaluated the efficacy and safety of oral lenalidomide 10 mg once daily in subjects with CRPS type 1 based on pilot data indicating that lenalidomide had acceptable safety and some evidence of efficacy in CRPS.[35] Although the current outcomes show no differences in efficacy between lenalidomide and placebo for the primary and secondary endpoints, subjects tolerated daily lenalidomide for up to 2 years without significant safety issues, demonstrating that lenalidomide can be well tolerated in a population other than cancer patients. Importantly, all AEs reversed after lenalidomide was discontinued, and neurophysiologic surveillance revealed no evidence of treatment-induced peripheral neuropathy, in distinction to the neuropathy associated with thalidomide use.[28]

Both the pilot study and the phase IIb study helped identify design elements to consider for future CRPS trials. For efficiency purposes, we reevaluated the assessment tools and general tolerability measures used in the open-label pilot study, acknowledging that the potential for false positives was high, but the small sample ensured that fewer subjects would be exposed to the

Table 2. CRPS PI-NRS Summary of Change From Baseline at Week 12 in Observed Cases

	Lenalidomide				Placebo				
PI-NRS	Baseline	Week 12	Change	Adjusted Change*	Baseline	Week 12	Change	Adjusted Change*	P Value†
AM + PM, M (SD)	(n = 80) 7.1 (1.4)	(n = 80) 6.5 (2.1)	(n = 80) −.7 (1.7)	−.71	(n = 88) 7.0 (1.6)	(n = 88) 6.6 (2.3)	(n = 88) −.4 (1.5)	−.43	.26
AM, M (SD)	(n = 80) 6.9 (1.5)	(n = 80) 6.3 (2.1)	(n = 80) −.6 (1.7)	−.63	(n = 88) 6.9 (1.7)	(n = 88) 6.5 (2.3)	(n = 88) −.3 (1.5)	−.36	.28
PM, M (SD)	(n = 80) 7.3 (1.4)	(n = 80) 6.6 (2.1)	(n = 80) −.7 (1.7)	−.78	(n = 87) 7.1 (1.6)	(n = 87) 6.7 (2.3)	(n = 87) −.4 (1.5)	−.51	.27

Abbreviations: M, mean; SD, standard deviation.
*Adjusted mean change from baseline in Pain Intensity Ratings (observed cases) at week 12. No imputation was employed for these data. Negative change indicates improvement.
†No adjustment for multiplicity was made, because the *P* value is for reference only; the *P* value is from the analysis of covariance model adjusting for center and baseline score.

Table 3. Summary of Selected Secondary Efficacy Assessments

Mean Adjusted Change From Baseline at Week 12	Lenalidomide	Placebo	P Value*
Daily sleep assessment	(n = 85)	(n = 92)	.35
	−.11	−.24	
SF-MPQ	(n = 85)	(n = 92)	
Total	−6.36	−3.94	.09
Sensory	−4.55	−2.85	.12
Affective	−1.77	−1.15	.16
Activity level rating (NRS)	(n = 85)	(n = 85)	.90
	.17	.19	
Allodynia NRS score	(n = 76)	(n = 87)	.16
	3.65	4.37	

Abbreviation: SF-MPQ, Short-Form McGill Pain Questionnaire.
*No adjustment for multiplicity was made, because the *P* value is for reference only; the *P* value is from the analysis of covariance model adjusting for center and baseline score.

experimental agent in this initial study. The open-label pilot study accurately predicted safety, but not efficacy, in the current, adequately powered, controlled study. The lenalidomide 10-mg/d dose was well tolerated in this study; however, some AEs were observed. Given

Table 4. Concomitant Medication Use During the Study Treatment Phase

Treatment Group and Outcome Status	Concomitant Medications								
	TotM	AD	MR	OP	LA	AC	NSAID	BZ	Other
Lenalidomide									
Total									
n	86	18	17	66	11	39	16	7	21
M	2.9	.2	.2	.8	.1	.5	.2	.1	.2
Responder									
n	14	3	2	10	2	9	3	0	2
M	2.6	.2	.1	.7	.1	.6	.2	.0	.1
Nonresponder									
n	72	15	15	56	9	30	13	7	19
M	3.0	.2	.2	.8	.1	.4	.2	.1	.3
Placebo									
Total									
n	90	18	24	69	10	43	17	7	15
M	2.7	.2	.2	.8	.1	.5	.2	.1	.2
Responder									
n	15	2	5	9	2	7	4	0	2
M	2.3	.1	.3	.6	.1	.5	.3	.0	.1
Nonresponder									
n	75	16	19	60	8	36	13	7	13
M	2.7	.2	.1	.8	.1	.5	.2	.1	.2

Abbreviations: TotM, total medications used, including multiple agents within a class; AD, antidepressants, including tricyclic agents; MR, muscle relaxants and baclofen; OP, opioids; LA, local anesthetic preparations; AC, anticonvulsants, including gabapentin and pregabalin; NSAID, nonsteroidal anti-inflammatory agents; BZ, benzodiazepines, including clonazepam; Other, alpha adrenergic agents, mexiletine, and acetaminophen; M, mean.
NOTE. The n value reflects the incidence of a particular category of medication used during the treatment phase. If >1 medication from a category was used by a subject, each unique medication was counted separately. The average incidence of medication use is the total incidence divided by the total subjects in that group. Four subjects (3 receiving placebo and 1 receiving lenalidomide) do not have concomitant medication data.

Table 5. Concomitant Nondrug Therapy (Double-Blind Phase)

Nondrug Therapy	Lenalidomide, n		Placebo, n	
	Total (n = 87)	Responders (n = 14)	Total (n = 93)	Responders (n = 15)
None	72	0	82	0
TENS	3	0	2	0
Acupuncture	5	1	1	
Spinal cord stimulation	1	0	3	2
Psychological treatment	2	0	0	0
Physical therapy	10	4	7	1
Chiropractic therapy	0	0	2	0
Stellate ganglia blocks	1	1	0	0

Abbreviation: TENS, transcutaneous electrical nerve stimulation.
NOTE. The total will not equal the sample size as some subjects received >1 concomitant drug therapy.

the lack of clear efficacy and the dose dependency of AEs with moderate to long-term administration of lenalidomide, higher doses approaching 25 mg are not advised. The quantitative sensory testing and measurements of limb volume used in the pilot study, initially thought important to include, proved difficult to execute and were inconsistently applied in the pilot, and thus they were not employed in this study, which focused on pain endpoints. Streamlining the battery of assessments was judged to be critical for larger studies. In future studies of CRPS, the need for objective assessments in pain clinical research must be balanced by feasibility considerations.[17]

The current study is the largest controlled study of people with CRPS and one of the first to employ the Budapest research criteria for defining CRPS. These provide a useful tool for carefully selecting subjects, but this symptom-based definition does not address potential heterogeneity in etiology or disease mechanisms, which may have affected study results. This study was

Table 6. Rescue Medication Use (Double-Blind Phase)

Rescue Medication	Lenalidomide, n		Placebo, n	
	Total (n = 87)	Responders (n = 14)	Total (n = 93)	Responders (n = 15)
None	72	8	61	10
Opioids	12	4	17	4
Acetaminophen	2	0	1	0
NSAID	3	0	5	0
Steroids	1	1	2	1
Muscle relaxants	2	1	4	0
Clonazepam	1	0	0	0
Lidoderm patch	1	0	0	0
Antiepileptic drug	0	0	3	0
Other	0	0	1*	0

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.
NOTE. The total will not equal the sample size, as some subjects received >1 concomitant drug therapy.
*Isometheptene mucate, dichloralphenazone, and acetaminophen combination for migraine.

Table 7. Subject Assessment of CRPS Signs and Symptoms at Baseline Sorted by Treatment Phase Responders and Nonresponders

	Total Data		Nonresponders		Responders	
CRPS Signs and Symptoms	Lenalidomide (N = 67)	Placebo (N = 83)	Lenalidomide (N = 57)	Placebo (N = 69)	Lenalidomide (N = 10)	Placebo (N = 14)
Skin sensitivity						
M	2.4	2.4	2.5	2.5	2.3	1.9
SD	.8	.7	.8	.7	.8	.6
Deep joint pain						
M	2.3	2.3	2.3	2.3	2.2	1.9
SD	.8	.9	.8	.8	1.0	1.1
Temperature						
M	2.1	2.0	2.1	2.0	2.1	2.0
SD	.8	.8	.9	.8	.6	.8
Color						
M	2.0	1.7	2.0	1.7	2.0	1.7
SD	.8	.9	.8	.9	.8	1.0
Swelling						
M	1.9	1.7	1.9	1.7	1.9	1.7
SD	.9	.9	.9	1.0	.8	.8
Sweating						
M	1.4	1.3	1.4	1.4	1.2	.8
SD	1.1	1.1	1.1	1.1	1.1	.9
Range of motion						
M	2.2	2.2	2.2	2.2	2.5	2.1
SD	.9	.9	.9	.9	.8	1.0
Start movement						
M	2.1	2.0	2.1	2.1	2.3	1.5
SD	.8	1.0	.9	.9	.6	1.1
Tremor						
M	1.4	1.5	1.4	1.6	1.4	1.2
SD	1.0	1.0	1.0	1.0	1.0	1.2
Cramp/spasms						
M	1.8	1.8	1.9	1.9	1.4	1.2
SD	1.0	1.0	1.0	.9	.8	1.1
Skin, hair, and nail symptoms						
M	1.6	1.3	1.5	1.4	1.6	1.0
SD	1.1	1.0	1.1	1.0	1.1	.9
Skin ulcer/sores						
M	.4	.8	.4	.9	.0	.4
SD	.9	1.3	1.0	1.4	.0	.9

Abbreviations: M, mean; SD, standard deviation.

NOTE. In the assessment of CRPS symptoms, subjects were presented with 12 questions based on the Budapest Criteria for the Diagnosis of CRPS.[17] Only subjects with unilateral limb involvement of CRPS completed the assessment. Each question asked the subjects to compare or rate the difference between the index (of CRPS affected) limb and the normal (nonaffected) side "over the past week including today." The responses are given as 1 to 4, with 1 being no difference, 2 minimal difference, 3 moderate difference, and 4 extreme or great difference compared with normal. The only exception to this pattern was question 12 regarding skin ulcers or sores. In this question, subjects were asked to assess their skin on a 5-point graded scale, with 1 being no ulcers or sores, 2 healed ulcers or sores, 3 healing ulcers or sores, 4 nonhealing or open ulcers or sores, and 5 new ulcers or sores since last visit. Data presented are for subjects who completed the baseline subject's assessment of CRPS signs and symptoms; the scale is expressed as mean score and standard deviation. In the lenalidomide group, 20 subjects did not have baseline values for CRPS signs and symptoms (including 4 responders). In the placebo group, 10 subjects did not have baseline values for CRPS signs and symptoms (including 1 responder).

initiated in 2005, when only limited early cytokine research (particularly for TNF-α) was available. In the future, selecting subjects based on biomarker analysis or similar mechanisms may allow potential therapies to be better targeted to subsets of potentially responsive subjects, as is becoming routine in cancer treatment. In this study of a population not enriched for any specific characteristics of CRPS subtypes, the degree of inflammatory symptoms did not predict responder status. Cluster analysis has revealed distinct CRPS populations, identifying a subgroup with significant increases in plasma cytokines, chemokines, and their soluble receptors.[1] This subgroup might be a better target for trials of immunomodulatory agents. In addition to altered plasma cytokine levels, other significant changes reported in people with CRPS include altered levels of plasma amino acids,[41] serum and saliva antioxidative parameters,[11] blood levels of inflammatory monocytes,[31] and altered intestinal microbial communities.[29] These markers might help define subgroups amenable to specific treatments.

Duration of CRPS is another consideration for trial design. Persistent CRPS is often complicated by structural changes (eg, contractures, bone resorption) that can be painful due to independent mechanisms that would

Table 8. Adverse Events Reported in ≥10% of Subjects

	Double-Blind Phase		Cumulative Adverse Events		
Adverse Event	Lenalidomide (N = 87)	Placebo (N = 93)	Lenalidomide (N = 87)	Placebo-to-Lenalidomide (N = 93)	Total (N = 180)
Rash (NOS)	27 (31)	9 (10)	32 (37)	34 (37)	66 (37)
Diarrhea	11 (13)	11 (12)	23 (26)	26 (28)	49 (27)
Nausea	14 (16)	18 (19)	19 (22)	24 (26)	43 (24)
Fatigue	10 (12)	12 (13)	14 (16)	21 (23)	35 (19)
Insomnia	7 (8)	5 (5)	12 (14)	13 (14)	25 (14)
Dizziness	9 (10)	6 (7)	13 (15)	10 (11)	23 (13)
Pruritus	10 (12)	4 (4)	13 (15)	11 (12)	24 (13)
Sinusitis (NOS)	5 (6)	3 (3)	12 (14)	16 (17)	28 (16)
Constipation	9 (10)	6 (7)	11 (13)	16 (17)	27 (15)
Headache	9 (10)	14 (15)	11 (13)	24 (26)	35 (19)
Nasopharyngitis	7 (8)	5 (5)	11 (13)	14 (15)	25 (14)
Pyrexia	6 (7)	4 (4)	11 (13)	8 (9)	19 (11)
Pharyngitis	6 (7)	4 (4)	10 (12)	7 (8)	17 (9)
Vomiting (NOS)	5 (6)	5 (5)	9 (10)	10 (11)	19 (11)
URI (NOS)	1 (1)	3 (3)	9 (10)	10 (11)	19 (11)
Muscle cramp	5 (6)	6 (7)	7 (8)	9 (10)	16 (9)
UTI (NOS)	5 (6)	7 (8)	6 (7)	17 (18)	23 (13)
Fall	3 (3)	6 (7)	6 (7)	13 (14)	19 (11)
Contusion	4 (5)	6 (7)	6 (7)	8 (9)	14 (8)

Abbreviations: NOS, not otherwise specified; URI, upper respiratory infection; UTI, urinary tract infection.
NOTE. Values are n (%).

not be expected to respond to the same therapies. The inflammatory contribution to CRPS pain may be more important early, with neuropathic and structural causes of pain dominating later.[16,20,21] For instance, the changed cytokine profiles in CRPS type 1–affected limbs reportedly resolve within the first 6 months after onset.[23] In addition, chronic pain is associated with changes in central mechanisms that can sustain it. In a mouse model of arthritis, early pain responded to anti-inflammatory agents such as ketorolac and etanercept, but later, only gabapentin produced analgesia.[5] What appears early to be an inflammatory disease, if prolonged, may evolve into a more neuropathic condition. The chronic, variable duration of CRPS in the current study (≥1 year) likely contributed to a mechanistically heterogeneous sample in which subjects may have comorbid conditions related to immobility and contractures also contributing to pain. We recommend that future studies of CRPS treatments consider disease duration. Of note, early CRPS has a high rate of spontaneous resolution that complicates assessment of treatment benefits.

Future studies might also consider subjects' use of concomitant medications. This study enrolled many subjects with significant pain despite polypharmacy. On average, the subjects enrolled took >2 and as many as 10 concomitant medications, with no relationship to response status. Perhaps they represent the intractable subset, and no further pharmacotherapy would be efficacious. Enrolling treatment-naïve patients or patients who have used just a few medications should be considered.

Study design details also influence outcomes. For example, randomized withdrawal paradigms are gaining popularity in analgesic trials. Here, subjects are treated with active medication until optimal benefit is attained, and then they are randomly assigned to continue using active medication or placebo. This can help enrollment because every subject receives active medication at the beginning, and return of pain may not be as susceptible to placebo response as the onset of pain relief.[18] Randomized withdrawal design studies; studies incorporating single-blind or double-blind, variable-duration, placebo run-in phases; or other methods might better distinguish between treatment and placebo responses. Databases of clinical trials for other neuropathic pain indications could be examined to identify study design factors that can influence study outcomes.[10]

In summary, because the current study found no evidence of efficacy of lenalidomide in the sample studied, despite its relative safety, it cannot be endorsed for the broad population of people with CRPS. Given that failure rates are high in parallel-group, placebo-controlled trials of pain therapies, it may be reasonable to consider additional study of lenalidomide in specific subgroups of patients. Factors to consider in designing future CRPS trials include better characterization of potential subjects, stratification by disease duration, use of concomitant medications, and selection of outcome measures. The findings demonstrate the feasibility of conducting large, controlled studies in CRPS patients. Our hope is that elements of this study design will enhance and advance the search for other therapies to treat CRPS.

Acknowledgments

The authors would like to thank Jerome B. Zeldis, MD, PhD, and Herbert Faleck, DO, for their assistance with study design.

References

1. Alexander GM, Peterlin BL, Perreault MJ, Grothusen JR, Schwartzman RJ: Changes in plasma cytokines and their soluble receptors in complex regional pain syndrome. J Pain 13: 10-20, 2012

2. Arezzo JC, Rosenstock J, LaMoreaux L, Pauer L: Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: A double-blind placebo-controlled trial. BMC Neurol 8:33, 2008

3. Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B: Neurological findings in complex regional pain syndromes—Analysis of 145 cases. Acta Neurol Scand 101: 262-269, 2000

4. Celgene Corporation Web site. Revlimid® granted approval for treatment of relapsed or refractory multiple myeloma in Japan [press release]. June 24, 2010. Available at: http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-newsArticle&ID=1441682&highlight. Accessed January 10, 2014

5. Christianson CA, Corr M, Firestein GS, Mobargha A, Yaksh TL, Svensson CI: Characterization of the acute and persistent pain state present in K/BxN serum transfer arthritis. Pain 151:394-403, 2010

6. Corral LG, Kaplan G: Immunomodulation by thalidomide and thalidomide analogues. Ann Rheum Dis 58(Suppl 1): I107-I113, 1999

7. Costigan M, Scholz J, Woolf CJ: Neuropathic pain: A maladaptive response of the nervous system to damage. Annu Rev Neurosci 32:1-32, 2009

8. de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC: The incidence of complex regional pain syndrome: A population-based study. Pain 129:12-20, 2007

9. Dirckx M, Stronks DL, Groeneweg G, Huygen FJ: Effect of immunomodulating medications in complex regional pain syndrome: A systematic review. Clin J Pain 28:355-363, 2012

10. Dworkin RH, Katz J, Gitlin MJ: Placebo response in clinical trials of depression and its implications for research on chronic neuropathic pain. Neurology 65:S7-19, 2005

11. Eisenberg E, Shtahl S, Geller R, Reznick AZ, Sharf O, Ravbinovich M, Erenreich A, Nagler RM: Serum and salivary oxidative analysis in Complex Regional Pain Syndrome. Pain 138:226-232, 2008

12. European Medicines Agency Web site. Revlimid [summary of product characteristics]. July, 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Product_Information/human/000717/WC500056018.pdf. Accessed January 10, 2014

13. Goebel A: Complex regional pain syndrome in adults. Rheumatology (Oxford) 50:1739-1750, 2011

14. Goebel A, Baranowski A, Maurer K, Ghiai A, McCabe C, Ambler G: Intravenous immunoglobulin treatment of the complex regional pain syndrome: A randomized trial. Ann Intern Med 152:152-158, 2010

15. Goebel A, Barker CH, Turner-Stokes L: Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care. London, UK, Royal College of Physicians, 2012. Available at: http://www.rcplondon.ac.uk/sites/default/files/documents/complex-regional-pain-full-guideline.pdf. Accessed January 10, 2014

16. Groeneweg JG, Huygen FJ, Heijmans-Antonissen C, Niehof S, Zijlstra FJ: Increased endothelin-1 and diminished nitric oxide levels in blister fluids of patients with intermediate cold type complex regional pain syndrome type 1. BMC Musculoskelet Disord 7:91, 2006

17. Harden RN: Objectification of the diagnostic criteria for CRPS. Pain Med 11:1212-1215, 2010

18. Hewitt DJ, Ho TW, Galer B, Backonja M, Markovitz P, Gammaitoni A, Michelson D, Bolognese J, Alon A, Rosenberg E, Herman G, Wang H: Impact of responder definition on the enriched enrollment randomized withdrawal trial design for establishing proof of concept in neuropathic pain. Pain 152:514-521, 2011

19. Hideshima T, Chauhan D, Shima Y, Raje N, Davies FE, Tai YT, Treon SP, Lin B, Schlossman RL, Richardson P, Muller G, Stirling DI, Anderson KC: Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood 96:2943-2950, 2000

20. Huygen FJ, de Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ: Evidence for local inflammation in complex regional pain syndrome type 1. Mediators Inflamm 11:47-51, 2002

21. Huygen FJ, Niehof S, Zijlstra FJ, van Hagen PM, van Daele PL: Successful treatment CRPS1 with anti-TNF. J Pain Symptom Manage 27:101-103, 2004

22. International Association for the Study of Pain, IASP Taxonomy Working Group. International Association for the Study of Pain (IASP) website. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Second edition (revised). 2012. Available at: http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf. Accessed October 27, 2014

23. Lenz M, Uçeyler N, Frettlöh J, Höffken O, Krumova EK, Lissek S, Reinersmann A, Sommer C, Stude P, Waaga-Gasser AM, Tegenthoff M, Maier C: Local cytokine changes in complex regional pain syndrome type I (CRPS I) resolve after 6 months. Pain 154:2142-2149, 2013

24. Oaklander AL, Fields HL: Is reflex sympathetic dystrophy/complex regional pain syndrome type I a small-fiber neuropathy? Ann Neurol 65:629-638, 2009

25. Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R: Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). Pain 120:235-243, 2006

26. Parkitny L, McAuley JH, Di Pietro F, Stanton TR, O'Connell NE, Marinus J, van Hilten JJ, Moseley GL: Inflammation in complex regional pain syndrome: A systematic review and meta-analysis. Neurology 80:106-117, 2013

27. Perez RS, Zollinger PE, Dijkstra PU, Thomassen-Hilgersom IL, Zuurmond WW, Rosenbrand KC, Geertzen JH: Evidence based guidelines for complex regional pain syndrome type 1. BMC Neurol 10:20, 2010

28. Rajkumar SV, Fonseca R, Witzig TE: Complete resolution of reflex sympathetic dystrophy with thalidomide treatment [letter]. Arch Intern Med 161:2502-2503, 2001

29. Reichenberger ER, Alexander GM, Perreault MJ, Russell JA, Schwartzman RJ, Hershberg U, Rosen G: Establishing a relationship between bacteria in the human gut and complex regional pain syndrome. Brain Behav Immun 29: 62-69, 2013

30. Revlimid [package insert]. Summit, NJ, Celgene Corporation, September 2014

31. Ritz BW, Alexander GM, Nogusa S, Perreault MJ, Peterlin BL, Grothusen JR, Schwartzman RJ: Elevated blood levels of inflammatory monocytes (CD14+ CD16+) in patients with complex regional pain syndrome. Clin Exp Immunol 164:108-117, 2011

32. Sabatowski R, Galvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P, Versavel M: Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: Results of a randomised, placebo-controlled clinical trial. Pain 109:26-35, 2004

33. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA: Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain 103:199-207, 2003

34. Scholz J, Woolf CJ: The neuropathic pain triad: Neurons, immune cells and glia. Nat Neurosci 10:1361-1368, 2007

35. Schwartzman R, Irving G, Wallace M, Rauck R, Dogra S, Raja S, Cooper A, Faleck H, Zeldis J, Manning D: A multicenter, open-label 12-week study with extension to evaluate the safety and efficacy of lenalidomide (CC-5013) in the treatment of complex regional pain syndrome type 1 [poster 1627–P130]. Presented at 11th World Congress on Pain, Sydney, Australia, August 21-26, 2005

36. Schwartzman RJ, Chevlen E, Bengtson K: Thalidomide has activity in treating complex regional pain syndrome. Arch Intern Med 163:1487-1488, 2003

37. Sherman D, McCormick GE: Celgene wins Chinese regulatory OK for Revlimid. New York, NY, Thomson Reuters, 2013. Available at: http://in.reuters.com/article/2013/02/11/us-celgene-revlimid-idINBRE91A0KC20130211. Accessed January 10, 2014

38. Sudeck P: Über die akute entzuü ndliche knochenatrophie. Arch Klin Chir 62:147-156, 1900

39. Uceyler N, Eberle T, Rolke R, Birklein F, Sommer C: Differential expression patterns of cytokines in complex regional pain syndrome. Pain 132:195-205, 2007

40. Veldman PH, Reynen HM, Arntz IE, Goris RJ: Signs and symptoms of reflex sympathetic dystrophy: Prospective study of 829 patients. Lancet 342:1012-1016, 1993

41. Wesseldijk F, Fekkes D, Huygen FJ, Heide-Mulder M, Zijlstra FJ: Increased plasma glutamate, glycine, and arginine levels in complex regional pain syndrome type 1. Acta Anaesthesiol Scand 52:688-694, 2008

42. Woolf CJ: Central sensitization: Implications for the diagnosis and treatment of pain. Pain 152:S2-S15, 2011