CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-785

Medical Review(s)

Supervisory Review of NDA 20-785
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I. INTRODUCTION

This is a supervisory medical review of NDA 20-785, a marketing application submitted by Celgene Corporation for thalidomide (trade name Thalomid) for the treatment of erythema nodosum leprosum (ENL), a designated orphan indication. The application was originally submitted on 12/24/96.

The drug thalidomide has a long FDA history. Thalidomide was approved in Europe in 1957. A US marketing application was reviewed by the Agency in 1960 and was not approved because of concerns about neuropathy associated with use of the drug. While the Agency was awaiting answers to these concerns, the link between thalidomide use and an epidemic of congenital malformations (phocomelia and other organ defects) occurring in Europe was recognized and the drug was withdrawn from marketing. The tragedy played a part in the debate around the 1962 amendments to the Federal Food, Drug, and Cosmetic Act that resulted in specific effectiveness requirements for drugs.

A chance observation in the 1960's suggested that thalidomide might be useful in the treatment of patients with erythema nodosum leprosum (ENL), an inflammatory complication of certain forms of Hansen's Disease. Subsequently, many controlled and uncontrolled trials were published in the medical literature reporting effectiveness of the drug in controlling the cutaneous manifestations of ENL, and the drug was recommended by the World Health Organization as effective in this disorder. In the US, thalidomide has been made available under IND for over 20 years to patients with ENL being treated at the National Hansen's Disease Center in Carville, Louisiana, under the auspices of the US Public Health Service. A stable source of high-quality product could not be obtained for this use, and the Hansen's Disease Center often had to formulate a final dosage form from imported bulk drug. The US FDA provided assistance in maintaining product availability by testing the bulk product.

Celgene is seeking approval to market thalidomide for this indication.

II. PURPOSE OF SUPERVISORY REVIEW

The Celgene application for thalidomide was considered by FDA's Dermatologic and Ophthalmic Drugs Advisory Committee on Sept. 4-

5, 1997. After presentations by FDA and Celgene, as well as interested members of the public, including representatives from the Canadian Thalidomide Victims Association, the Committee voted 6-1 that thalidomide is effective for the treatment of the cutaneous lesions of ENL. Subsequently, on Sept 9-10, 1997, an open public scientific workshop was held to discuss the potential benefits and risks of thalidomide.

A number of important issues were raised about the use of thalidomide in ENL, either at the Advisory Committee, or at the workshop, or both. As is common in matters of regulatory judgment, there have been differences of opinion about these issues. This review is intended to provide FDA's final conclusions regarding the issues and the basis for those conclusions. In addition, this review concurs with the decision of the Director of the reviewing Office of New Drug Evaluation Office, where the authority for approval of new molecular entities reviewed by the Office is delegated.

The issues addressed in this review include: the basis for concluding that thalidomide is effective in the treatment of ENL; the basis for "bridging" the literature data (derived from other manufacturers' products) to the Celgene product and making dosing recommendations; the safety evaluation in ENL; and the adequacy of the restricted distribution program proposed by the firm. These will be addressed in sequence. The Celgene application has been reviewed by all relevant disciplines, and those reviews are documented. Therefore, this review does not attempt to be comprehensive or to address all areas of the application.

III. EVALUATION OF THE EFFECTIVENESS DATA IN ENL

A. Data Sources

The Celgene NDA is primarily a literature submission for the purposes of effectiveness data. It contains additional primary information for one of the published trials (Hastings, et al) that was obtained during an attempt to reconstruct the records for the trial from the patients' hospital notes from many decades ago (see III.B.3.b). In addition, effectiveness data were obtained from medical records of treatment made available under IND 11,359 held by the Public Health Service and submitted under the NDA (see III.C).

B. Published Literature

1. Two double-blind controlled trials evaluated the effectiveness of 100 mg thalidomide four times daily in

controlling the cutaneous manifestations of ENL. They are discussed in the following:

a. *Iyer GCS, Languillon J, Ramanujam K, Tarabini-Castellani G, Terencio De Las Aguas J, Bechelli LM, Uemura K, Dominguez V and Sundaresan T. "WHO Coordinated Short-Term Double-Blind Trial with Thalidomide in the Treatment of Acute Lepra Reactions in Male Lepromatous Patients" Bull World Health Org 1971, 45, 719.*

This active controlled trial compared the effects of a 7-day course of 100 mg thalidomide four times a day to 400 mg aspirin four times a day.

This was a double-blind, crossover trial conducted at four centers around the world under the auspices of the World Health Organization.

Inclusion criteria: Men only. Clearly demonstrable dermatological manifestations of ENL. Patients with neuritis were permitted to be entered. Seriously ill patients were to be excluded from the study.

Study Medications: Tablets were manufactured and bottled centrally. Bottles were assigned numbers according to a master randomization sheet. Breaking the code required inquiry to WHO.

Dosage regimen: Patients over 50 kg received study medication four times daily. Patients of lower weight received fewer daily doses.

Concomitant medications: No concomitant medications were permitted.

Schema: Patients were randomly allocated to a 7-day course of drug or active control. On day 8, patients were evaluated and those with "marked improvement" were taken off therapy; those with "slight" or "no" improvement were restarted on another 7-day course allocated by the numbering scheme to the alternate treatment, i.e., drug or active control. Markedly improved patients who later relapsed could be retreated. This continued for up to four courses.

Primary endpoint: Although the protocol was reported to have a formal statistical design, the primary endpoint was not clearly reported in the publication. The presence of fever, cutaneous lesions, and other manifestations of the lepra

reaction were evaluated at the beginning of treatment, 48 and 96 hours, and on day 8.

Other evaluations: Limited laboratory and clinical safety evaluations were reported.

Results:

92 patients were randomized initially, 57 had second courses of treatment, 39 had third courses, and 26 completed a fourth course for a total of 214 evaluations.

All patients were over age 14, a few were over age 55, the majority were young to middle aged males.

Patients: Patient characteristics were reported for the initial evaluation for each of the 214 courses of treatment. Not surprisingly, on account of the crossover design, patients were quite comparable with respect to lepra symptoms, number and duration of reactions prior to the trial, and previous therapy. Although skin lesions were required on entry, 5% of thalidomide treated patients and 4% of aspirin treated patients did not have skin lesions at the initial evaluation: presumably these were initial evaluations from courses of treatment subsequent to initial enrollment. Most patients were fairly ill, with fever, skin lesions, pain, anorexia and nerve lesions reported on initial evaluation.

Effect on temperature: Thalidomide was observed to have a marked effect on fever compared to aspirin. For example, in patients with temperatures greater than 38.5 °C, 44 were initially assigned to thalidomide and 24 to aspirin. At 48 hours 5 thalidomide treated patients and 19 aspirin treated patients still had temperatures greater than 38.5 °C, and at day 8 the numbers were 2 and 12 respectively.

Effect on skin lesions: At initial evaluation, 95% of thalidomide and 96% of aspirin patients were reported to have skin lesions. At subsequent evaluations, the following results were observed (table adapted from Table 7, p. 724 of publication):

Observation Time	State of Skin Lesions (%)		
	Improved	Absent	Unimproved
48 hours			
Thalidomide	63	6	31
Aspirin	28	6	66
96 hours			
Thalidomide	48	40	12
Aspirin	38	12	50
8 days			
Thalidomide	14	75	10
Aspirin	25	26	49

Compared to baseline (if courses in patients without skin lesions at the start [6 thalidomide and 4 Aspirin]are not counted), 75% of thalidomide courses and 25% of aspirin courses were reported to result in a complete skin response as assessed at day 8. Including improvement, responses were reported to be 90% for thalidomide and 51% for aspirin.

Effect on other lepra manifestations: There were not significant differences in outcomes at 8 days for nerve, eye, testis, or other lesions although there were trends favoring thalidomide in some areas.

Effect on relapse: Throughout the three courses of therapy where relapse could be evaluated, patients treated with thalidomide had a lower probability of subsequent relapse than aspirin-treated patients. For example, after the first course of treatment 48% of thalidomide-treated patients relapsed during the trial, while 69% of aspirin-treated patients relapsed.

Safety evaluation: This short-term trial could only evaluate safety issues related to brief administration of thalidomide. No serious adverse events were reported.

Drops in diastolic blood pressure and pulse rate over that related to aspirin therapy were observed.

Drops in total white blood cell and neutrophil counts were observed.

No significant effect on liver enzymes, renal function tests, urinalysis or sedimentation rate was observed.

No difference in reported drowsiness was noted between the two groups.

Commentary: This was a rigorously planned study conducted at multiple sites around the world under the auspices of the World Health Organization. It evaluated the effect of thalidomide in patients with fairly severe manifestations of ENL, but ENL of an acute rather than chronic nature. The dose of the aspirin active control used (1600 mg/day) would be expected to have some analgesic and antipyretic effects in adults, but probably not maximal, and certainly would not be considered an adequate anti-inflammatory dose. Therefore, the control can be considered to approximate a placebo, and this trial does not represent a comparison to an adequate dose of an antiinflammatory agent. The 22% complete skin response at 8 days on aspirin may represent the spontaneous improvement rate in this population. These patients were untreated with other medications during the duration of their evaluations, so that confounding by other therapies should not have been an issue.

Entry criteria for the trial were not rigidly specified, except that patients should have cutaneous ENL manifestations and not be severely ill. Entry criteria in trials are often designed more narrowly to decrease variability and improve the chances of detecting a drug effect; however, broad entry criteria increase the generalizabilty of the results to a wider patient population and do not necessarily imply a poor design.

Crossover designs can pose problems due to the inability to separate effects of the prior drug on the subsequent course. However, the treatment effect is large and was observed on the first course of thalidomide vs aspirin as well as subsequent courses. Additionally, the dose (and effect) of aspirin was small. Therefore, any effects from the crossover would favor aspirin and diminish the apparent effect of thalidomide.

At the 8-day assessment, little effect was found on systemic manifestations of ENL other than fever. This is not at all surprising given the short course of therapy.

Evaluation of a published report does not provide access to the primary data and therefore leaves some questions unaddressed. The major issue of concern in interpretation of the effectiveness data is the issue of adequate blinding. The design of the study appeared adequate to prevent unblinding due to characteristics of the test medication's physical characteristics. However, side effects of thalidomide, particularly drowsiness, could allow assessors

to guess treatment assignment and thus introduce bias. The study reports drowsiness as specifically absent in 58 instances in thalidomide patients and 52 instances in aspirin patients: specifically present in 6 instances in thalidomide patients and 4 instances in aspirin patients and "no information" (it is not clear if this means not recorded) in approximately equal instances for both drugs. Based on this attribution of side effects, it is not likely that assessors were able to distinguish between aspirin and thalidomide on the basis of drowsiness. However, since thalidomide has sedative properties, this remains a possibility.

Another concern is the lack of specificity about what constitutes a skin response. For this reason, "skin lesions absent" was selected by this reviewer for comparison, since this is not very subjective. It is more difficult to ascertain exactly what was meant by "skin lesions improved" when no scoring system or scale was provided. Nevertheless, if the blinding were maintained, whatever criteria were used would be applied equally to patients in each arm. Therefore, the lack of a quantitative scoring system does not invalidate the results.

In summary, this 1971 study was well-designed for its time and provides fairly convincing evidence of a beneficial effect of a short course of thalidomide on fever and skin lesions of acute ENL. It also provides evidence of prevention or delay of relapse by thalidomide therapy at 400 mg/day.

b. Sheskin J and Convit J, "Results of a Double-blind Study of the Influence of Thalidomide on the Lepra Reaction." Int J Lep 1969, 37,(2), 135.

This double-blind, placebo-controlled trial evaluated the effects of a 7-day course of 100 mg thalidomide four times a day in primarily hospitalized patients with chronic (longer than 3 months)ENL.

This was a single-center study conducted in Caracas, Venezuela.

Inclusion criteria: Men and women were entered into the study. Patients (including all women) were hospitalized or requested to report daily for evaluation. Patients were required to have lepromatous leprosy and have clearly demonstrable dermatologic, neurologic, or other

manifestations of the lepra reaction. In addition, patients had to have "at least some" additional symptoms of systemic inflammation, such as fever, adenopathy, arthralgia, and anorexia.

Study medications: Each patient was given a consecutive number upon study entry and was assigned to a numbered bottle according to a coded list. The code was not known to the investigators. A different bottle was used for each 7-day course of medication. The code was not revealed until after study completion. If a patient's condition required unblinding, the patient was dropped from the study.

Dosage regimen: Patients over 50 kg received 100 mg t.i.d., patients weighing less than 50 kg received approximately 6 mg/kg/day.

Concomitant medications: Patients on sulfone therapy were continued at a stable dose, as were patients who were receiving long-term ACTH or steroids. No other medications were permitted.

Schema: Patients were allocated to either placebo or test drug and treated for 7 days (no comment in paper on method of randomization). Patients with improvement were then discontinued from treatment and watched. Unimproved patients were continued on 7 more days of the same treatment, up to four consecutive treatments. Improved patients who relapsed were started on a new regimen.

Outcome measures: The lepra reaction was classified as R.3 (Intense or severe), R.2 (Less intense) and R.1 (General condition good) with additional coding of neuritic phenomena. The patient outcome at the end of 7 days of therapy was to be classified as total improvement (all dermatologic manifestations in an advanced state of remission, no new elements, disappearance of lepra reaction symptoms); striking improvement (approximately 50% improvement in skin lesions, no new elements); partial improvement (25% skin improvement and no new elements); no change or deterioration. Patients were scored by two observers.

Primary endpoint: A formal endpoint was not specified; analysis of the patient outcomes classified by the above measures was carried out.

Other evaluations: Clinical evaluation of side effects was performed. Skin biopsies were performed for bacteriologic and histologic evaluation. Laboratory tests were done, but not clearly reported in the publication.

Results:

- Fifty-two patients (37 male and 15 female) ranging from age 17 to 58, were enrolled. Forty-nine patients were hospitalized for most of the time. Forty-eight patients suffered from "continuous" lepra reactions, forty of the patients had a duration of lepra reaction of over 1 year.

- Over the 129 day study period, 173 treatment regimens were administered; 85 thalidomide and 88 placebo. Twenty-five patients received 4 regimens, 13 received 3, 13 received 2, and 8 were treated only once. [Seven patients were re-entered into the study and permitted more than 4 courses.]

- Effect on primary endpoint: Scoring of the primary endpoint was basically a dermatologic score that also required no deterioration in other manifestations of ENL. Of the 85 thalidomide courses, 78 were scored as improved (partial, striking or complete) for a 92% response rate, versus 24 of the 88 placebo courses, for a 27% response to placebo. If only "complete' and "striking" responses are evaluated, reflecting 50% or greater skin improvement, 66% of thalidomide courses resulted in improvement versus 10% percent of placebo-treated courses. Similarly, 51% of thalidomide courses resulted in "complete" responses, versus 5% of placebo courses. No thalidomide patients were scored as worsening on treatment, whereas 20 (23%) patients were scored as deteriorated while taking placebo.

- Other evaluations: Evaluation of improvement in erythema nodosum and erythema multiforme, as well as in constitutional symptoms such as pain, malaise, anorexia, and arthralgia followed the general pattern of the primary score. In this trial, thalidomide was also reported to have a favorable effect on neuritis in the patients who had this symptom.

Safety: Dizziness was reported in 8 cases of thalidomide administration as well as drowsiness in 20. There were no

cases in placebo. Two thalidomide patients had urticaria that "remitted spontaneously" vs none on placebo.

Commentary: This double-blind, placebo-controlled trial in patients with longstanding ENL was conducted and reported in the 1960's. The description of the trial and the data analysis are not as rigorous as those from trials conducted in the 1990's. However, sophisticated analysis is not required because of the magnitude and robustness of the treatment effect observed.

The major concern would be that the trial was effectively unblinded due to characteristics of the study medications or to side effects of thalidomide. There were 28 cases out of the 173 courses where patients reported either dizziness or drowsiness, symptoms that could lead the observer to conclude the patient was taking thalidomide. Even if all these cases were assumed to be in the thalidomide-responsive group, and if 28 responses were then discounted because of potential biased assessment of outcome, a large treatment effect of thalidomide would still be observed.

The crossover design, as the investigators themselves discovered, favors placebo when the comparator drug is active and the effect is long lasting (because patients who were responding to thalidomide but had not responded fully were switched over to placebo and continued to improve).

The patient population in this trial included individuals on stable doses of sulfones and on steroids, and who had longstanding ENL. The short-term treatment regimen evaluated in this trial is not capable of assessing definitive effects on neuritis or other serious systemic manifestations of ENL.

The results of this trial provide substantiating evidence that thalidomide is effective in the treatment of ENL.

2. A single publication reports the results of two double-blind placebo-controlled trials of 100 mg thalidomide three times daily in patients with ENL.

Waters MFR. "An Internally-Controlled Double-blind Trial of Thalidomide in Severe Erythema Nodosum Leprosum" Lepr Rev 1971, 42,26-42.

This paper reports the results of two consecutive, double-blind, placebo-controlled crossover studies in hospitalized patients with severe, chronic, steroid-dependent ENL conducted in Malaysia.

Inclusion criteria: Patients with lepromatous leprosy with severe, histologically proven ENL. Only patients requiring at least 15 mg. prednisolone or 18 international units ACTH daily for control of ENL symptoms were eligible. All patients were taking dapsone.

Study medications: Allocation to study medications was randomized. Dispensing of tablets from prepared envelopes was handled by hospital personnel separate from the assessors. Reportedly nursing staff were not aware that 2 different tablets were being used.

Dosage regimen: Placebo or 100 mg thalidomide three times daily

Concomitant medications: Patients were given 100 mg dapsone twice weekly. Aspirin, paracetamol, or other mild analgesics were given PRN.

Schema:

- First trial: This was a 16 week trial with four 4-week treatment periods. All patients were hospitalized at the start of the trial and underwent a 4-week observation period. During the second 4 weeks, patients were randomized to thalidomide or placebo. At the beginning of the third 4-week period, patients were crossed over to the other study medication. During the last 4-week period, patients were observed off study medication.

- Second trial: This trial was of identical design, except that the four periods were each 6 weeks long, for a total duration of 24 weeks.

Primary endpoint: The primary endpoint was a comparison of total weekly steroid dosage. Patients were seen 6 days a week, and their steroid dosage titrated to control fever and cutaneous ENL symptoms. Upon worsening, prednisolone dose was usually raised, but this could be supplemented by ACTH if deemed necessary. ACTH units were converted to prednisolone equivalents via a formula. The state of the ENL

was also formally assessed at the end of each week using a scoring system.

Other evaluations: Daily temperatures, weekly weight, blood counts every 2 weeks, urinalysis every 4 weeks, complete leprosy evaluation at the end of every 4 or 6 week trial phase.

Results:

- 16 week trial:

  Nine adult male patients were enrolled, ranging from 21-56 yrs of age. All had moderately severe or severe chronic ENL and were receiving a mean dose of 28 mg prednisolone (1 pt was receiving ACTH alone). The duration of ENL was from 9 months to 3½ years with continuous steroid treatment averaging 12 months. All ENL was biopsy proven.

  Effect on steroid dosage. During the 4-week run-in period, 6 of 9 patients had relatively stable steroid requirements, 2 had increases of 20-30% and 1 had a doubling of dose.

  Five patients were randomized to thalidomide in the second 4-week period. Four of the 5 had major reductions in steroid use by the end of 4 weeks: 1 patient was tapered off steroids, 3 others were reduced from 105 to 6, 140 to 43, and 140 to 48 mg prednisolone per week respectively. At the same time, the clinical condition of the ENL for these patients was scored as improved. One patient did not respond and had a markedly increased steroid dose by the end of the period.

  Four patients were randomized to placebo for the same 4 weeks. Three of the 4 required increases in steroid dosage, the fourth remained stable.

  Upon crossover in the third 4-week period, the 4 apparent thalidomide responders slowly relapsed and again required increased steroids. Three of the 4 crossed-over placebo patients had major reductions in steroid dosage on thalidomide accompanied by improvements in their ENL scores.

In the final 4 weeks, the 3 responders from the third period slowly relapsed toward their previous steroid requirements with ENL scores deteriorating.

Overall, the 7 patients responding to thalidomide had between 61-100% reductions in steroid requirements between the week preceding thalidomide and the 4 week of therapy.

- 24 week trial:

Eight patients were studied in this trial, 7 of the 8 were also in the prior trial.

Effect on steroid dosage: In the initial 6-week observation period, no patient had greater than a 25% fluctuation in steroid dosage.

In the second 6-week period, 3 patients were randomized to receive thalidomide. Two of 3 were able to stop steroids, the other had a 2/3 reduction in steroid dose. No major changes occurred for 4 of the 5 patients on placebo, 1 placebo patient had a significant (approx 50%) reduction in dosage.

In the third 6-week period, patients were crossed over. One of the thalidomide-treated patients relapsed, while the 2 who had stopped steroids remained stable. All 5 thalidomide-treated patients (crossed over from placebo) had major reductions in steroid dosage (greater than 60% reduction); 1 patient was able to stop steroids.

In the fourth 6-week period, 4 of the 5 thalidomide responders from the third period relapsed.

Other observations: In thalidomide-treated patients, decreases in white blood counts were observed (most patients had leukocytosis initially), 4 patients had rash and eosinophilia which was treated with antihistamines in 2 cases and recurred on rechallenge in these 2 cases but did not result in stopping drug. Two patients reported sleepiness in the 24 week trial only.

Commentary: This was a set of well-controlled trials in hospitalized patients conducted in Malaysia over 25 years ago. Such long duration in-hospital trials are not commonly

seen today. These trials allowed close observation and steroid dose titration for these severely affected patients.

The results of both the 16 and 24 week studies are similar. Steroid dosage was relatively stable for most patients during the initial observation period, confirming the fact that these patients had unremitting disease. The majority of patients had striking reductions in steroid requirements when thalidomide was introduced, while at the same time their ENL was scored as improved. Any effects on fever are difficult to interpret due to the as-needed provision of aspirin and paracetamol.

The lack of a washout period between treatments, as in the previous crossover designs, favors placebo when an active test drug is used. Similarly, the use of stibophen in the run-in period, and in the final study phase, mitigated against finding an effect of the test drug (assuming stibophen had an effect), but did not confound the results. Despite the small number of patients enrolled, the study demonstrated a treatment effect of thalidomide due both to the large magnitude of the effect and the power of the crossover design.

Although this trial enrolled a small number of patients, it had a very elegant design that clearly demonstrated the effectiveness of thalidomide both in the initial randomized second phase (where response of thalidomide-treated patients can be directly compared to placebo-treated patients), and in the crossover, where the consequences of withdrawal can be evaluated. There is no regulatory requirement for "size" of effectiveness trials; they only have to be as large as needed to persuasively demonstrate the effect of the drug. This is in contrast to regulatory requirements for patient exposures to evaluate safety prior to marketing.

Extraordinary (for the time) efforts to maintain blinding were made. However, it is possible that the blind was compromised and that bias was introduced. Nevertheless, it is unlikely that observer bias alone could permit the significant reductions in steroid dosage reported in these ill patients.

This trial provides substantial support for the effectiveness of thalidomide in severe, steroid-dependent chronic ENL.

3. Other Controlled Trials in the Literature.

a. *Pearson JMH, Vedagiri M. "Treatment of Moderately Severe Erythema Nodosum Leprosum with Thalidomide--A Double-blind Controlled Trial" Lepr Rev 1969, 40, 111-116.*

This double-blind, placebo-controlled trial was conducted in Malaysia. Twelve patients with longstanding ENL were randomly allocated to placebo or thalidomide, then crossed over after 6 weeks to 6 weeks of the other treatment. The primary endpoint was a scoring system devised by the authors that took into account ENL symptoms, fever, WBC, and stibophen requirements. Interpretation of this score is not possible due to the many variables. In addition, prednisolone dose was allowed to vary in patients taking it and patients were allowed paracetamol.

The results show that patients taking thalidomide had a better clinical score than patients on placebo, despite taking less stibophen, paracetamol, and prednisolone. However, the degree of improvement of the patients is not discernable from the published report.

b. *Hastings RC, Trautman JR, Enna CD, Jacobson RR. "Thalidomide in the treatment of erythema nodosum leprosum. With a note on selected laboratory abnormalities in erythema nodosum leprosum." Clin Pharm Ther 1970, 11,481-487.*

This report summarizes the results of therapeutic 4-day trials of thalidomide 100 mg four times daily or placebo in hospitalized patients with chronic ENL at the US Public Health Service Hospital in Carville, Louisiana. Forty-four trials were conducted in 22 patients; 21 of the trials were not double-blinded. Thirty-one of the trials were administered in the context of acute steroid withdrawal as the patients were admitted to the infirmary, withdrawn from steroids, observed for 4 days, and enrolled if they had active disease. An attempt was made to reconstruct the records for this trial from the hospital notes since all study records including the randomization schedule had been lost. The FDA reviewers attempting to reconstruct this trial had difficulty doing so, and the context (short-term treatment after steroid withdrawal in the majority of cases) is less germane than that from other studies.

4. Unblinded Studies Reported in the Literature

The sponsor submitted additional unblinded studies from the literature in support of thalidomide for the treatment of ENL. Twenty-eight of these studies evaluated, in an open label fashion, the effectiveness of thalidomide in treating ENL. Many of the studies enrolled patients with severe steroid-dependent disease who would not be expected to have a high rate of spontaneous remission. The literature reports were written by approximately 26 different groups in 14 different countries. Investigators reported findings of prompt relief of cutaneous symptoms and fever, steroid sparing in relevant patients, and prevention of relapse, with efficacy rates very similar to those reported in the controlled studies.

Although these experiences were not controlled, they generally report a very robust treatment effect occurring in a substantial majority of patients in a short time after initiation of therapy, a combination of events not likely in the course of the natural history of the disease. These independent reports provide additional evidence of the effectiveness of thalidomide in the treatment of ENL.

C. Data from Retrospective Chart Review

Patient records from 102 patients treated under IND 11,359 were evaluated. The overall interpretation of these records is difficult, due to the spontaneous fluctuation of disease, possible confounding effects of other treatments, and the non-prospective nature of the data. However, of the 46 patients not recorded to be on prednisone, high-dose aspirin, or clofazamine, 24 patients had at least 1 "positive" challenge-dechallenge result, with remission of ENL lesions on thalidomide and recurrence upon thalidomide withdrawal. Some patients had as many as 7 challenge-dechallenge episodes in which ENL skin lesions were controlled on thalidomide and recurred after withdrawal. (See Office Director's Review dated Sept. 19, 1997, and Dr. Gao's review of Aug. 7, 1997.) Although these data are retrospective and not concurrently controlled, the multiple challenge-dechallenge-rechallenge observations are highly supportive of both the effectiveness of thalidomide and of its ability to prevent relapse, because of the unlikelihood of such repeated occurrences being observed by chance alone. The observed response rate to thalidomide in this series appeared lower than that reported in the literature; however, the doses used were much lower. Control of ENL symptoms was observed to occur at a dose of 100 mg daily in many of the episodes.

D. Ongoing Study

The sponsor is conducting a dose-comparison trial in the Philippines. This trial evaluates the response of ENL to 100 or 300 mg thalidomide for 7 days, and may provide additional information on the most effective starting dose.

E. Discussion of Efficacy Data

The majority of the effectiveness data supporting this orphan indication for thalidomide are derived from the published medical literature, primarily from studies conducted over 25 years ago. These data are supplemented by the retrospective information from IND 11,359. As recently outlined in FDA's guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998), FDA can, in certain circumstances, rely on published reports alone to support approval of a new product.

Four double-blind, placebo-controlled trials of thalidomide in ENL were discussed above. The trials, conducted by 3 different investigators in 3 different countries, and evaluating different patient populations with respect to disease severity and duration, provided similar conclusions about the effectiveness of thalidomide. The drug was found to have a rapid onset of action, to favorably affect the majority of patients treated, and to have a much larger effect than placebo or active control. While each of these studies provides independent evidence for thalidomide's effectiveness, the consistency of results across studies is also striking. The conclusions are also supported by the results of a large number of open-label trials reported in the literature in which a similar rapid onset and robust effect were observed, often in patients with unremitting disease. Although the reported endpoints (skin lesions, steroid sparing) are more subjective than endpoints such as mortality, the reported effect size is also much larger than that demonstrated for most interventions. As a rheumatologist experienced in the management of patients with severe inflammatory and vasculitic disorders, I find these endpoints appropriate for the disease being treated and adequately objective when large differences in outcomes are being evaluated (e.g., a 60% reduction in steroid dose or an absence of skin lesions). Therefore, I find that the published literature may be relied upon to support the approval of thalidomide for ENL.

Although many studies have reported beneficial effects of thalidomide on fever and other systemic manifestations of ENL, the effectiveness of the drug for systemic symptoms is not well

supported, and the indication should be limited to the treatment of cutaneous manifestations.

Data from the retrospective chart review, along with literature reports also support the use of thalidomide to prevent relapse in ENL. Treating physicians should attempt to reduce and then discontinue medication in patients whose disease has remitted.

A number of questions have been raised about the availability of effective alternative treatments for ENL. Corticosteroids have been shown in clinical practice to be useful in controlling ENL. However, the very serious adverse effects of long-term corticosteroid administration are well-documented. Extended high- or moderate-dose steroid therapy is not a desirable alternative. Clofazimine is an FDA approved anti-leprosy drug that is additionally approved for the treatment of ENL. Clofazimine was approved for the ENL indication based on the results of a retrospective, historically controlled study of patients with ENL treated at the National Hansen's Disease Center in Carville, Louisiana, supported by controlled trials reported in the literature. (Medical Officer's Review, April 16, 1985.) Particularly since it has a slow onset of effect in ENL, estimating the magnitude of clofazamine's treatment effect from results of an historically controlled trial is difficult. In addition, effective blinding of trials using clofazamine is highly challenging, since non-dark-skinned patients develop red skin pigmentation within about 2 weeks of starting therapy. Because of these factors, while it is clear that clofazamine is effective in ENL, the magnitude and speed of onset of the effect is not precisely known. The side effect of skin pigmentation is unacceptable to many ambulatory patients (suicides have been reported), and the drug also causes an enteritis that can be fatal and was reported in a number of ENL patients in trials. Therefore, clofazamine, while an effective alternative, also has drawbacks and cannot be considered an ideal alternative for ENL. Currently available treatments for ENL may entail, as does thalidomide, serious or unacceptable side effects for some patients.

IV. BRIDGING DATA FROM EFFICACY TRIALS AND BASIS FOR DOSE RECOMMENDATIONS

The controlled and uncontrolled literature data, as well as the retrospective IND experience data, were derived from thalidomide formulations made by manufacturers other than Celgene. The "bridging" issue concerns how to ensure that the Celgene product, at a particular dose, will have an effect similar to that

observed in any particular clinical trial in which another product was used. In practical terms, for this product, the question is how to arrive at specific dosing recommendations.

The products studied in the 1960's and 1970's have long exceeded their expiry dates. Direct comparisons are not possible. The sponsor submitted a pharmacokinetic trial comparing the bioavailability of Celgene thalidomide to that of another manufacturer, whose product was used in some of the US Public Health Service experience. The lot-to-lot consistency and degree of manufacturing controls of this product are not known to FDA. The results of this trial demonstrated that the foreign manufacturer's product was absorbed at a much slower rate than Celgene's thalidomide. The foreign product was only somewhat less bioavailable overall, but primarily had a much lower (approximately half) C_{max} than the Celgene product. (Clinical Pharmacology/Biopharmaceutics Review, April 13, 1998) Since the pharmacokinetics of products used in the clinical efficacy trials of thalidomide are not known, the results of this trial are not particularly illuminating.

The efficacy of thalidomide for ENL has been shown, using various manufacturers' products, at doses between 100 and 400 mg daily, with responses to 50 mg reported in the IND experience. Except for patients with very severe disease, a prudent course would be to start at 100 to 300 mg and titrate up if the symptoms are not controlled. Despite potential variations due to formulation differences, this dose of Celgene thalidomide is very likely to result in blood levels within the range achieved by 50-400 mg doses of other manufacturer's products. This is a reasonable dosage recommendation for an intervention that is expected to have a prompt effect on clinical symptomatology.

An ongoing study in the Philippines compares the initial response of ENL to 100 or 300 mg thalidomide. This should provide additional information on whether there are any benefits in starting at the higher end of the dosing recommendations.

The adequacy of safety information is considered separately in the following section.

V. SAFETY EVALUATION

The overall adverse reaction profile of thalidomide is well understood from decades of clinical use. More frequent or severe adverse events include the following:

A. Acute effects

Drowsiness is an expected event in a proportion of patients taking this drug with known sedative properties. This can be somewhat mitigated by dosing at bedtime. Possibly related and fairly frequent effects include tremor, lowered blood pressure, pulse rate, and dizziness, or orthostatic hypotension.

B. Teratogenesis

This effect is well known, has been reported to occur with a very low single dose (50 mg), and occurs at a time during gestation when many women are not aware of pregnancy. This effect raises the greatest concerns about availability of thalidomide.

C. Neuropathy

Peripheral sensory neuropathy is a known complication of thalidomide therapy, and probably the most significant risk to patients consuming the drug. Few reports have occurred in ENL patients compared to those with other conditions. Whether this is due to failure to manifest symptoms, failure to recognize the complication, or lack of susceptibility of these patients is not known. The fact that this complication may be related to cumulative dose makes the recommendations for tapering and discontinuation quite important. The potential for neuropathy and recommendations for early detection are laid out in the warnings section of the label and also in the patient information.

D. Allergic drug reactions

Rashes, eosinophilia, urticaria, and related reactions occur with some frequency in thalidomide-treated patients. These problems resolve with discontinuation, but must be distinguished from the underlying disease being treated.

E. Hematologic effects

Lowered white blood counts, including neutropenia, have been reported in patients taking thalidomide, particularly patients with underlying disorders that may affect the hematologic system (e.g., HIV infection). Severe hematologic reactions are not a serious concern in ENL patients who do not have other predisposing diseases; therefore, no specific monitoring schedule is recommended in the label.

F. Viral load in HIV-infected individuals

In the course of studying the effects of thalidomide on HIV-related illnesses, it was observed that viral load increased during drug administration. Further study is needed to evaluate this observation, and caution should be used in any HIV-positive individual.

The adverse event profile discussed above was generated from clinical experience over decades using a wide variety of manufacturers' thalidomide formulations. One issue that has arisen is how this safety information may be extrapolated to recommendations about Celgene's thalidomide. Since the recommended use of thalidomide in ENL involves titration to a desired effectiveness result, the principal question is whether the Celgene product has a different acute safety profile compared to previously used products. The Celgene product has been administered to patients in both controlled trials and open label studies, generally at doses from 100-400 mg per day. The ongoing Philippine trial in ENL has enrolled 19 patients. This study involves 7-day administration of 100 or 300 mg thalidomide/day, followed by a taper over several weeks. The reported adverse event profile to date from this study is what would be expected from previous clinical experience with the drug (e.g., primarily somnolence, dizziness, rash). In addition, a controlled clinical trial of Celgene thalidomide was conducted in patients with HIV infection and wasting. Doses of 100 or 200 mg were compared to placebo. The incidence of somnolence reported was 36% in the 100 mg dose, 38% in the 200 mg dose, and 11% on placebo. The approximately 25% excess of somnolence in the treated arms is consistent with other reports of drowsiness after thalidomide administration.

Other than teratogenesis, the most serious side effect of thalidomide administration in this population is peripheral neuropathy. Since this has been reported infrequently in ENL patients using any formulation of the drug, the dose-dependency, time course, and rate of progression is not well described with any formulation. The recommendations in the label, which involve patient and physician vigilance towards the development of early symptoms of sensory neuropathy, are appropriate.

The overall safety experience with thalidomide is exceedingly large in proportion to the intended ENL population (estimated at approximately 100 new cases per annum in the US). This situation is quite unusual for a new molecular entity, where the target population frequently may be 100- or 1000- fold larger than the number of individuals studied premarketing, a circumstance that

introduces additional risk of the occurrence of rare, not-yet-detected serious adverse reactions. While not all thalidomide patients were studied in clinical trials, the prescribing circumstances closely resemble the intended use conditions of the product, a real-life scenario that is likely to elicit the fullest range of adverse experiences that will be encountered during marketing.

The actual safety experience with Celgene's thalidomide, although quite small, represents a much larger ratio of the number of premarket patients studied to the number of postmarket patients than is expected for most drugs, due to the fact that only a very small number of US patients have this orphan-designated condition.

Concern has been raised about the safety issues involved with off-label use of any approved thalidomide. Physicians have been using investigational thalidomide for a variety of very serious or life-threatening diseases under the "single-patient" and "open protocol" INDs set up by the FDA in cooperation with various manufacturers for this purpose. Any investigational use or off label use of a drug represents greater risk, because less information about safety (and effectiveness) for the indication is available. Approval of thalidomide for ENL would not mean that adequate safety information is available for other indications. Safety information in indications other than those for which marketing approval is sought is not a requirement for product approval. Due to the paucity of information on other uses, the known teratogenic effects of thalidomide, and the potential for peripheral neuropathy, the decision to use thalidomide for an off label use should not be taken lightly by physician or patient, and prudence dictates that such use occur only in very serious or life-threatening illnesses without satisfactory alternatives. The extraordinary restrictions on distribution of this drug, combined with the extensive educational efforts, should accomplish this objective.

VI. RESTRICTED DISTRIBUTION UNDER 21 CFR 314.520

This product is being approved under the "restricted distribution" provisions of the regulations. The restrictions on use include the following:

A. Restriction to prescribers and pharmacies registered with the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program (this program includes educational materials).

B. Requirement for patient informed consent, and completion of educational materials including video.

C. Mandatory 100% patient registry and monthly survey completion.

D. Agreement by patient to comply with provisions of program, including not sharing medications, or donating blood or sperm.

E. For women with childbearing potential, agreement to use two methods of birth control, and mandatory monthly or biweekly pregnancy testing.

F. For men taking thalidomide, agreement to use barrier contraception when sexually active with a woman of childbearing potential (because the woman could be pregnant.)

G. Restriction on prescribing or dispensing more than a 28 day supply of drug.

All elements of this program have been extensively reviewed by a variety of FDA experts and consultants. The input of staff of the Centers for Disease Control and Prevention has been very helpful in the evaluation.

The current restrictions strike a balance between the need to prevent fetal exposure to the drug and the need to make the drug available without extraordinary burdens on patients and prescribers. The restrictions create a sufficient burden to deter any prescribing that is not carefully considered; however, they should not pose insuperable obstacles to health professionals and patients. The 100% registry and opportunity for follow-up allow a second tier of safeguards beyond that created by the restrictions at the prescribing level.

This represents the first time that the restricted distribution provisions under 21 CFR 314.520 have been invoked. These regulations were specifically directed to products with safety issues that could not be addressed under the conditions of ordinary approval.

The restricted distribution program for thalidomide is specifically designed to ensure that no fetal exposure to the drug occurs. Any suspected fetal exposure will be considered a serious, unexpected adverse reaction that should be reported in an expedited fashion to the FDA.

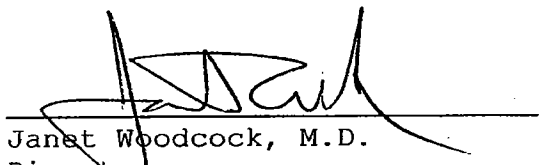
A response team at FDA has been formed to oversee postmarketing adverse event reporting and rapidly investigate any report of suspected fetal exposure. Any such verified event would represent a failure of the system and would mandate additional actions or restrictions on the drug depending on the circumstances of the failure.

This novel approach of restriction on distribution will require careful oversight to ensure that it is functioning as designed. FDA will provide a third tier of safeguards by directly inspecting the various elements of the program within the first quarter of operations, and periodically thereafter.

The provisions of 21 CFR 314.530 provide for withdrawal of any drug approved under 314.520 if the restrictions on distribution prove inadequate to ensure the safe use of the product. This represents the final tier of safety assurance under these regulations.

VII. CONCLUSIONS

The Celgene application meets the standard for demonstrating effectiveness of the drug for the intended use. The restricted distribution program under 21 CFR 314.520 enables the product to be used safely for the proposed indication of ENL. Continuing vigilance will be required by both the sponsor and the FDA to ensure that this product is used safely when it is commercially available in the US.



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

cc:
Orig NDA 20-785
HFD-001/Woodcock
HFD-002/Lumpkin
HFD-540/Div File
HFD-105/Walling

Secondary Medical Officer's Review of NDA 20-785
Addendum Review of Draft Data Listings for Study E-003/P

SEP 3 1997

NDA 20-785	Desk Copy Submission date: 8/28/97 Review Completed: 9/3/97
Sponsor:	Celgene Corporation 7 Powder Horn Drive Warren, NJ 07059 (908) 271-1001
Drug:	Thalidomide; Synovir™
Pharmacologic Category:	Immunomodulator
Proposed Indication:	Erythema Nodosum Leprosum (ENL)
Dosage Form:	Thalidomide 50 mg Capsules
Route of Administration:	Oral
NDA Drug Classification:	1P
Related Drugs:	None

A desk copy of "draft" data listings and tables was received. It contains previously submitted data for the first nine patients in the Sponsor's ongoing trial E-003/P, previously unreviewed data for 8 additional ENL patients, and data for 3 patients who were re-randomized.

Two of these repeat randomizations were treatment failures (01 and 05) in the group submitted with the original NDA submission (patients 01-09). Dr. Kook explained in teleconference August 29 that these patients were assigned numbers from the end of the randomization code, since it is unlikely that 50 patients will be enrolled and they have informed the investigator not to re-enroll any additional patients. She also explained that there may be some differences in the listings for patients 01-09 from the originally submitted listings, but that a list of the location of changes was not available. She stated that the changes are not significant.

Reviewer's Comment: A complete review will follow when analyzed data has been submitted and more time is available. In the limited time available for this review, it was not possible to address efficacy regarding the secondary endpoints or during the tapering period.

The primary endpoints for the acute treatment period will be summarized for each of the new cases based on cross-referencing dates of observations from the various data listings and tables. It must be remembered that the draft material submitted is not in narrative form, but rather a series of tables and tabulations for various data parameters. Thus, these summaries are my best reconstructions of each case at this time. It is also important to note that this trial is on-going and the blind has not been broken (the 2 arms are 100mg and 300 mg thalidomide per day). Thus, it is unknown at this time whether the results stratify by dose.

The Sponsor's assignment for response to acute treatment is followed by my reason for any re-assignments. Similarly, I note reasons for re-assignment of any patients in the original group (01-09).

Finally, a brief overview of new safety information will be presented.

Notes Regarding the Protocol:

1) The primary efficacy endpoints are absence of acutely inflamed ENL lesions and absence of fever at Day 7. A partial response is defined as either the absence of acutely inflamed lesions (old lesions may still be resolving) OR a complete resolution of fever, but not both. A complete response requires absence of both acutely inflamed lesions and fever.

2) Fever is defined in the protocol as an oral temperature greater than 99.7. In the original submission, the Sponsor noted very clearly that the actual measured temperatures at the site were axillary. In the new submission, the temperature column is labeled "oral". For the patients shown in both listings (01-09), the numbers are identical to the decimal place in every case examined. Dr. Kook confirmed in teleconference that the "oral" column heading is an error and that all of the data in the submission refer to axillary temperatures.

As noted in the original review of the first 9 patients, the endpoint appears to have been conserved at 99.7 (see attached excerpt from original NDA study report), despite the fact that axillary temperatures are lower than oral temperatures (DeGowin&DeGowin 6th Ed., pg 42). This review will state the temperatures as they appear in the listings; the actual temperature will be viewed as one degree higher than the recorded temperature.

3) The protocol states that "the need for antipyretics after 72 hours will result in discontinuation due to treatment failure."

4) The post-hoc algorithm used to "convert" estimated lesion counts from the CRFs has been changed (expanded). Specifically:
5-10=7, 10-20=15, 20-30=25, >10=12, >5=7, <10=7, few=2, some=4, more=5, most=7, <20=17, <5=3, >100=105, >15=17, >20=23, >21=23, >25=27, >40=43, >50=53, 3-5=4. According to the original submission, "...in some cases, the clinic recorded approximations that were translated into numbers of lesions using a conservative algorithm". As noted in the original review, this complicates interpretation of the lesion endpoint, since the numbers of resolving lesions are sometimes greater than the number of prior acute lesions.

Patients Not Re-Assigned

Patient 01: Categorized as a Treatment Failure.

Patient 03: Categorized as a Complete Response.

Patient 05: Categorized as a Treatment Failure.

Patient 06: Categorized as a Partial Response due to new acutely inflamed lesions.

Patient 09:

Categorized as a Complete Response. Lesion listings in the original submission note 13 new acutely inflamed ENL nodules appearing on Day 4, but no acutely inflamed lesions at Day 7. There were no acute lesions and 84 resolving lesions at the first follow-up visit, Week 3. Comments for Week 3 indicate "new ENL appearing on the L arm, but no associated signs and symptoms". The new submission corrects the contrast between the lesion listing and the comments for Week 3, showing 5 acute lesions at the Week 3 follow-up. Although this patient's lesion status is somewhat unclear, the patient is not re-assigned pending verification of the lesion counts.

Patient 10:

This patient was categorized as a Complete Response. The listings show a Day 7 (endpoint) temperature of 98.8. Although temperatures less than this are coded in the listings for baseline "ENL symptom assessment" as fevers, it is very close to the protocol cut-off for fever (oral 99.7) and so the patient is not re-assigned.

Patient 13: Categorized as a Partial Response at Day 7 due to acute lesions (2).

Patient 15: Categorized as a Partial Response at Day 7 because of acutely inflamed lesions.

Patient 17: Categorized as a Complete Response. No listings were found for the follow-up period.

Patients Re-assigned Because of Fever at Acute Treatment Endpoint or Concomitant Antipyretics After 72 Hours

Patient 02:

Categorized as a Complete Response. This patient had a fever at Day 4 with no concomitant treatment listed in the original submission. However, the new listing shows that paracetamol was prescribed on day 4 as an antipyretic. Although technically considered a CR in my original review, the new listing confirms this as a Treatment Failure. This assessment is supported by the persistence of anorexia, malaise, and edema (mild) at the Day 7 endpoint.

Patient 07:

Categorized as a Complete Response. This patient had a temperature on Day 7 of 99 and no concomitant paracetamol listed in the original submission at Day 3 for an axillary temperature of 101.7. In this new listing, however, paracetamol is listed for 7/21 (start/stop) and 7/23/96 (start/stop), the reason noted: antipyretic. These dates are Days 5 and 7 (acute endpoint). This patient is thus reassigned as a Treatment Failure, both for fever at endpoint and concomitant antipyretics after 72 hours.

Patient 08:

Categorized as a Complete Response. This patient had a Day 7 axillary temperature of 99 degrees. This is higher than the baseline temperature of 98.6 for which paracetamol was listed in the concomitant medications listing. This patient is re-assigned as a Partial Response.

Patient 11:

This patient was coded as a Partial Response because he had 9 acute lesions at day 7. The listings for concomitant medications show paracetamol started 11/25 and stopped 11/29 as an antipyretic. 11/29 is Day 7 according to the temperature charting. Thus, this patient is re-assigned as a Treatment Failure.

Patient 12:

This patient is coded as a partial response due to 109 acutely inflamed lesions at Day 7. The vital signs listing shows a day 7 temperature of 99.6. The secondary endpoint listings shows Day 7 with severe anorexia and mild malaise and pain. The severity of the baseline conditions is notable: 497 nodules, 8 pustules, a baseline fever of 100.9 with a pulse of 120 ("severe fever"), mild chills, moderate arthralgia, and severe malaise and anorexia. An examination of the Concomitant medications listings suggests that this patient's prednisone was decreased from 30 mg to 25 mg to 20 mg (11/22 to 12/12) and then was stopped 5 days before the baseline visit. The available data do not reveal the patient's condition at the time of the prednisone taper or discontinuation. This case will be discussed further under "Safety". For the purposes of efficacy assessment, the combination of acute lesions and fever prompt re-assignment to Treatment Failure.

Patients Un-Assigned Due to Unclear Data

Patient 04:

Categorized as a Complete Response. This patient had no acute ulcers after baseline and no resolving ulcers at day 4. On Days 5, 6, and 7 there were 48 resolving ulcers. The response assignment for this patient is unclear, since the origin of resolving ulcers without previous acute ulcers is unclear.

Patient 16:

This patient was coded as a Complete Response at Day 7 and had no data entered thereafter. The temperature at baseline was 96.9, coded as a "moderate" fever in the ENL Symptom Assessment Dataset. At Day 7 the temperature listing shows 98.7. If the temperature at baseline (96.9) was a moderate fever, fever status at Day 7 is unclear.

Patients Not Categorized by Sponsor

Patient 14:

The Sponsor notes that this patient was not evaluable for the protocol defined response definition because he lacked ENL lesions or fever at baseline. It was further noted by the Sponsor that "at baseline, the patient reported severe neuritis, arthralgias, vasodilatation, and nerve enlargement and tenderness. All but nerve enlargement and tenderness resolved by Day 7 and all resolved by the final tapering visit at week 7."The Day 1 notation shows that the neuritis and arthralgias were "mild": "left ulnar nerve slightly enlarged and less tender, apparent improvement seen". On Day 6 the enlargement is coded as "moderate", at Day 7 again "mild". From the Sponsor's statement noted above, it appears that the neuritis persisted beyond the acute treatment period. I was able to find ENL symptom assessment listings for baseline to Day 7, not for the tapering period, so it is not exactly clear how many weeks the neuritis persisted and to what degree. This patient will be discussed further under "Safety".

Patient 46:

This was patient number 10 re-randomized. The response as patient 46 was not included in the Sponsor's "Response Categorization". Day 5 notation shows "deep seated papules, hard and tender on palpation". The "Index of Lesion Extent" table for this patient shows no acutely inflamed lesions after day 2.

Patient 47:

This was re-randomization of patient 01, a Treatment Failure in the initial submission. That submission noted that a "verbal report" by the investigator indicated that this patient responded to open label treatment at 300 mg per day after the study. It appears from the current line listings that the patient may have been discontinued from the second study due to a UTI (temperature at Day 7 100.3 with antibiotics listed for UTI). The lesion counts show 10 acutely inflamed nodules. In any event, this case will not be further considered at this time because of the known deleterious effects of underlying infection on the course of ENL.

Patient 48:

This patient was re-randomization of patient 05, a Treatment Failure in the initial submission. That submission noted that a "verbal report" by the investigator indicated that this patient responded to open label treatment at 300 mg per day after the study. The current listings for the second study show Day 7 with 5 acutely inflamed nodules, mild pain, and a temperature of 98.4.

These categorizations are shown in tabular form:

	Sponsor's Efficacy Category	Reviewer's Efficacy Category
Complete Response	N=9: (02,03,04,07,08,09 10,16,17)	N=4: (03,09,10,17)
***Partial Response**	N=5: (06,11,12,13,15)	N=4: (06,08,13,15)
Treatment Failure	N=2: (01,05)	N=6: (01,02,05,07,11,12)
Unassigned	N=4: (14, 46, 47, 48)	N=6: (04,14,16,46,47,48)
Total:	N=20	N=20

*The Sponsor was advised that a Partial Response as defined in the protocol is not considered a success for regulatory purposes.

Brief Summary of Additional Safety Data:

Patient 12: An examination of the Concomitant medications listings suggest that this patient's prednisone was decreased from 30 mg to 25 mg to 20 mg from 11/22 to 12/12 and then was stopped 5 days before the baseline visit (12/17). The available data do not reveal the patient's condition at the time of the prednisone taper or at the seemingly abrupt discontinuation of steroids. As described in the previous section, the severity of the baseline ENL parameters was notable: 497 nodules, 8 pustules, a baseline fever of 100.9 with a pulse of 120 ("severe fever"), mild chills, moderate arthralgia, and severe malaise and anorexia. Again, the available data at this time consists only of draft tabulations and may not reflect the actual management of this patient.

This patient also is coded one week into the taper with a moderate rash ("fine reddish follicular eruption on the chest, trunk, arms, which are itchy and blanch on pressure"), possibly related to drug. The listing then notes that it became worse after taking 9 caps amoxicillin (medication listings show tooth abscess). The concomitant medications indicate treatment of the rash with an antihistamine. The outcome is coded as resolved.

Patient 14 was described above. As noted in the submission, he presented as follows: "at baseline, the patient reported severe neuritis, arthralgias, vasodilatation, and nerve enlargement and tenderness. All but nerve enlargement and tenderness resolved by Day 7 and all resolved by the final tapering visit at week 7." The line listings do not show concomitant treatment for this severe neuritis with prednisone. Naproxen is listed on 2/20-2/22/97 for nerve pain. The study baseline date is 2/25/97 according to the vital signs table, which shows a temperature of 99.1. Again, the available data at this time consists only of draft tabulations and may not reflect the actual management of this patient.

In a previous submission to the NDA (Volume 4), the Sponsor states: "Other manifestations of ENL, particularly neuritis and uveitis, often take longer to improve, commonly a week or more. While many studies and the on-going Study E-003/P describe rapid relief of neuritis following treatment with thalidomide alone, other investigators and studies comment that the onset of action is slow. Thalidomide is used effectively in combination with corticosteroids in order to obtain more rapid relief, since the greater the length of time of inadequate treatment the higher the likelihood of residual damage. In general practice, once the neuritis has been ameliorated, corticosteroids are discontinued and the underlying ENL is controlled through continued treatment with thalidomide."

Patient 16 had moderate drowsiness which resolved.

Patient 48 had "tingling sensation both feet occasionally felt" coded on Day 2 and Week 3. This patient was one of the re-randomized patients. In addition, the original submission noted that a "verbal report" by the investigator indicated that this patient "responded" to open label treatment at 300 mg per day after the study. The total extent of exposure needs to be addressed in the context of a possible drug related neuropathy.

Finally, a note regarding vital signs: all of the patients appear to be tachypneic (respiratory rates between 20-28). This was recorded in the original submission as well. The reason for this is unknown, but it seems unlikely that these represent actual tachypnea, since they are present before thalidomide is started (ie. not drug related) and persist in patients who are complete responders (presumably not disease related).

Conclusion:

1) As noted before, the dosing blind for this on-going study has not been broken and stratification of the efficacy results by dose is unknown at this time. In addition, review time did not allow analysis of the draft efficacy results based on baseline ENL severity. Within that context, 4 of the 16 patients evaluated by the Sponsor meet the protocol defined Complete Response definition for the primary endpoints based on this draft data. Two possible Complete Responses were not included due to unclear data at this time. As noted in the primary review, interpretation of the results in this trial would be enhanced by measuring oral temperatures and performing exact lesion counts.

2) Only one patient in the new group experienced a rash during treatment, as compared to 3 patients in the first group of 9. Likewise, drowsiness is listed for only one patient in this new group, as compared to 6 in the first group.

3) Additional information is needed for Patients 12 and 14 in order to determine whether additional protocol changes should be instituted regarding use of prednisone for severe ENL.

Kathryn O'Connell MD 9/3/97

Kathryn O'Connell, M.D., Ph.D.
Secondary Clinical Reviewer

cc: HFD-540
HFD-540/CSO/White
HFD-540/Chem/Decamp
HFD-540/Pharm/Hill/Jacobs
HFD-540/Stats/Gao/Thomson/Srinivasan/Harkins
HFD-540/MO/Vaughan/OConnell/Walker
HFD-540/Biopharm/Bashaw
HFD-540/DivDir/Wilkin 9/3/97

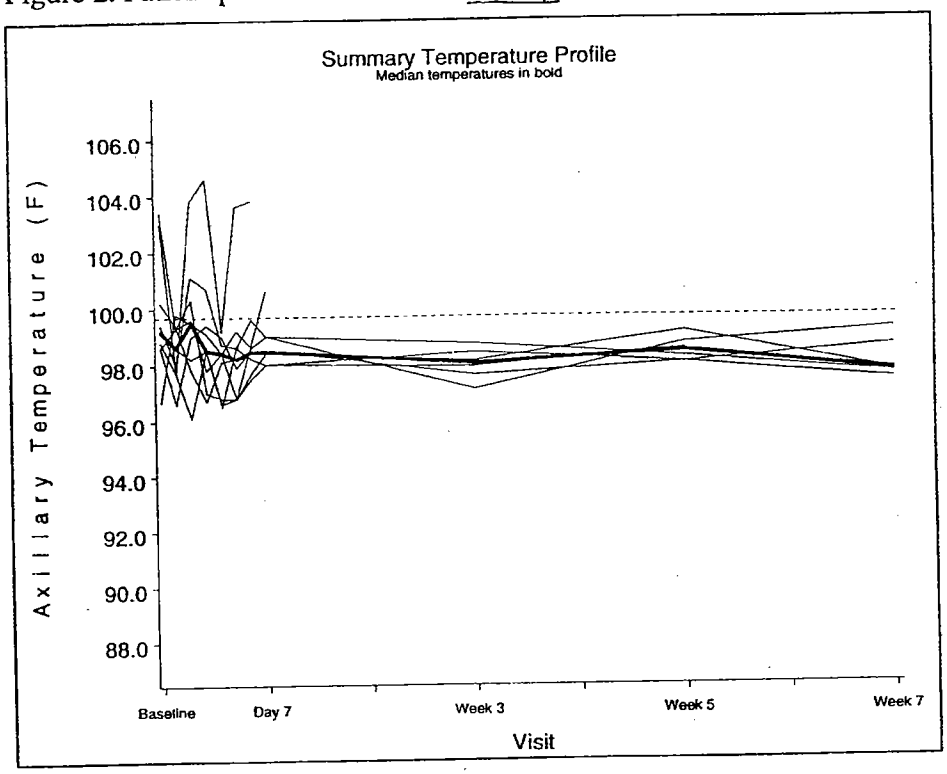
Table 6. Response of each patient at end of tapering period (week 7)

Response	Patient Number
Complete	02, 04, 06
Partial	03, 07, 08, 09

2. Fever

Escalating fever was present in the 2 treatment failures. The complete and partial response patients had in-clinic axillary temperatures that decreased and/or did not exceed 99.7°F (37.6°C) during the 7-day treatment period; their temperatures stayed low during the tapering period. The following figure shows the temperature profile of each patient. The median temperature for all of the 9 patients at each visit is overlayed with a bold line. A dotted line is drawn at 99.7°F.

Figure 2. Patient profiles of in-clinic axillary temperature



Patients 03, 05, and 09 each had one low outlying temperature recorded that was excluded from Figure 2. See Figure A1 for individual patient graphs that denote these points and Table B2 for the data listing of temperature values. Other temperature graphs are provided in Figures A2-A3 in Appendix A.

Secondary Medical Officer's Review of NDA 20-785

Addendum to Major Amendment Review

SEP 3 1997

Date of Addendum: September 3, 1997

Sponsor:

Celgene Corporation
7 Powder Horn Drive
Warren, NJ 07059
(908) 271-1001

Drug: Thalidomide; Synovir™

This addendum addresses my efficacy review of the June 17, 1997 major amendment based on data collected by the Agency from one of the USPHS sites under IND 11,359 (LAC/USC). As noted then, the review was based on summary tables and scatter plots generated by our Biostatisticians from the database.

In that review, I addressed a number of assumptions, in the absence of data, as the groundwork for my assessment of the report. These included use of aspirin/ NSAIDS and the fact that the ENL assessments in the database pertained to cutaneous lesions only.

Subsequent to that review deadline, I looked at one record chosen randomly, number 106. The chart showed 4 different visits where aspirin or Motrin were prescribed. The Motrin dosages were 600 mg TID, 400mg QID, and 600 mg TID. The reason for prescribing appeared to be knee and back pain, shoulder pain, pain in extremities, joint pains. It was not possible to determine the duration of treatment. Thalidomide was prescribed as well, except for a 2 week period when it was discontinued due to a complaint of paresthesias. Notes suggesting new ENL skin lesions were not found over the approximately 3 year time frame represented, but there were notes regarding occasional fever, chills, weakness, arthralgia. In addition to this information, the chart also shows an entry "blackout spells x3 since increase (up arrow) thalidomide". The dose at that visit was 200 mg.

This information is offered only as an isolated example of two of the assumptions addressed in my review: 1) use of aspirin and NSAIDS and 2) ENL assessments in the database for cutaneous lesions only.

This isolated record suggests that additional information relevant to efficacy might be extractable from the charts. This case also suggests that further analysis of the charts would contribute to the overall safety database in ENL patients.

Kathryn O'Connell MD 9/3/97

Kathryn O'Connell, M.D., Ph.D.
Secondary Clinical Reviewer

cc: HFD-540
HFD-540/CSO/White
HFD-540/Chem/Decamp
HFD-540/Pharm/Hill/Jacobs
HFD-540/Stats/Gao/Thomson/Srinivasan/Harkins
HFD-540/MO/Vaughan/OConnell/Walker
HFD-540/Biopharm/Bashaw
HFD-540/DivDir/Wilkin 9/3/97

AUG 13 1997

NDA 20-785

Medical Officer's Review of NDA 20-785
Original

NDA 20-785
Original

Submission date: 12/20/96
Received date: 12/24/96
Assigned date: 01/02/97
Review Completed: 7/28/97

Sponsor: Celgene Corporation
7 Powder Horn Drive
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(908) 271-1001

Drug: Thalidomide; Synovir™

Pharmacologic Category: Immunomodulator

Proposed Indication: Erythema Nodosum Leprosum (ENL)

Dosage Form: Thalidomide 50 mg Capsules

Route of Administration: Oral

NDA Drug Classification: 1P

Related Drugs: None

Related IND/NDA(s): IND 48,177 and IND 11,359

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3 **Material Reviewed** NDA Volumes 2.1, 2.20 - 26, 2.30-38, 2.46 - 2.48, Vols 3-10, and major amendment 6/17/97 11.1-4; IND 11,359; IND 48,177; Division of Dermatologic & Dental Products (HFD 540) Division Files.

4 **Chemistry/Manufacturing Controls**

See Chemistry review (not completed at time of this review)

5 **Animal Pharmacology/Toxicology** *See Pharmacology/Toxicology review*

Reviewer's Comment: *Discoloration of urine was noted in mice and dogs receiving the Celgene formulation of thalidomide. The color was reddish-pink in mice and greenish-blue in dogs. The identity of the responsible substance was not determined by the Sponsor. The clinical significance is unknown. In an on-going clinical study conducted by the Sponsor using their formulation in ENL patients, all 9 post-treatment urine specimens, collected at the end of tapering (approximately 2 months after initial dosing), were yellow. In the pharmacokinetic study line listings examined, urine color was not noted with the urinalysis results.*

6 **Background**

This NDA seeks approval for the use of thalidomide, under Orphan Drug designation 95-907, in the treatment of erythema nodosum leprosum (ENL), a reactional complication which occurs in a subset of leprosy patients. The proposed indication is as follows: "Thalidomide is indicated for the acute treatment of moderate to severe erythema nodosum leprosum (ENL) [

] Thalidomide is also indicated as maintenance therapy for prevention and suppression of ENL recurrence."

This submission is somewhat unique in that it is supported by the following sources of clinical data: 1) a retrospective review of a controlled clinical trial conducted in 1968-69 with additional primary data; 2) a retrospective review of 16 years experience under an on-going open label IND sponsored by the USPHS; 3) a literature review for safety and efficacy, including 5 controlled clinical trials for which supporting primary data are not available and a consultant's review of peripheral neuropathy; 4) preliminary results from 2 on-going clinical trials, one of which is open-label and the other dose-ranging (14 enrolled patients); and 5) the results of 3 pharmacokinetic studies.

Administrative History Summary:

A detailed administrative summary is found in the Division of Dermatologic & Dental Drug Products' (DDDDP) Division file (HFD 540). At the time this NDA was filed, two major issues regarding the submission remained unresolved. The first issue concerned the proposed indication. Specifically, whether the available data would support safety and efficacy of thalidomide as monotherapy or adjunctive therapy, given that ENL is a systemic disorder and most of the evidence appeared to be focused on the cutaneous lesions and fever. The second issue concerned the on-going clinical trial being conducted in the Philippines. Specifically, the main focus was the inclusion of patients with neuritis and concomitant use of corticosteroids. These issues were considered of critical importance by the division because peripheral nerve damage is the one of the most debilitating aspect of leprosy and thalidomide is a known neurotoxin.

In addition, the sponsor requested that the submission be considered under 21 CFR Subpart E and 314 Subpart H (for drugs intended to treat life threatening or seriously debilitating conditions with no acceptable treatment alternatives). Although review under 21 CFR Subpart E was not formally granted because adequate evidence supporting this designation was not provided by the sponsor, the sponsor was granted frequent meetings with the division.

6.1 Clinical Background (partially excerpted from NDA)

Thalidomide, (∝-N-phthalimidoglutarimide), was released in Germany in 1957 under the trade name of Contergan. Once thought to be remarkably safe, thalidomide was released without prescription as a sedative. Thalidomide was prescribed under a variety of trade names (e.g. Distaval, Kevadon) at oral doses of 50 to 200 mgs daily. In 1960, reports associating prolong use of thalidomide with neurotoxicity began to appear and the use in Germany was converted to prescription-only-drug classification. Thalidomide had also been used worldwide as an anti-emetic in pregnancy. With the independent reporting by two physicians of a suspected link between the use of thalidomide and the birth of children with severe malformations, the drug was withdrawn from the market in the latter half of 1961. It is estimated that between 7000 to greater than 10,000 children were born with deformities induced by thalidomide (ref. Drugs as Teratogens). Thalidomide was never approved in the United States because of Dr. Francis Kelsey's (FDA) safety concerns regarding reports of neuropathy.

Thalidomide was utilized by Sheskin in Israel in 1963 as a sedative/tranquilizer in a few erythema nodosum leprosum (ENL) patients suffering insomnia and discomfort from their reactional symptoms. A chance observation was made that, following dosing, signs and symptoms of ENL were rapidly ameliorated.

Following the reporting of the usefulness of thalidomide in the treatment of erythema nodosum leprosum by Sheskin in 1964, several unblinded and blinded trials were conducted which extended Sheskin's initial observations. One of the supportive double-blind controlled trials was conducted

by Hastings et al., at the United States Public Hospital (USPH), Carville, Louisiana. Preliminary results were reported at the Third Annual Leprosy Research Conference in 1968. The final report was published in 1970. Thalidomide was recommended as the treatment of choice for ENL by the WHO Expert Committee on Leprosy for males and postmenopausal females (females of reproductive potential were excluded because of thalidomide's well known embryopathic effects).

ENL is a systemic disorder associated with borderline lepromatous (BL) and lepromatous leprosy (LL) and is quite variable in its presentation and natural history. At times it may be associated with fever, neuritis, malaise, anorexia, insomnia, tender lymphadenitis, swollen joints, edema, proteinuria, leukocytosis, and anemia. ENL may also result in synovitis, nephritis, iritis, lymphadenitis, and epididymoorchitis. Individual patients may experience one or any combination of these manifestations. The severity may vary from episode to episode within the same patient. ENL will be discussed in detail at the end of this section.

Leprosy or Hansen's Disease, is a chronic, communicable disease, caused by the obligate intracellular acid-fast bacillus (AFB), *Mycobacterium leprae* (*M. leprae*). The mode of transmission of leprosy remains uncertain. The most commonly held view is that it is spread from human to human, primarily as a nasal droplet infection. The incubation period for leprosy is uniquely long among bacterial diseases, a minimum of 2 to 3 years, averaging 5 to 7 years, and can be as long as 40 or more years. Household contacts of untreated lepromatous leprosy cases are at highest risk. Even among such household contacts, residence in an endemic country imposes a greater risk of disease than is posed in nonendemic locales (Leiker 1980). It is entirely unclear whether these differences are a result of hereditary predisposition, prior mycobacterial contact and consequent immunity, or even route of transmission.

Though leprosy may affect people of all ages, the peak age of onset is in young adults with children rarely developing lepromatous leprosy. It is estimated that fully 90% of individuals are naturally immune. The disseminated, lepromatous form of leprosy is twice as common in men than women.

M. leprae invades the cooler tissues of the body, the skin, peripheral nervous system, upper respiratory tract, anterior chamber of the eyes and testes. The clinical picture can vary from the presence of an insignificant area of hypopigmented skin that heals spontaneously to widespread damage to the skin, peripheral nervous system, upper respiratory tract, anterior chamber of the eyes and testes. Most of the serious sequelae are a result of *M. leprae*'s having unique tropism for peripheral nerves. Small nerve fibers are most commonly functionally impaired, resulting in loss of fine touch, pain, and hot and cold sensation; position and vibration sense are generally maintained. Both major nerve trunks and microscopic dermal nerves may be affected in leprosy patients, the most common nerve trunk impairment being the ulnar nerve at the elbow, leading to clawing of the fourth and fifth fingers, loss of dorsal interosseous musculature, and loss of sensation of the hand in the ulnar distribution. Nerve damage appears to result from either bacterial multiplication within Schwann cells or granulomatous damage to the perineurium. Loss of protective sensation in the feet may result in troublesome, recurrent plantar ulceration, generally at the metatarsal heads. Leprosy

results in peripheral nerve enlargement.

Complications of leprosy not only result from direct invasion of the nontoxin producing organism but also to the response of the host's immune system referred to as reactional states. These intercurrent immune-mediated reactional states (Lepra Type I and Lepra Type II) can be the source of considerable morbidity and disability.

Leprosy is a disease with a well-defined clinical, histologic, and immunologic spectrum (Ridley et al., 1966). The form of leprosy is important in predicting disease complications, reactional states likely to be encountered, and the intensity and duration of required chemotherapy.

Clinical Manifestations of Leprosy

On one pole of the leprosy spectrum is the patient with lepromatous leprosy (LL). Lepromatous patients have symmetric skin nodules, plaques, and a thickened dermis. Since *M. leprae* grows best at low temperatures, the cool areas of the body, such as the ear lobes, are commonly affected. The warmer areas, the scalp, axilla, groin, and midline of the back are generally spared. Lepromatous leprosy patients may have loss of eyebrows, especially the lateral portions, and at times eyelashes and body hair. In untreated lepromatous leprosy patients a high-level afebrile continuous bacteremia is frequently found which may be so profuse that organisms are found in stained smears of peripheral blood "buffy" coats (Drutz et al., 1972).

In lepromatous patients, the upper respiratory system, particularly the nasal mucosa, is infiltrated with organisms, leading to chronic nasal congestion and epistaxis. In the preantibiotic era and occasionally even today, this process may extend to the nasal cartilage, leading to septal collapse and a "saddle nose" deformity. Peripheral neuropathy in lepromatous patients, when present, is often generalized and symmetric and frequently is associated with acral distal anesthesia of the hands and feet.

Tuberculoid leprosy (TT) represents the other pole of the leprosy spectrum. Patients with tuberculoid leprosy have one or a few hypopigmented anesthetic macules with distinct, often elevated and erythematous borders. Large and pathologic asymmetric peripheral nerve trunk involvement, often spatially associated with skin lesions, is found.

The majority of leprosy patients have manifestations intermediate between the two polar forms, a condition termed borderline leprosy. Depending on whether these manifestations are closer to the tuberculoid pole or the lepromatous pole, they are classified as borderline lepromatous or borderline tuberculoid.

Epidemiology

Worldwide, there are an estimated 6 million people with leprosy, 3 million of whom are still untreated. Leprosy is endemic in Asia, Africa, Latin America, and the Pacific; Africa has the highest disease prevalence, and Asia has the greatest number of cases. Eighty percent of worldwide cases are found in five countries: India (accounting for 60% of cases worldwide), Myanmar, Indonesia, Brazil, and Nigeria. Except as imported cases, leprosy is virtually absent from Canada, Northern and Western Europe, and the United States. In the United States there are about 7000 patients, mostly immigrants from Mexico, Southeast Asia, the Philippines, and the Caribbean. The annual incidence of newly diagnosed patients is about 200. Within the United States, Hawaii, Louisiana, California and Texas still report rare cases in individuals without a history of travel to endemic areas.

Therapy of Leprosy

Lifelong therapy for lepromatous leprosy, usually monotherapy with dapsone, had become standard from 1943 to 1970. With the advent of rifampin, which is far more bactericidal, shorter courses of multidrug therapy are advised.

Chemotherapy in leprosy rapidly renders the patient non-contagious to others, probably within the first few weeks of therapy. However, viable drug-sensitive bacterial persistence (Waters et al., 1978; Waters et al., 1987), despite prolonged multidrug regimens, including rifampin treatment, presents vital concerns, according to the submission. In 1982, the WHO (WHO Expert Committee on Leprosy, 1988) proposed and advocated multidrug regimens of limited duration after the model of chemotherapy for tuberculosis. For multibacillary leprosy the WHO (WHO Expert Committee on Leprosy, 1988) recommends dapsone 100 mg daily, plus clofazimine 50 mg daily, and monthly (supervised) rifampin 600 mg, plus clofazimine 300 mg for 2 years or until smear negativity.

For paucibacillary leprosy the WHO (WHO Expert Committee, 1988) recommends dapsone, 100 mg daily, plus monthly (supervised) rifampin, 600 mg, for a total duration of 6 months. The rationale behind the regimens was that multidrug chemotherapy (MDT) rapidly eradicates contagion, can be inexpensive (hence monthly and not daily rifampin), prevents drug resistance, and as a limited or short course, will improve compliance and is operationally more feasible.

According to the NDA submission, these WHO recommendations for MDT of limited duration antedated supportive clinical trials. The tremendous bacillary load of lepromatous leprosy, the long time to relapse after discontinuation of rifampin-containing regimens (averaging 7 years), and the affordability of available chemotherapy (as in the United States), caused some leprologists to resist these recommendations. Although relapse rates in multibacillary patients were reportedly low initially, relapse rates have ultimately been reported as high as 20% to 40% depending on the initial bacterial load (Jamet et al., 1995).

It is reported that many American leprologists have opted to use more conservative regimens until

firm scientific evidence of the efficacy of limited short-course regimens has been proven. Multibacillary leprosy is treated in the United States with dapsone, 100 mg, daily for a lifetime and rifampin, 600 mg, daily for the initial 3 years or until AFB skin smear negativity. For paucibacillary leprosy, 100 mg daily for a total of 5 years is the recommended therapy.

In the United States, clinically relevant primary dapsone resistance does not occur (Gelber et al., 1990). Therefore, dapsone's efficacy as effective monotherapy for paucibacillary or as a part of multidrug therapy for multibacillary leprosy can be relied on in the United States. This abrogates the need for rifampin additionally for paucibacillary leprosy and the requirement for clofazimine, in addition to dapsone and rifampin, for multibacillary disease. Furthermore, in multibacillary leprosy daily rifampin therapy has proven to be more effective than various intermittent rifampin schedules (Pattyn, 1993), and, because in the United States daily rifampin is certainly affordable, it is recommended that rifampin be administered daily for the initial 3 years of therapy.

Reactional States

Several types of reaction occur and are different clinically and immunologically. These reactions are the reversal and downgrading reactions (Lepra Type-1), erythema nodosum leprosum (ENL, Lepra Type-2), and a third, less common reaction, Lucio phenomenon.

Erythema Nodosum Leprosum (Lepra Type-2)

Erythema nodosum leprosum (ENL) occurs in half of borderline lepromatous and lepromatous leprosy patients and is an important cause of morbidity in these patients. Although ENL may be seen on initial presentation and be a precipitating cause for a patient to seek medical attention, it more commonly (90% of the time) develops within the first few years after bactericidal therapy has commenced. Episodes of ENL generally resolve spontaneously after about 5 years of treatment. However, at times ENL may persist even longer and exacerbate even after 5 to 10 years of specific antimicrobial therapy in patients who are apparently bacteriologically negative.

In the past, ENL often prompted discontinuation of specific antileprosy chemotherapy, particularly that of dapsone, although there is evidence that discontinuation of dapsone therapy in lepromatous leprosy patients does not actually alter the course of ENL. According to the Sponsor, many practitioners remain unconvinced: "...both patients and physicians often decide to discontinue antimicrobial therapy." Thus, because of intervening ENL, according to the Sponsor, some leprosy patients may go untreated for considerable periods of time, even indefinitely (Vol 2.1, pg. 08 4936).

Reviewer's comments:
Although not stated explicitly, the statements in the NDA, noted above, pertaining to physicians deciding to discontinue therapy appears to be a historical account and not the standard of practice today. 'Standard of practice' offers various therapies, most often Thalidomide, to ameliorate SIS of ENL.
MMC

The most common clinical manifestation of ENL is crops of painful erythematous nodules of the skin and subcutaneous tissues. If ENL is severe, pustules develop which can ulcerate, causing suppurative wounds and subsequent scarring. Unlike erythema nodosum, ENL is not limited to the lower extremities, and may be found virtually anywhere, but most often on the extensor surface of the forearms, medial thighs, and occasionally the face. Unlike erythema nodosum, individual lesions of ENL last only a few days. ENL is a systemic disorder at times associated with fever, neuritis, edema, malaise, anorexia, leukocytosis, and anemia. ENL may also include synovitis, nephritis, iritis, lymphadenitis, and epididymorchitis.

The syndrome of ENL is quite variable. Individual patients may experience one or any combination of the aforementioned manifestations. Attacks of ENL may be mild or severe in nature and some patients may experience the full range and severity of symptoms on different occasions. The course of a reaction may extend over a period of weeks or may show a chronic and at times stable debilitating course over several years.

ENL is a complication of leprosy that, in its most severe form, can result in serious debility, possibly even in fatality, according to the sponsor. *(The sponsor did not provide the reference for the general toxicity of ENL resulting in fatality).* Patients who present with systemic signs and symptoms such as fever, malaise, and arthralgias, are at risk of permanent damage if not adequately treated. Certain of the end organs affected by the inflammation of ENL, namely the peripheral nerves, testes, the anterior chamber of the eye, and kidneys may also be permanently damaged and may result in serious disability. Much of the morbidity and, in fact, deformity of leprosy, according to the sponsor, is a consequence of its associated neuropathy, ENL neuritis (peripheral nerve damage can also result from lepromatous leprosy in the absence of ENL). Progressive nerve damage may culminate in both insensitivity and muscle weakness, clawed hands, plantar ulcers and amputations of the distal extremities. The uveitis of ENL may result in cataracts and glaucoma, leprosy along with ENL being one of the leading causes of blindness in endemic areas of the world. The orchitis of ENL can cause hypogonadism with decreases in testosterone levels and aspermia, and consequently impotence and male infertility. Serious glomerulonephritis with hematuria and red blood cell casts occurs in ENL, with some patients ultimately developing hypertension, chronic glomerulonephritis, amyloidosis and even renal failure.

In many patients, ENL may be chronic and recurrent with skin lesions and fevers for several years, not uncommonly associated with an anemia of chronic infection, which involves both decreased red blood cell formation and an increased rate of red blood cell destruction. As a consequence these patients are often chronically ill and fatigued. They are often in chronic pain and suffer from insomnia. Furthermore, individual skin lesions can pustulate and ulcerate leading to obvious scarring, or may heal with either hypopigmentation or hyperpigmentation, disfiguring the patient.

Histologically ENL shows infiltrates of lymphocytes, macrophages, and particularly neutrophils, sometimes accompanied by a leukocytoclastic vasculitis that can involve both the dermis and subcutis. C3 and IgG can be present in the walls of venules (Waters et al., 1971). Thus, ENL is

histologically an acute vasculitis or panniculitis, widely thought to be secondary to immune complex deposition.

Approved therapy for ENL

Mild ENL episodes (only a few tender skin lesions with no ulcerations and no nerve or other organ involvement) can be treated symptomatically with antipyretic/anti-inflammatory analgesics and bed rest. Other conditions (i.e., pregnancy, stress, infections, successful vaccinations) which are possible precipitating causes should be identified.

Corticosteroids and clofazimine are approved and available therapies for acute and chronic recurrent episodes of ENL, respectively. Corticosteroids are effective in treating the ENL syndrome and particularly effective in the treatment of the acute neuritis of ENL. However, debilitating side effects are well known with prolonged corticosteroid therapy. Clofazimine is valuable not only as an antibacterial drug, but also as an anti-inflammatory agent for the treatment of ENL. It has been reported that the incidence of ENL was 5% where the MDT regimen is used, and this is thought to be because of the use of clofazimine (The Star, June 1996, a draft publication from Carville submitted to the Division in response to a query).

Clofazimine, 200 to 300 mg daily for six weeks, used adjunctively with corticosteroids may be useful in eliminating or reducing corticosteroid requirements. Clofazimine may cause gastrointestinal side effects, including rare reports of severe abdominal symptoms. Clofazimine also produces a reversible red-brown discoloration of the skin; however, it may take several months to years to fade after conclusion of therapy. According to the sponsor's submission, ENL patients refuse to take the medication because of the skin discoloration. However, advantages of clofazimine are that it is neither teratogenic nor neurotoxic and has antileprosy properties.

6.1 Relevant human experience

Thalidomide has been identified by the World Health Organization Expert Committee as the preferred ENL treatment in most patients. There are an estimated 5.5 million cases of Hansen's disease worldwide occurring primarily in sub-tropical regions of the world, with India, Brazil, Nigeria, and Myanmar (Burma) having the highest prevalence of cases. The number of new cases reported to the World Health Organization (WHO) in 1992 was approximately 690,000. According to the National Hansen's Disease Registry [maintained by the Gillis W. Long (GWL) Hansen's Disease Center, United States Public Health Service Hospital, in Carville, Louisiana], as of January 1995 the prevalence in the United States is about 7355, with an additional 246 cases registered in Puerto Rico. Approximately 250 new cases of leprosy are reported annually to the GWL Hansen's Disease Center. Approximately 10 new ENL patients were anticipated during 1996. ENL occurs in up to 50% of patients with LL (submitted as personal communication, between Leo Yoder, M.D., March 1995 and Celgene) and over 25% of patients with BL, with onset most common in the second and third years of treatment.

Thalidomide was a known teratogen and a reported neurotoxic agent at the time of withdrawal worldwide in 1962. There has been renewed interest in the putative immune-modulating properties of thalidomide; however, there has not been an approval for any indication. The use of thalidomide has been allowed for single-patient INDs for debilitating diseases where approved therapies have failed or cannot be tolerated.

Reviewer's comments:

1. *For over three decades since the first papers were published, thalidomide has been advocated by some leprologists for the treatment of ENL. However, thalidomide remains an investigational drug in the United States. The WHO Expert Committee on Leprosy (1988, Section 3.6.1, pg,. 18) was general in its recommendation and did not provide specific indications (acute initial episode, recurrent episode, or chronic suppressive therapy). The recommendation stated that "The treatment of choice for ENL is thalidomide and the importance of making the drug available cannot be overstressed". It was pointed out that it should only be given to men and postmenopausal women. Treatment of women of child-bearing age should never be thalidomide, instead clofazimine should be supplemented with corticosteroids for controlling severe ENL reactions and complications, such as persistent neuritis and iritis.*

   Thalidomide's use in the treatment of ENL has not been universally accepted by leprologists. Dr. C. L. Crawford has been critical of the recommendation by WHO Expert Committee on this recommendation and has commented on the difficulty of differentiating thalidomide neuropathy from leprous neuropathy (Adverse Drug React. Toxicol. Rev. 1994, 13(4) 177-192). Dr. Crawford has expressed opposition to the use of thalidomide from a safety perspective, as it is a teratogen and neurotoxin. Dr. Crawford contends that, contrary to the acceptance by some leprologists of the rarity of thalidomide-induced neuropathy in ENL patients, thalidomide-induced neuropathy has not been ruled out. Dr. Crawford stresses that a detailed sensory examination of the peripheral nervous system should be carried out and recorded before starting thalidomide treatment and contends that this can be accomplished without specialized equipment. Any deterioration in function while thalidomide is being administered should be assumed to be due to the drug, since sensory loss in lepromatous leprosy occurs late in the disease. The issue of peripheral neuropathy in patients with ENL will be reviewed in depth under Section 10.

2. *The entire syndrome of ENL was named for the most common clinical manifestation, which is the crops of painful erythematous nodules of the skin and subcutaneous tissues. According to Pfaltzgraff and Ramu, 1994 " Type 2 reactions are also known as erythema nodosun leprosum (ENL). The skin lesions are only one manifestation of the reaction, possibly the most common but not the most serious ... ".*

In reviewing drugs for the indication of ENL, it is crucial to differentiate between efficacy for the systemic syndrome and efficacy confined to the cutaneous manifestations, for which the systemic disorder is named.

Most of the published studies in the treatment of the ENL syndrome were conducted in the middle 1960s to the early 1970s. Since those early reports and clinical trials, the management of ENL has changed. Initial reports had suggested that thalidomide is efficacious in all aspects of the ENL syndrome. More recent recommendations are as follows:

"Any patient with evidence of neuritis should be treated with prednisone", is advocated in the text of Treatment of ENL in Management of Reactions In Hansen's Disease, The Star (June 1996). Table 2, of the publication, Treatment of Reactions, lists, in addition to other recommendations under ENL treatment: ... "Always use prednisone for neuritis...".

Dr. Leo Yoder, in his October 30, 1996 response to a Division query to Celgene regarding the safety of including patients in Protocol E-003/P with ENL neuritis coupled with the exclusion of the use of corticosteroids, stated that "...thalidomide's therapeutic effect on acute neuritis is too slow to be used alone in most cases".

Gelber, R.H. and Kawamura, L.M., recommend in Leprosy, Chapter 112, pg 1002, the following: "... if episodes are severe with multiple erythema nodosum leprosum skin lesions generalized with symptoms of fever and malaise, or are associated with neuritis, orchitis, lymphadenitis, arthritis, or other similar condition, initiation of treatment with prednisone is indicated." The authors contend that thalidomide in doses of 100 to 300 mg per night is as effective as prednisone in treating ENL, but thalidomide alone has a more delayed onset of action, generally several days to a week. However, initial doses of prednisone of 40 to 60 mg daily rapidly improve symptoms within 24 to 48 hours and can be abruptly discontinued in one week.

According to the original protocol for IND 11,359 "Any patient having ENL may be treated with thalidomide provided that the following requirements have been met... item (8) No significant neuritis is present...." (Vol. 1.1, pg.15). The definition of "significant" is unstated.

3. *No scientific basis, such as dose-ranging studies, for the dosages of thalidomide used historically has been presented. Dosages in clinical reports range from 100 to 600 mg of thalidomide daily.*

6.2 Important information from related INDs and NDAs

IND 11,359 will be reviewed in detail under Study L-002.

IND 48,177 will be reviewed under Study E-001 and E-003/P

6.3 Foreign experience

Celgene has not marketed thalidomide in any country. While thalidomide from other sources was commercially available in Europe and elsewhere in the late 1950s and early 1960s, Celgene has not reported access to any data obtained from this era.

6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

(This section was co-authored by the primary and secondary reviewers)

Although thalidomide has been used for more than 30 years, pharmacokinetic data have only recently been obtained. The development program undertaken by Celgene to describe the pharmacokinetics and bioavailability of thalidomide includes characteristics of pharmacokinetics, dose proportionality over the recommended clinical range, and metabolism in patients with Hansen's disease. Steady state plasma and urine levels of thalidomide in patients with ENL, chronically receiving thalidomide, are being collected.

Aspects of the PK data relevant to the safety of thalidomide are reviewed briefly below; see Biopharmaceutics review for additional information.

A Celgene Sponsored Ongoing Studies:

1. PK-003 is a 200 mg dose drug interaction/oral contraceptives study in 12 healthy volunteers

2. PKUK-001 is a crossover 100 and 200 mg dose proportionality study in 15 HIV-seropositive patients

3. E-001 is a steady-state PK study in an unstated number of ENL patients (dose not specified)

Reviewer's comments:

The number of ENL patients and the dose of thalidomide was not provided for the steady-state PK of Study E-001, and the status of the study is unclear (see PK review).

B Planned Studies:

1. E-003/P is a steady-state PK study in an unstated number of ENL patients (dose not specified)

2. PK-006 is a 200 mg dose, food vs fasting study in healthy volunteers.

C Completed Studies:

Study Site: [

]

Investigator: [ ]

Study Dates: *(not provided)*

Overview: Thirty-eight subjects were exposed to single doses of thalidomide given on one or three occasions with 1- to 2- week washout periods between doses.

Table 1. **<u>Completed</u> Single Dose Clinical Pharmacology Studies Conducted with Thalidomide** (October 31, 1996)

Study No.	Population/No	Design	Dose(s)
PK-001	Healthy Volunteers/17	Crossover Bioequivalence	200 mg
PK-004	Healthy Volunteers/15	Crossover Dose proportionality	50 mg 200 mg 400 mg
PK-005	Hansen's Disease Patients/6	Single Dose	400 mg

Table 2 Demographics (PK Studies 001, 004 and 005):

Demographic Feature	Number of Patients
Gender:	
Male	33 (87%)
Female	5 (13%)
Ethnicity/Geographic Category:	
Caucasian	31 (82%)
Hispanic	4 (11%)
Asian or Polynesian	2 (5%)
Black	1 (3%)
Age (Years):	
Mean	33.5 years
Range	20 to 69
Healthy Volunteers	32
Hansen's disease patients	6

Study PK-001

Title: Single dose, open-label, three-way, cross-over study (N = 17).

Objective: A single dose, open-label, three-way, cross-over study designed to investigate the bioequivalence of three thalidomide capsules: Celgene's proposed commercial formulation used in ongoing clinical studies (E-001 and E-003/P), Celgene's clinical trials formulation used in many of the ongoing AIDS-related indications, and a non-Celgene formulation manufactured by Tortuga, a Brazilian manufacturer who most recently supplied the U.S.P.H.S.G.W.L. Hansen's Disease Center (IND 11,359).

Procedure: Subjects were randomly assigned to one of three treatment groups. Each group received thalidomide in three different sequences. In each period, the dose was administered with 240 ml of water after a 10-hour overnight fast. Fasting continued for 4 hours post-dose. There was a one week washout period between dosing.

Results: Celgene's two formulations are bioequivalent based on confidence interval calculations. However, the Tortuga formulation was not bioequivalent to either of the Celgene formulations.

Reviewer's Comment:

The possible clinical implications of the lack of bioavailability between the Tortuga formulation and the Celgene formulations will be discussed under Section 10.4 Safety.

Adverse Experiences PK-001

In addition to the AEs listed in the overall summary of adverse experiences for the PK studies at the end of this section, the following were noted by the Sponsor :

1. EKGs were normal pre- and post-treatment, except for Nos. 3 and 8 who were noted as having bradycardia post-treatment, with an otherwise normal EKG.

2. Two subjects (Nos. 2 and 7) experienced hypotension upon standing, diaphoresis, and lightheadedness. In one case, a 23 year old male, the standing blood pressure of this symptomatic subject "could not be obtained" 45 minutes post-dosing with 200mg of the Celgene clinical trial formula. At the 3.75 hour measurement, his standing vital signs were BP 79/43, P 112 (seated BP 100/61, P78). The second subject, a 35 year old male, experienced somnolence and light-headedness 30 minutes after dosing. He became diaphoretic with pallor with a standing BP of 89/55 (also 45 minutes post-dosing; this was the Celgene commercial formulation). Both events were considered to be "almost certainly" related to the study drug by the investigator.

3. Overall, at approximately 0.75 to 11.75 hours after dosing, there is a small (mmHg) decrease in systolic and diastolic blood pressure, with a return to pre-dose values approximately 23.5 hours after dosing. Seated and standing vital signs (blood pressure and pulse) were summarized.

Reviewer's Comments:

1. *A temperature peak above 99.5^{0}F was noted in 12 patients, most commonly occurring at 11.75 hours (range 3.75 to 35.75 hours) after dosing. Temperature peaks were recorded as high as 100.1^{0}F, with normal baseline readings with the exception of Patient No. 1. Exit temperature recordings had returned within the normal range at the 47.75 study hour exit. The clinical significance of this observation is unknown. Statistical analysis has not been performed. No comment regarding this observation was made by the Sponsor.*

2. *It is noted that both subjects who experienced drug related symptomatic postural hypotension received Celgene formulations, both of which, as reviewed by Biopharmaceutics, are much more bioavailable than the Tortuga formulation. It is also noted that the standing BPs followed a measurement in the seated position instead of a prone*

position and therefore the observations may be an underestimate of the incidence and degree of postural hypotension.

Study PK-004

Title: Single Dose, Open-label, Three-way Crossover Study (N = 15)

Objective: Phase 1 single dose, open-label, three way crossover study. The study was conducted in 14 healthy male and female volunteers, to characterize the single dose pharmacokinetics of thalidomide and to assess its dose proportionality over the clinical dose range of 50 mg to 400 mgs.

Adverse Experiences:

1. One patient, a 33 y.o. Caucasian female discontinued participation after the first period of study PK-004, during which she received the Celgene commercial formulation. Discontinuation was due to pharyngitis for which she received penicillin.

2. At approximately 1.75 to 5.75 hours after dosing, there is a slight (mmHg) decrease in systolic and diastolic blood pressure among all dose groups, with a return to baseline values approximately 47.5 hours after dosing.

Reviewer's comments:

1. The disposition of all patients entered is unclear. There is a discrepancy in the numbers of patients listed above, specifically, between the number of patients provided in the "Summary of Pharmacokinetic Parameters Following Single Doses" (N=15) and the reported "Mean seated blood pressure and pulse by dose" (N=12).

2. Vital signs for this study are discussed with the next study.

Study PK-005

Title: A Phase 1 Single Dose Study of Thalidomide Pharmacokinetics in Patients with Hansen's Disease

Objectives: This study had two objectives. One objective was to characterize the single dose pharmacokinetics of thalidomide in patients with Hansen's Disease. The other objective was to assess the metabolism of thalidomide following a 400 mg dose.

Procedures: Six patients with a diagnosis of Hansen's disease (lepromatous or borderline

lepromatous leprosy) were screened within 30 days prior to study enrollment by Leo Yoder, M.D., and flown to Phoenix AZ, for the study.

Adverse Experiences:

According to the Sponsor, statistical analysis has not been performed; however, there appears to be a possible decrease in systolic and diastolic blood pressures 6 hours-post-dose, with no change in pulse. On average, the decrease was 15 mmHg in systolic blood pressure; a 12 mmHg decrease was observed in diastolic blood pressure.

Sponsor's Safety Summary:

In PK-001 study, there appeared to be approximately a 5 mm Hg decrease in seated and standing systolic and in standing diastolic pressures during the time periods when thalidomide concentrations are maximal. This effect was seen in Study PK-004 where only seated vital signs were measured. There did not appear to be any dose-relationship to this effect.

Table 3 **Adverse events in single dose pharmacokinetic studies: total and summarized by dose** (as reproduced from NDA submission)

Adverse Event (Preferred Term)	Total (%) (N=38)	By Dose		
		50 mg (N=14)	200 mg (N=32)	400 mg (N=20)
Body as a Whole				
Headache	15(39%)	2(14%)	7(22%)	7(35%)
Asthenia	12(32%)	--	12(37%)	--
Pain - chest wall	2(5%)	--	2(6%)	--
Pain abdo	1(3%)	--	--	1(5%)
Pain	1(3%)	--	1(3%)	--
Cardiovascular System				
Hypotension	2(5%)	--	2(6%)	--
Pallor	2(5%)	--	2(6%)	--

Digestive System				
Nausea	4(16%)	--	3(9%)	1(5%)
Diarrhea	4(11%)	1(7%)	--	3(15%)
Constipation	3(8%)	--	--	3(15%)
Dry mouth	2(5%)	1(7%)	--	1(5%)
Dyspepsia	1(3%)	--	--	1(5%)
Vomit	1(3%)	--	--	1(5%)
Nervous System				
Dizziness	33(87%)	2(14%)	27(84%)	13(65%)
Somnolence	29(76%)	1(7%)	18(56%)	10(50%)
Hypertonia	3(8%)	1(7%)	1(3%)	1(5%)
Coordination abnormal	1(5%)	--	1(3%)	--
Paresthesia(1 or 2 patients)	2(5%)	--	2(6%)	--
Cramps leg	1(5%)	--	--	1(5%)
Silly feeling	2(5%)	1(7%)	--	--
Respiratory System				
Cough(ing)	2(5%)	--	1(3%)	1(5%)
Pharyngitis	2(5%)	1(7%)	1(3%)	--
Skin and Appendages				
Abrasion	1(3%)	--	1(3%)	--
Rash	1(3%)	--	1(3%)	--
Rhinitis	2(5%)	--	1(3%)	1(5%)
Sweat(diaphoretic)	2(5%)	--	2(6%)	--
Blister(left lower lip)	1(3%)	--	--	1(5%)
Redness	1(3%)	--	1(3%)	--
Cold	1(3%)	--	1(3%)	--

Reviewer's Comment:

1. *The occurrence of postural hypotension in PK Studies -004 and -005, cannot be assessed because standing blood pressures in these studies were not performed as in PK-001, where the two cases of hypotension noted would not have been detected unless standing blood pressures were measured. For this reason, the above table is misleading because the denominator for hypotension is 38, the total number of subjects for all 3 PK studies. In fact, the incidence is 12% of the subjects who received Celgene formulations and were assessed, from a sitting to standing position, for postural hypotension.*

2. *The occurrence of temperature spikes in PK Studies -004 and -005 cannot be assessed because complete temperature data were not collected in these studies, as they were in PK-001 where a distinct temperature peak was noted in 12 of 17 subjects.*

3. *In PK-004, all 14 screening pulses (-13.5 hrs) were lower than those measured 30 minutes prior to administration of the drug (the last pre-dose measurement). In 6/14 cases this difference was greater than or equal to 15 BPM and in 3 of these subjects the screening pulses were in the 40s (42-49). The reason for this is unknown. A statistical analysis by our statisticians indicate that among all 3 doses, for which there was no dose response relationship, 15 subjects had a pulse recorded below 50 and 28 did not. For unknown reasons, the table above, submitted by the sponsor, does not list bradycardia.*

6.6 Directions for Use

Dosage and Administration:

For an acute episode of ENL, thalidomide dosing should be initiated at 100 to 200 mg/day, administered once daily with water, preferably at bedtime and at least one hour after the evening meal.

In patients with a severe ENL reaction, or who have previously required higher doses to control the reaction, dosing may be initiated in doses as high as 300 to 400 mg/day, once daily at bedtime or in divided doses with water, at least one hour after meals. Thalidomide should be administered in conjunction with corticosteroids. Once the most serious symptoms predictive of irreversible morbidity, such as neuritis, orchitis, uveitis, nephritis, extensive cutaneous lesions that may be ulcerating and high fever, are under control, the corticosteroids may be tapered and discontinued.

Dosing with thalidomide should continue until systemic signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.

Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of ENL or who flare during tapering, should be maintained on the minimum dose necessary to control the reaction. Tapering off medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.

Reviewer's comments: *These Directions are as submitted by the sponsor; they will be addressed throughout the review.*

7 Description of Clinical Data Sources

Table 4 Data Sources

Name of Study	Type of Information
L-001	Retrospective Primary Data Review of Published Study
L-002	Retrospective Review of 16 Year Experience Under USPHS IND 11,359 Through 1994
L-003	Review of Published Literature - Efficacy, ENL
L-004	Review of Published Literature - Safety, ENL
L-005	Review of Published Literature - Safety, non-ENL
Neurologic Report	Review of Published Literature - Peripheral Neuropathy
E-003/P	Preliminary Progress Report, On-going Celgene Sponsored Clinical Trial, ENL
E-001/E-003/P	Adverse Event Summary, On-going Celgene Sponsored Clinical Trial, ENL

8 Studies Study L-001

Reviewer's comment: *The review of Study L-001 is arranged in three sections:*

A) The results of the original published placebo controlled trial, "Thalidomide in the treatment of erythema nodosum leprosum with a note on selected laboratory abnormalities in erythema nodosum leprosum" (Hastings RC, JR Trautman, CD

Enna, RR Jacobson. Clin Pharm and Therapeutics 11: 481-87, 1970)

B) The results of the retrospective corroboration and expansion of the Hastings et al., 1970 Study," A Retrospective Collection of Source Documents for the Study Entitled "Thalidomide in the Treatment of Erythema Nodosum Leprosum" (Study L-001) as presented by the Celgene Corporation.

C) Medical Officer's review of the retrospective data submitted (Study L-001).

Note that this review is not intended as a scientific critique of the merits of Dr. Hasting's paper. Instead, the review is intended to analyze whether the Sponsor was able to adequately provide supportive documentation for efficacy and safety of thalidomide from this patient database.

Background

Study L-001, a retrospective study of the medical records of patients with active lepromatous leprosy and erythema nodosum leprosum reactions who were treated at a United States Public Health Hospital with thalidomide in the late 1960's under an investigators protocol, is being submitted by the Sponsor in support of this NDA. The results of the placebo controlled study were published in 1970, Thalidomide in the treatment of erythema nodosum leprosum With a note on selected laboratory abnormalities in erythema nodosum leprosum. Clinical Pharmacology and Therapeutics Vol 11 pages 481 - 487, 1970.

According to the Sponsor, Dr. Hastings provided Celgene access to the supportive medical records in order to allow confirmation of the results of the published study. This report (L-001) reflects a retrospective review of the medical records of the patients who participated in the study.

The objective of Study L-001 was to corroborate and expand upon Dr. Hastings' publication and thereby demonstrate the safety and efficacy of thalidomide 400 mg/day in treating acute ENL in persons with LL, in support of this NDA.

8.1 Indication: Chronic Erythema Nodosun Leprosum

8.1.1 Reviewer's Trial # 1 Sponsor's Protocol # L-001

A Published Study

Title: Thalidomide in the treatment of erythema nodosum leprosum with a note on selected laboratory abnormalities in erythema nodosum leprosum, Hastings et al., (1970)

(Celgene Corporation's Final Study Report L-001)

8.1.1.1 Objective/Rationale

Dr. Robert C. Hastings of the Public Health Services Hospital (PHSH) in Carville, LA, conducted a clinical study in the late 1960s in patients with chronic ENL reactions. The purpose of the investigation was "to evaluate thalidomide in the treatment of erythema nodosum leprosum (ENL) reactions occurring in lepromatous leprosy with the use of two rigidly defined objective criteria for success or failure. The design of the investigation also afforded an opportunity to study some aspects of the pathophysiology of ENL by means of selected, serially performed laboratory determinations".

The results of the placebo controlled trial, Thalidomide in the treatment of erythema nodosum leprosum with a note on selected laboratory abnormalities in erythema nodosum leprosum (Hastings RC, JR Trautman, CD Enna, RR Jacobson. Clin Pharm and Therapeutics 11: 481-87, 1970) a copy is attached **(Appendix 1).**

8.1.1.2 Design

A one center, randomized, placebo controlled, in part single-blinded and in part double-blinded study was conducted in the United States under the direction of the Principal Investigator, Dr. Robert C. Hastings. The study was conducted in the inpatient infirmary of what is now called the National Hansen's Disease Research Center (NHDRC), also known as the Gillis W. Long Hansen's Disease Research Center.

According to the published report, a total of forty-four trials of thalidomide or placebo were conducted in 22 patients with active lepromatous leprosy (LL) and chronic ENL reactions. The first 21 trials were single-blinded (the physician observer, R.C.H., was aware of the treatment but the patient was blinded) and the last 23 trials were "double-blinded". One patient participated in five trials and two patients in four trials each, with the remainder involved in three trials or less. Approximately half of the trials were with thalidomide and the remaining with placebo in those patients involved in more than one trial.

8.1.1.3 Protocols

According to the Sponsor, Dr. Hastings indicated that a protocol and randomization code were used in the conduct of the study but that all original records, other than a listing of all patients treated with thalidomide at NHDC and patient medical records, were lost when Dr. Hastings moved from the NHDC to the University of Louisiana. According to the Sponsor, Dr. Hastings indicated to Celgene that a complete description of the study protocol was published (Hastings et al, 1970) and is summarized in the study participation note inserted into the patient's medical record. According to Celgene, Dr. Hastings also indicated that he carried out the study according to the protocol.

Original Published Protocol Procedures:
(as stated in the published article)

Male or post-menopausal female patients with lepromatous leprosy and chronic ENL reactions were selected and admitted to the hospital infirmary at the United States Public Health Service Hospital, Carville, LA. Patients were allowed to continue antileprosy treatment while in the study.

1) All antireaction treatment was discontinued, including corticosteroids, aspirin, and any other antipyretic, anti-inflammatory, or other drug known or thought to be of benefit in the treatment of ENL, except in five cases. In the five exceptions noted, prednisone 2.5 mg TID was continued orally every 8 hours (because of the possibility of iatrogenic adrenal insufficiency due to prolonged use of corticosteroid).

2) The patients were observed for three days while current antileprosy chemotherapy was continued.

3) The only new drugs prescribed were codeine, meperidine, and secobarbital as needed for pain and sleep.

4) Oral temperatures were taken each day at 7 AM, 11 AM, 3 PM, and 7 PM, and clinical examinations were made daily in the morning for the presence of freshly appearing ENL skin lesions.

5) Laboratory determinations were made at the time of admission to the infirmary and were repeated three times weekly during the ensuing periods of observation and treatment with thalidomide or placebo.

6) On the morning of the fourth day of observation, patients were admitted into the trial if they had had a daily temperature maximum exceeding 99.6^0 F. (37.6^0 C.) and freshly appearing lesions were present.

7) Each patient admitted into the trial was given thalidomide, 100 mg four times daily by mouth, or an identical placebo, four times daily for four days.

8) On the fourth day of treatment the trial was classed as:

   a success, if no freshly appearing ENL lesions were present and the temperature maximum was less than 99.6^0F (37.6^0C), or

   a failure, if freshly appearing ENL lesions were present or the temperature maximum was 99.6^0F (37.6^0C) or greater.

8.1.1.3.1 Population

Twenty-two patients, male or post-menopausal female, with lepromatous leprosy and chronic ENL

reactions were selected and admitted to the hospital infirmary at the United States Public Health Service Hospital, Carville, LA.

Reviewer's comment: *Other demographic data were not provided in the published report.*

Published Results:

Thalidomide was successful in 8 of 13 single-blind trials, and placebo was classified as a failure in 8 of 8 single-blind trials. In the double-blind trials, thalidomide was successful in 11 of 15 and placebo failed in 8 of 8 cases.

According to the published text, the chi square test was applied to the results which related to the effectiveness of thalidomide in the treatment of ENL. The t ratio test for paired observations was applied to the maximum daily temperatures and the laboratory data.

Table 5 The effectiveness of thalidomide in the treatment of ENL as published. (results from 21 single-blind and 23 double blind trials)

Treatment	Cases classed as:			
	Success		Failure	
	Number	%	Number	%
Thalidomide	19	68	9	32
Placebo	0	0	16	100

Statistically significant at the 1 percent level.

Table 6 The effectiveness of thalidomide in the double-blind treatment of ENL (extrapolated from published text)

Double-blind Treatment	Cases classed as:			
	Success		Failure	
	Number	%	Number	%
Thalidomide	11	73	4	27
Placebo	0	0	8	100

Original Study Published Conclusion:

"Forty-four trials of thalidomide or an identical placebo have been conducted in 22 patients with active lepromatous leprosy and erythema nodosum leprosum (chronic ENL) reactions. Thalidomide is significantly superior to placebo in completely alleviating the two principal signs of ENL, fever and skin lesions...Despite its teratogenic effect, thalidomide is less toxic than corticosteroids and therefore seems to represent a major advance in the management of ENL. Its mechanism of action in ENL is unknown."

Reviewer's Comments:

This study did not assess or provide a discussion of the effect of thalidomide on acute neuritis or other debilitating aspects of the ENL syndrome.

B. Retrospective Study Protocol Study (Study L-001)

Title: **A Retrospective Collection of Source Documents for the Study Entitled "Thalidomide in the Treatment of Erythema Nodosum Leprosum" (Protocol L-001).**

Objective: The objective of Study L-001 was to corroborate and expand upon Dr. Hastings' publication and thereby demonstrate the safety and efficacy of thalidomide 400 mg/day in treating acute ENL in persons with LL, in support of this NDA.

Design: Twenty-six double-blind placebo controlled trials, identified as those trials conducted between June 12, 1967 and February 10, 1969, representing "the original study sample".

Procedures: A strategy was devised to identify patients who participated in the study and to retrospectively collect data from medical records. A protocol for data collection and Case Report Forms (CRFs) were created for the purposes of data collection, entry, and analysis. These CRFs were designed on the basis of Dr. Hastings' publication prior to the initiation of data collection, and were reviewed by Dr. Hastings. Medical records reviewed included hospital admission records, medication and treatment records, narrative summaries, history of present illness, doctor's progress notes, doctors orders, nursing notes, and temperature records as available for each patient.

Data Collection:

The Case Report Forms (CFRs) for data collection were based upon the published study. Data were initially collected by a hospital employee and then during two separate trips to the NHDRC by Celgene Corporation personnel. During these visits, selected data from the

original patient medical records were transcribed onto the CFRs. Portions of the patient records were also photocopied and retained. However, photocopying of the source documents was not done for all sources of data. Data was collected for the duration of open-label treatment for up to 20 months for some patients.

The first date that the double blind treatment with "Bottle A" was received was called the "index date". Bottle "A" contained thalidomide or an identical placebo. Bottle "B" contained the alternate treatment (submission dated 3/6/97, pg. 000238).

Data regarding treatments received in the months prior to the study participation were collected. Collection for safety and efficacy data began as follows:

1) the 4-day pre-treatment observation period immediately preceding the start of the index date, designed as Days -4, -3, -2, and -1,

2) data collection continuing through the double-blind period designated as Days 1, 2, 3, and 4, and

3) data collection of continued treatment beyond the double blind period.

Data Creation:

Using the CFRs as a template, a Paradox database was designed to score the transcribed patient data. Data entered into the form were automatically recorded in one of the many parameter-specific tables contained within the database.

Study Population

Patients who participated in Dr. Hastings' clinical study were identified from a listing maintained by the NHDRC of all patients who at any time had received thalidomide (Appendix 3). One hundred twenty-four patients were identified, with the earliest date of treatment listed as March 14, 1966 and the most recent date of treatment listed as April 1991.

Fifty-three patients were identified who initiated treatment with thalidomide prior to 1970. Twenty-six of the 53 patients were treated by physicians other than Dr. Hastings and were not included in the retrospective study.

Twenty-seven patients were identified as treated by Dr. Hastings, entering the double-blind study between June 12, 1967 and February 10, 1969. These patients are considered "the original study sample" and were entered into the retrospective study. Two of the "original study sample" patients

discontinued prior to receiving double-blind treatment. Patient No. 2553, a 65 y.o. Asian male, died of acute myocardial infarction on [ ] prior to treatment with thalidomide and patient No. 2862, a 36 y.o. Caucasian male did not have a history of chronic ENL. Twenty-five patients received the study drug and comprised the study sample.

Reviewer's Comments:

The following comments are related to the "Listing of Patients at the National Hansen's Disease Center in Carville, LA", who at any time had received thalidomide and from which Celgene identified patients.

1. *In order to interpret the entries for the "Listing of Patients at the National Hansen's Disease Center in Carville, LA" (Appendix 3), additional information would be needed regarding the listed dates. Specifically, the dates listed do not always correlate with the index dates for study initiation.*

2. *Patient 2553, a 65 y.o. Asian male who died of acute myocardial infarction on [ ] is listed in the "Listing of Patients at the National Hansen's Disease Center in Carville, LA" as receiving 4 doses on [ ] Volume 2.20, page 08 0067 states that the patient died the day treatment was to have commenced. The Sponsor indicated that "A review of the medical chart showed no evidence that he received any doses of Bottle A".*

3. *Dr. Yoder (verbal communication 6-4-97) indicated that the "Listing" had been maintained for a number of years at Carville by an non-medical employee in the Medical Records Department at the NHDRC and the "Listing" could not be relied upon for accuracy.*

4. *Two patients were identified in a June 17, 1997 submission, originally submitted as "the original study sample", who were treated with thalidomide by investigators other than Dr. Hastings.*

A **Demographics:** (Dr. Hastings' Original Study Sample as identified by Celgene Corporation)

Table 7

Demographic Feature	Number of Patients (N = 25)
Gender:	
Male	22(88%)
Female	3(12%)
Reproductive Status (if female):	
Post-menopausal	3
Surgically Sterilized	0
Using Contraception	0
Ethnicity/Geographic Category:	
Hispanic	12 (48%)
Asian or Polynesian	8 (32%)
Black	3 (12%)
Caucasian	2 (8%)
Age (Years):	
Mean± S.D.	47.4 ± 16.2
Range	20 - 87

Disease Characteristics and Prior Treatment:

All patients had a diagnosis of chronic ENL. Date of the first ENL episode was not available for 3 patients (Nos. 1274, 2603, and 2643); however, for the remaining 22 patients, the first ENL episode occurrence ranged from 1 to 36 years. Patients were allowed to continue on antileprosy treatment while on this study. Dapsone monotherapy was most commonly used.
Within the year prior to the index date:

1) seventeen patients received corticosteroids including prednisone, prednisolone, dexamethasone, and corticotropin (ACTH); topical and ophthalmic steroid preparations were also used

2) seven patients received aspirin or indomethacin

3) additional medications taken to control ENL or its sequelae included Darvon, codeine, demerol, bicillin, declomycin, and griseofulvin

4) three patients had received open label thalidomide previously; a fourth patient had received placebo only

Pre-treatment Observations

Table 8 : Celgene's Listing of patients receiving steroids prior to and at the time of study entry

	N	Thalidomide Patient Numbers	Placebo Patient Numbers
Corticosteroids discontinued at study entry	9	1707, 1983, 2033, 2078, 2720, 2840, 2861	2274, 2643
Prednisone 2.5 mg TID continued	2		2847, 2603
Corticosteroids discontinued within one month prior to entry	2	869, 1274	
Prednisone recorded (no stop dates)	3	2757	2323, 2793

Nine patients in the thalidomide group and 2 patients in the placebo group were identified as having discontinued corticosteroids at study entry. Two patients continued prednisone 2.5 mg TID.

Reviewer's comments:

1. *More than three patients should be listed as having received thalidomide prior to the index date of the double-blind study. The submission stated that 3 patients had received thalidomide prior to the index date and these three were not identified. Based on the published article, forty-four trials of thalidomide or placebo were conducted in 22 patients. The first 21 trials were single-blinded (the physician observer, R.C.H., was aware of the treatment but the patient was blinded) and the last 23 trials were "double-blinded". One patient participated in 5 trials and 2 patients participated in 4 trials each, with the remainder involved in 3 trials or less. In the instances in which the patient was involved in more than one trial, approximately half the trials were with thalidomide and the remaining with placebo.*

2. *A listing which clearly identified the dates of the single-blind treatment periods was not provided.*

3. *There is an unexplained imbalance in the number of ENL patients who discontinued corticosteroid therapy at trial entry who were assigned to the thalidomide treatment arm (N=7) vs patients assigned to the placebo arm (N=2).*

Retrospective Study Protocol (Study L-001)

In addition to the initial double-blind trial period described in the original published study, data collection by Celgene continued through "continued treatment periods" ranging up to 20 months for some patients.

After selection and admission to the infirmary, the patient was placed on a protocol (example admission sheet provided in Appendix 2). The efficacy assessments for L-001 are as follows:

1) On the fourth day of double-blind treatment period, a response to treatment assessment was made as follows:

   a success, if no freshly appearing ENL lesions were present and the temperature maximum was less than 99.6^{0}F (37.6^{0}C), or

   a failure, if freshly appearing ENL lesions were present or the temperature maximum was 99.6^{0}F (37.6^{0}C) or greater.

2) Patients were continued on treatment in a double-blinded fashion for four additional days in the event of a response or switched to Bottle "B" (the alternative treatment) in the event of treatment failure. The physician's rationale for switching was stated in the progress notes.

Randomization: *The randomization code was not provided.*

Treatment Assignment, ENL Lesion Assessments, and Response to Therapy:

Double blind treatment was identified for 25 of the 26 treatment courses (in 24 of the 25 patients). The first date that the double blind treatment with "Bottle A" was received was called the "Index Date".

The Sponsor attempted to document the content of "Bottle A" assignment (thalidomide or placebo) for each of the 25 patients, from the following sources: doctor's progress notes, doctor's orders, nursing notes, and medication records.

Collection for efficacy and safety began with the 4-day pre-treatment observation period preceding the index date, designated as Days -4, -3, -2, and -1, with Day-1 the day immediately preceding the start of the double blind treatment. Data were collected beyond the double blind treatment period. The length of continued treatment data collection ranged up to 20 months.

Reviewer's comments: *The rationale was unstated regarding the differences between patients in duration of data collection after the end of the blinded treatment.*

ENL Lesion Assessments:

Doctor's progress notes were reviewed for comments regarding the presence of new ENL lesions. Lesion assessments were available for Day 4 of the double blind study for 13 patients (14 episodes). For the remaining 11 patients, lesion assessments for other days were reviewed to evaluate efficacy.

Enrolled patients, designated as " the original study sample" by Celgene, are as follows: Sponsor's assessment (All Patients)

Number of Patients = 25 **Number of Trials = 26[*]**

Pt#	Age	Sex/Race	Index Date	"Bottle A"
869	53	M/Asian	01/15/68	thalidomide
1274	49	M/Asian	07/08/68	thalidomide
1707	64	M/Hispanic	06/10/68	thalidomide
1983	68	F/Caucasian	01/15/68	thalidomide
2033	37	M/Caucasian	03/04/68	thalidomide
2078	65	M/Asian	03/04/68	thalidomide
2274	38	M/Hispanic	01/15/68	placebo
2323	41	M/Asian	02/10/69	placebo
2601	40	M/Hispanic	01/15/68	thalidomide
2603	41	M/Hispanic	01/15/68	placebo
2643	88	M/Hispanic	01/15/68	placebo
2655	27	M/Black	09/13/68	placebo
2703	49	M/Hispanic	01/29/68	placebo
2720	24	M/Asian	01/29/68	thalidomide
2757	47	M/Hispanic	05/27/68	thalidomide
2767	25	M/Asian	06/12/67	thalidomide
2773	48	M/Black	03/04/68	placebo
2793	61	M/Hispanic	07/26/68	placebo
2808[a]	40	M/Hispanic	05/27/68	placebo
2808[b]	40	M/Hispanic	02/17/69	placebo
2824	67	M/Hispanic	10/04/68	placebo
2840	64	F/Black	10/21/68	thalidomide
2847	57	F/Asian	01/15/68	placebo
2855	20	M/Hispanic	03/04/68	uncertain
2861	47	M/Asian	10/21/68	thalidomide
2892	42	M/Hispanic	02/10/69	placebo

Dosing Summary as Described by Sponsor:
Twelve patients were identified as having been randomized to thalidomide and 12 patients to placebo. One patient, (*)No. 2808, was randomized to a second course of placebo and completed 4 days of double blind treatment. A review of the medical records indicated that 11 of 12 thalidomide-treated patients and 9 of 12 placebo patients received 4 capsules of double blind study drug for four days, in accordance with the original protocol.

Patient No. 869, who was randomized to thalidomide, started treatment in the evening since his deteriorating medical condition did not allow waiting until the morning. Three patients (Nos. 2655, 2847, and 2892), randomized to the placebo arm, were discontinued prematurely.

Sponsor's Thalidomide Assignment Group (N = 12) and Response to Treatment:

Pt#	Age	Sex/Race	Index Date	"Bottle A"	Response
869	53	M/Asian	01/15/68	thalidomide	success
1274	49	M/Asian	07/08/68	thalidomide	success
1707	64	M/Hispanic	06/10/68	thalidomide	success
1983	68	F/Caucasian	01/15/68	thalidomide	failure
2033	37	M/Caucasian	03/04/68	thalidomide	success
2078	65	M/Asian	03/04/68	thalidomide	success
2601	40	M/Hispanic	01/15/68	thalidomide	success
2720	24	M/Asian	01/29/68	thalidomide	success
2757	47	M/Hispanic	05/27/68	thalidomide	success
2767	25	M/Asian	06/12/67	thalidomide	failure
2840	64	F/Black	10/21/68	thalidomide	success
2861	47	M/Asian	10/21/68	thalidomide	success

Sponsor's Placebo Assignment Group (N = 13) and Response to Treatment:

Pt#	Age	Sex/Race	Index Date	"Bottle A"	Response
2274	38	M/Hispanic	01/15/68	placebo	failure
2323	41	M/Asian	02/10/69	placebo	success
2603	41	M/Hispanic	01/15/68	placebo	failure
2643	88	M/Hispanic	01/15/68	placebo	success
2655	27	M/Black	09/13/68	placebo	failure
2703	49	M/Hispanic	01/29/68	placebo	failure
2773	48	M/Black	03/04/68	placebo	failure
2793	61	M/Hispanic	07/26/68	placebo	failure
2808[a]	40	M/Hispanic	05/27/68	placebo	failure
2808[b]	40	M/Hispanic	02/17/69	placebo	failure
2824	67	M/Hispanic	10/04/68	placebo	success
2847	57	F/Asian	01/15/68	placebo	failure
2892	42	M/Hispanic	02/10/69	placebo	failure

Sponsor's Unknown Treatment Assignment Group (N = 1) and Response to Treatment:

2855	20	M/Hispanic	03/04/68	uncertain	failure

8.1.1.3.2 Endpoints

There were two times designated for endpoint evaluation:

1) fourth day of treatment and

2) fourth day of the crossover to Bottle "B" or continuation of Bottle "A":

The trial was classed as a response (success), if:

1) no freshly appearing ENL lesions were present and

2) the temperature maximum was less than 99.6^0 F. (37.6^0 C.).

The trial was classed as a failure, if:

1) freshly appearing ENL lesions were present or

2) the temperature maximum was less than 99.6^0 F. (37.6^0 C.).

Celgene's Results of the Response of the Initial 4-Day Double-blind Treatment with Bottle "A":

Table 9 Summary of response for the 4-day double blind study (N = 25 treatment courses in 24 patients)*

Treatment (Number of treatment courses)	Response to Treatment	
	Number (%) of Courses Resulting in Treatment Success	Number (%) of Courses Resulting in Treatment Failure
Thalidomide (N = 12)	10 (83%)	2 (17%)
Placebo (N = 13)	3 (23%)	10(77%)

*Includes patients who were discontinued from dosing prior to Day 4; excludes No. 2855 for whom treatment assignment could not be determined.

Reviewer's Comments:

There is a difference between the number of patients and response to treatment identified as the study sample for Study L-001 and the number and treatment outcomes of the published Hastings' Study. Specifically, according to the L-001 Study Report, twenty-seven patients were identified as entering the double-blind study between June 12, 1967 and February 10, 1969. This group of patients was considered the original study sample, with two patients discontinuing prior to receiving double-blind treatment.

Twelve patients were identified as having received thalidomide during the double blind treatment period and 12 patients were identified as receiving placebo, with one patient (No. 2808) participating in two double blind placebo treatment courses. One patient, No. 2855, was not assigned.

However, the published report of the original study conducted by Dr. Hastings, identified 23 trials as double blinded, with 15 double blind trials being conducted with thalidomide and only 8 trials conducted with placebo. There were a total of 44 single and double blind trials conducted in 22 patients.

Response to Discrepancy Query:

An amendment was received from Celgene, dated May 23, 1997, which addressed the request to reconcile discrepancies in the number of patients as stated above. The following response was provided: "Celgene acknowledges that there is a discrepancy...The Celgene database is more comprehensive, having identified 5 more patients randomized to treatment than were included in the publication. One of the patients, Patient 2553, never received drug. The publication does not provide sufficient detail to allow a matching of patients, and there is no other written record available to Celgene to identify the 4 remaining patients who had been excluded from the publication. Nonetheless, the results based on the complete database in the study report and the subset in the publication are consistent in demonstrating a significant reduction in erythema nodosum leprosum (ENL) based on temperature and lesion assessment in the patients treated with thalidomide."

Reviewer's comments:

The data available for Study L - 001 cannot be validated:

1. *Celgene did not provide an accounting of all patients. As indicated by Celgene's response, there is no other written record available to Celgene to identify the 4 remaining patients who were excluded from the publication.*

   Therefore, it cannot be known whether the four patients were excluded from efficacy analysis because of protocol violations, failure to meet some other entry criteria, discontinuation,

etc. However, not only is there an unexplained difference in the number of patients published and group assignments as submitted by Celgene, there is a difference in the results reported. Specifically, in the reporting of the placebo group's response to therapy,

Celgene identified the following three placebo successes:
Pt. Nos.
2643 (Index Date - 1/15/68)
2824 (Index Date - 10/04/68)
2323 (Index Date - 02/10/69)

The publication of Dr. Hastings in Clinical Pharmacology and Therapeutics notes the following:
placebo successes N = 0 (0%)
placebo failures N = 16 (100%)

*Celgene's submission dated June 17, 1997, identifies two patients (Nos. 2323 and 2892) as being treated by physicians other than Dr. Hastings with Index Dates of February **1969**. They state that this is the date the trial was accepted for publication, and therefore these patients were unlikely to have been included in the publication. However, the published article submitted with the NDA indicates that the article was received for publication Feb. 5, **1970** and accepted for publication Feb. 25, 1970.*

2. *The use of dates alone, as a mechanism of identifying patients in the double-blinded trials is problematic. Identification of the single-blinded trials accompanied by supportive data would perhaps have assisted in differentiating the trial periods.*

3. *The protocol, randomization code, and all original records, other than the unreliable listing noted above, are unavailable.*

C. Reviewing Medical Officer's Analysis of the Submitted Data Study L-001

Revised Entry Criteria:

There were numerous missing entries, particularly ENL lesion assessments and temperature charting, as well as protocol violations involving qualifications for study entry and the use of anti-inflammatory and/or antipyretic medications. Other underlying precipitating factors (other than successful antileprosy therapy), such as infection, were not exclusion criteria. In some cases, treatment arm assignment, blinding, and treatment outcome had to be inferred by Celgene. There were some patient assessments in which the progress notes provided sufficient supportive evidence of double blinding, but there were others in which investigator bias could not be excluded.

The natural history of ENL is to wax and wane, with the tendency to be episodic and variable in

severity within the same patient. Often, the skin lesions last only a few days at times, and when mild, patients are known to respond to antipyretic/anti-inflammatory agents and bedrest. The number of patients in this study is too small to determine the impact of this variability or of thalidomide induced sedation on the course of ENL. However, these were chronic ENL patients, who would be expected to continue to have persistent reactions without intervention and who might not be expected to successfully respond to aspirin, sedation and bedrest without additional medication.

Therefore, in an attempt not to exclude patients from this small pool of only 25, the criteria were relaxed as much as possible.

1) The use of aspirin and indomethacin was accepted, even though such agents may control ENL and their use was a clear protocol violation.

2) On the morning of the fourth day of observation (Day 1), patients were admitted into the trial if they had had on Day -1 or at least sometime during Day 1, a temperature maximum at or above 99.6^0 F. (37.6^0 C.) and it could be inferred that the lesions were fresh.

3) All the trials were assumed as double-blinded.

4) On at least the fourth or fifth day of treatment, when the investigator made an assessment regarding continued or crossover treatment, and at the fourth or fifth day after the initial assessment, the following criteria were used for assignment as success or failure:

   if it could be inferred or documented from the progress notes that no freshly appearing ENL lesions were present and the temperature maximum could be documented to be less than 99.6^{0}F (37.6^{0}C), the assignment was a success or

   if freshly appearing ENL lesions were present or the temperature maximum was 99.6^{0}F (37.6^{0}C) or greater, the assignment was a failure.

   Equivocal reactions and crossover to Bottle "B" decisions were considered failures.

Results

Initial 4-Day Study Period (with notation of differences from Celgene's assessment):

A. Protocol Violation Exclusions (N = 2):

Patients 1707 and 2601 did not meet the "revised entry criteria", as stated above and were excluded from the efficacy analysis. Both had been assigned to the thalidomide treatment group. *(See rationale)*

B. Discontinuations (N = 3):

Patients 2655, 2847, and 2892 discontinued from the study at or prior to Day 3, and were excluded from the 4-Day efficacy analysis. All were assigned to the placebo group. *(See rationale)*

C. Treatment Group Re-assignments (N = 2):

Patients 2855 (Celgene's uncertain classification) and 2603 (placebo assignment) were re-assigned to the thalidomide treatment arm. *(See rationale)*

D. Response to Treatment Re-assignment:

Patients 2033, 2840, and 2861 were classified as thalidomide failures. *(See rationale)*

Thalidomide Treatment Arm:

Evaluable Patients (N = 13) and Response to Treatment Courses:

Success (N = 6) **Failure (N = 7)**

Pt#	Age	Index Date	"Bottle A"	Response
869	53	01/15/68	thalidomide	success
1274	49	07/08/68	thalidomide	success
1983	68	01/15/68	thalidomide	failure
2033	37	03/04/68	thalidomide	failure
2078	65	03/04/68	thalidomide	success
2601	40	01/15/68	thalidomide	success
2603	41	01/15/68	thalidomide	failure
2720	24	01/29/68	thalidomide	success
2757	47	05/27/68	thalidomide	success
2767	25	06/12/67	thalidomide	failure
2840	64	10/21/68	thalidomide	failure
2855	20	03/04/68	thalidomide	failure
2861	47	10/21/68	thalidomide	failure/equivocal

Placebo Treatment Arm:

Evaluable Patients (N = 8) and Response to Treatment Courses (N = 9):

Success (N = 3) **Failure (N = 6)**

Pt#	Age	Index Date	"Bottle A"	Response
2274	38	01/15/68	placebo	failure
2323	41	02/10/69	placebo	success

2643	88	01/15/68	placebo	success
2703	49	01/29/68	placebo	failure
2773	48	03/04/68	placebo	failure
2793	61	07/26/68	placebo	failure
2808[a]	40	05/27/68	placebo	failure
2808[b]	40	02/17/69	placebo	failure
2824	67	10/04/68	placebo	success

Reviewer's comment:

Patient 2808 was accepted and entered twice as "placebo treatment assignment" because of the small number of available patients with ENL; however, according to the published study report this patient should not have been assigned to the same treatment sequence for both trials.

Rationale for exclusions, re-assignments, and correction of treatment outcomes are as follows:

A) Failure to Meet Entry Criteria (N = 1):

Pt. 1707 did not have any ENL lesion assessments over the 4 day study period .

Specifically, this patient was excluded based on failure to meet entry criteria:

Pt.#	Temp Spike	Fresh ENL Lesions	Documentation
1707	yes	?	Temp. 100°F, 6/10/68 (Day 1). Discharge note (6/24/68)." Thalidomide course completed successfully." There were no progress note entries from 6/7/68 - 6/14/69 and from 6/16/68 - 6/ 23/68. However, temperature charting was available from 6/6/68 - 6/24/68. The index date listed for this patient was 6/10/68.

Reviewer's comment:

There was not enough information provided for this patient to qualify for entry. There were no ENL assessments while on the study and a total of 20 days from the pre-treatment observation (Day -4) and study completion. The majority of the other trials, where an end of study could be identified, were generally of 11 or 12 days duration.

B) Early Discontinuations:

Placebo Group Exclusions (N = 3)

Pt.#	Daily Temp Spike	New ENL Lesions	Documentation
2655	?	?	ENL Assessments: switched to Bottle "B" after 3 days because of, increasing ENL nodules, fever, edema, and pain (ASA, q 4 hr gr X, started on 9/20/68). There were no progress notes (Day-1 thru Day 3) prior to early termination on Bottle "A".
2847	Yes	Yes	ENL Assessment: Dropped from trial on Day 1. "Feel this is very hazardous in view of recent MI."
2892	Yes	?	ENL Assessment: Switched over on Day 3, no notes Day -1 to Day 2. ASA was prescribed for temp > 103^0F; however, not sure if given (no temp over 102.4^0F recorded, and not listed on concomitant medications list.

C) Group Re-assignments (N = 2):

Patients re-assigned to the thalidomide group: "Sponsor's Thalidomide Assignment Group" (from uncertain and placebo):

Pt# 2855 M/Hispanic Index Date - 03/04/68 uncertain

Reviewer's comments:

*The Sponsor's initial assignment group was "uncertain". The **Sponsor's transcription** of the progress note entry could be interpreted as referring to the use of thalidomide or to fever ("Pt now on Thalidomide once more has been afebrile +2 days") . Pt. 2855 was clearly a failure with either assignment group. However, the June 17 amendment included the **actual doctor's progress note**, dated 3/18/68, which clearly indicates that the initial assignment should have been to the thalidomide group ("Pt now on thalidomide once more. Has been afebrile +2 days")*

The key is the term once more with the following sequence:

thalidomide (3/4-3/7), febrile,
placebo (3/8-3/11), febrile,
thalidomide (3/12-3/28 qid, open label) ,
febrile (3/12-3/15),
afebrile (3/16-3/17), and again
febrile (3/18 and 3/20/68).

Pt# 2603 M/Hispanic Index Date - 01/15/68 failure

Sponsor's Source of Treatment Assignment (Appendix 16): Appendix 16 provided Celgene's rationale and source for treatment assignments to Bottle A as either thalidomide or placebo; however, these documentations were not submitted with the submission unless it happened to be stated in the ENL Assessment (progress notes).

A: Placebo	Dr.'s Orders 1/23/68:	Continue thalidomide
B: Thalidomide	Dr.'s progress noted 1/23/68	Patient continues thalidomide in decreasing doses after 8 days trial at 400 mg/day.
	Dr.'s progress notes 2/1/68	DC note: Thalidomide success.

Reviewer's comments:

From the progress note dated 1/23/68: "Patient continues thalidomide in decreasing doses after 8 days trial at 400 mgs/day." This would correspond to 1/15/68 or Day 1, unless this entry date was in error. Appendix 18 (Record of Dosing (Beyond 4-Day Study) is contradictory with tapering of thalidomide starting on 1/27/68.

D) "Response to Treatment" Re-assignment:

The following patients were re-assigned as thalidomide failures. The Sponsor submitted Appendix 20 for Study L-001, entitled: Treatment, Response Status, and Source Documentation For Response Status By Patient Number: Double Blind Study in support of the designated category of response (success) or failure to the contents of Bottle A during the double blind study. Reviewer comments follow with an explanation for the re-assignment of outcome.

1) Pt. 2033 M/Caucasian Index Date - 03/04/68 thalidomide group

Appendix 20 Treatment, Response Status, and Source Documentation For Response Status By Patient Number: Double Blind Study.

Progress notes 3/6/68 [Day 3]:	Overall ENL appears regression. No new ENL seen.
Progress notes 3/8/68 [Day 5]:	ENL generally (?) fading nicely and no new ENL seen. Temp. to 101^0F last p.m.

Reviewer's Comments:

Temperature charting was not available for this patient. Some temperatures were noted in the progress notes. This patient was a failure with a temp. of 101^0 F on 3/7/68 [Day 4] as noted in the progress note dated 3/8/68 [Day 5], "Temp. to 101^0F last p.m.". "Symptomatically continues to improve." was noted on 3/9/68, with scattered fresh lesions noted on 3/14/68. Pt. 2033, continued

to be febrile until the "formal thalidomide observation ended" on 3/18/68.

In addition, it was noted on 3/18/68, the end of the formal observation period, that there were "No fresh ENL. The pustular ENL remain although more are ulcerating and draining. Temp. max 3/15: 100, 3/16: 100, 3/17: 99.8." On 3/21/68, the progress note entry is as follows: "Has fresh fluctuant nodule on L wrist. Increase thalidomide to 5X/day."

There is no indication that this trial was a double-blinded study. The duration of the trial period (19 days) was also longer than the majority of the other trials (generally in the range of 11 to 12 days) which included the pre-observation, 4 or 5-day study, and 4 or 5-day crossover or continued use periods, before an end to the study period was declared. The ENL assessment of 3/8/68 may have reflected unintentional bias.

2) Pt. 2840 F/Black Index Date - 10/21/68 thalidomide group

Appendix 20 Treatment, Response Status, and Source Documentation For Response Status By Patient Number: Double Blind Study.

Progress notes 10/23/68 [Day 3]: "Remains afebrile. Swelling of hands is less. Skin lesions seem somewhat quieter!"
Progress notes 10/24/68 [Day 4]: "Still no objective evidence of change."

Reviewer's comments:

"No objective evidence of change", infers failure; however, this statement could be viewed as referring to neuritis and/or ENL lesions. At entry, 10/21/68 [Day 1], the progress note entry was as follows: "Temp did not spike this weekend. No objective worsening of reaction. Will begin the "T" today". This may not have been a double blinded trial and the patient did not qualify for entry per original protocol. The patient did have a temperature spike on Day 1 at 3 PM and 7 PM; however, ENL lesion assessment was not specifically addressed on Day 1.

This patient was re-assigned as a failure because of the following progress note entries:

1) "Temp did not spike this weekend. No objective worsening of reaction. Will begin the 'T' today", on Day 1,
2) "Still no objective evidence of change. Too soon to tell with the neuritis aspect. " on Day 4 (end of the 4-day double blind study)

3) Pt. 2861 M/Asian Index date - 10/21/68 thalidomide group

Appendix 20, (Treatment, Response Status, and Source Documentation For Response Status By Patient Number: Double Blind Study) provided the following rationale for assignment as thalidomide success:

Progress notes: 10/24/68 [Day 4] Afebrile with no fresh lesions.
Temp. recording 10/24/68 [Day 4] Temperature < 99^0F

The following entries were recorded in the progress notes (Appendix 11):

Day -1 (10/20/68)	Having ENL, left ulnar neuritis, left calf pain and temp greater 101F. Starts thalidomide tomorrow.
Day 1 (10/21/68)	Pt. appears very groggy this a.m. Essentially the same as yesterday but ENL less pronounced on arms and legs. Temp 101.2F
Day 2 (10/22/68)	No fresh ENL. Left ulnar still quite tender with no change in function. Temp 98.6 from 7 a.m. forward.
Day 3 (10/23/68)	*No entry.*
Day 4 (10/24/68)	Afebrile with no fresh lesions. Many small cherry red plaques with halo scale. Also severe seborrhea better on scalp.
10/25/68	No fresh lesions visible. Temp 99F this a.m. Will switch to Bottle B in a.m.
10/28/68	Afebrile with no fresh ENL. Seems more awake than last bottle. Does have auricular neuritis. L ulnar quiet continue Bottle B.
10/29/68	No fresh ENL. Greater auricular neuritis almost asymptomatic. L ulnar mildly enlarged above elbow but not symptomatically tender
10/31/68	No fresh ENL. However, L ulnar still more painful
11/1/68	Has minimal L ulnar tenderness
11/5/68	Obvious response to Bottle A on temp chart and this was thalidomide. Will therefore order thal. and taper off slowly since still getting mild L ulnar neuritis (no motor involvement)

Reviewer's comments:

1. Pt. 2861 assessment as failure rationale:

Pt 2861 was switched to the alternative treatment Bottle "B" (on 10/26/68) and continued past the usual 4 to 5 day crossover even with ulnar neuritis, which again became symptomatic and was again waning on 11 /1/68. This crossover infers an equivocal response or failure on Bottle "A" after the 5th day of treatment. Patients were to switch to Bottle "B" (the alternative treatment) in the event of treatment failure.

Pt. 2861, remained on placebo until the code was broken on 11/5/68. The progress note entry: "Obvious response to Bottle A on temp chart and this was thalidomide. Will therefore order thal. and taper off slowly since still getting mild L. ulnar neuritis (no motor involvement)" is a retrospective success assignment by the investigator, who evidently had some difficulty with assessing the skin lesions. Prior to Day 4, the investigator did not quantify the skin lesions, and there was no entry for Day 3 for comparison. Also, the patient actually remained afebrile while on placebo.

2. *The following discrepancy was noted:*
Progress note dated 10/25/68, "Temp 99F this a.m." does not correspond to the temperatures provided (Appendix 10) for 10/25/68.

Table 10 Aspirin Use During the Initial Double-Blind Study*

	Thalidomide Group						Placebo Group			
ASA Use	Success			Failure			Success	Failure		
	Pt. No.			Pt. No.			Pt. No.	Pt. No.		
Day -1			2757	2861			2643		2773	
Day 1	869	2720	2757	2861	2767		2643			2808[a]
Day 2		2720				2855	2643	2274		2808[a]
Day 3								2274		
Day 4										

Although, as discussed above, aspirin use was accepted in an attempt to include as many patients as possible, it must be noted that of the thalidomide successes, three had concomitant use of aspirin; two of these became afebrile with aspirin and thalidomide, one became afebrile only after thalidomide was started. Of the 6 thalidomide failures, three had concomitant ASA use. Pt. 2861 received only 2 ASA tablets on Day 1 and the amount is unknown on the second day (initially was

classified as success by the Sponsor; however, was reclassified by the reviewer as failure).

Reviewer's Comments:

The use of aspirin and other anti-inflammatory medications was clearly a protocol violation. The effects on treatment outcome cannot be assessed, because the rationale for prescribing is unknown. For example, Pt 869 was to receive aspirin q4hrs for temperatures 101, while Pt 2767 was to receive aspirin q4hrs for temperatures 104 or greater.

8.1.1.5 Conclusions Regarding Efficacy Data

The number of evaluable patients are:

Thalidomide Assignment Group (N = 13)
Placebo Assignment Group (N = 8)

Table 11 Response to Treatment

Treatment (Number treatment courses)*	Response to Treatment	
	Number (%) of Courses Resulting in Treatment Success	Number (%) of Courses Resulting in Treatment Failure
Thalidomide (N = 13)	6 (46%)	7 (54%)
Placebo (N = 9)	3 (33%)	6 (67%)

*Note assignment group may not be equal to number of courses

Reviewer's Conclusion:

There is insufficient evidence from study L - 001, as presented, to draw a valid conclusion regarding efficacy of thalidomide in the treatment of ENL.

Adverse Events (L-001)

The following summaries of adverse events (as extracted by Celgene) were submitted:

1) Summary of Adverse Events (AE) Recorded During the 4-Day Blind Study
2) Categorization of AEs Occurring During Continued Dosing By Body System
3) Neurological Symptoms Reported During Continued Dosing
4) Total Cumulative Dose of Thalidomide at the Onset of the First Neurological AE Occurring During Continued Dosing

Reviewer's comments:

1) *The published study reported on efficacy and selected laboratory testing and was silent on any associated adverse events during the trials other than edema. There was no discussion of other clinical ENL manifestations in the published article, other than a general statement of the purported safety of thalidomide as compared to the use of prednisone. Thalidomide was noted to be ineffective when used in patients with the dimorphous form of leprosy.*

2) *The primary efficacy assessment of no new ENL lesions did not address the status of the lesions which were already present. In some cases the lesions progressed to ulceration. One case was classified by the Sponsor as a success. Two were classified by the Sponsor as failures. All three developed ulcerations with continued thalidomide therapy:*

Pt. 2033 Progress note dated 3/18/68, "No fresh ENL. The pustular ENL remain although more are ulcerating and draining." The thalidomide dose was 400 mg daily from 3/4/68 -3/20/68 and had been classed as a success by the Sponsor.

Pt. 2767 Progress note dated 6/19/67, "Several new ENL today.... The large old ulcerated ENL on right calf is considerably larger than at the start of trial." The patient was classed as a failure by the investigator.

Pt. 2855 Progress note dated 3/6/68 (Day 3), "Scattered fresh ENL today. Individual lesions are moderate in severity. Some ulcerating ENL on L (medial) leg."

3) *The original NDA submission did not provide details, rationale, or the selection process employed for the exclusion of notes when the sponsor prepared the CRFs. However, the sponsor claimed to make exclusions only of administrative comments during discussions between the Sponsor and the Division on 06/04/97. The completeness of transcription is especially important given the multi-system nature of ENL and possible serious adverse events associated with thalidomide. Valuable safety information may have been omitted in this retrospective data gathering (the medical expertise of the transcriber was unstated). One example follows:*

Patient No. 2078 suffered a syncopal episode. The Nurse's note was transcribed onto the listing of adverse events. It states "While sitting in chair-getting a shave & haircut from patient-V.N.-suddenly began drooling from mouth with no focusing of eyes-put to bed." Upon request, the actual patient record was subsequently provided by the sponsor. A detailed Doctor's Note was found which provided standing and sitting vital signs, (pulse was 56), administration of 25 gm glucose solution IV, and an assessment: "(1) hypoglycemia ? (2) dehydration...(illegible)."

Thus, it would appear that clinically relevant data were not always transcribed. The adverse

event tables constructed by the Sponsor cannot be verified and will not be reproduced here.

Reviewer's Conclusion Regarding Safety

There is insufficient evidence from study L - 001, as presented, to draw a valid conclusion regarding the safety of thalidomide in the treatment of ENL.

Note: See Statistics Review for further analysis of Study L-001

8.2 Indication Chronic Erythema Nodosum Leprosum

8.2.1 Reviewer's Trial # 2 Sponsor's Protocol # L-002

Reviewer's comments: *The review of Study L-002 is arranged in two sections:*

*A) Review of the original protocol submitted under IND 11,359, "**Thalidomide in the Long-Term Control of Erythema Nodosum Leprosum Phase III (dated January 27, 1975).***

*B) Review of Study L-002, "**Summary of the Safety and Efficacy of Thalidomide in the Treatment of Erythema Nodosum Leprosum (IND 11,359)"***

Background

A study of thalidomide for the therapy of erythema nodosum leprosum (ENL) in the United States under IND 11,359 began in 1975. The Sponsor of the IND is the United States Public Health Service (U.S.P.H.S.) and the principal investigators were Dr. Robert Hastings (until 1993) and, from 1993 to present, Dr. Leo Yoder *(Comment: Dr. Yoder has since submitted a letter to the IND stating his retirement effective July 2, 1997; the principal investigator will now be Dr. Kirk Webster)* of the Gillis W. Long Hansen's Disease Research Center (GWLHDC), Carville, Lousianna. Data collection was computerized into a formal database in 1978.

8.2.1 Original Protocol *(the following was extracted in part from IND 11, 359, Vol. 1.1)*

Title: **Thalidomide in the Long-Term Control of Erythema Nodosum Leprosum Phase III (dated January 27, 1975)**

Objective: To determine the long-term effectiveness, minimal effective dose, and side effects of thalidomide in the treatment of erythema nodosum leprosum (ENL) occurring in lepromatous leprosy.

Design: An open-labeled, multi-centered, ten-year study.

Rationale: "Quite a number of reports have appeared supporting Sheskin's original claim that thalidomide is useful in lepra reactions, including work from Carville. At this point there seems to be little doubt that the drug is of benefit in the acute management of ENL. The present investigation is designed as a Phase 3, multi center, uncontrolled, long-term study of thalidomide for this indication. "

Study Plan Summary:

All patients with ENL severe enough to require steroids were candidates for thalidomide. Both male and female patients with ENL were admitted to the trial. Where possible, the female patient was to be hospitalized for one week, during which time it was to be ascertained that the patient (if female) was not pregnant.

Each patient was to be seen at regular intervals not to exceed 2 months by one or more of the investigators. Not more than 60, 100 mg tablets of thalidomide were to be given to any one patient at any one time.

All patients treated with thalidomide were to continue on their Dapsone or other anti-leprosy chemotherapy.

Patient Selection and Follow-up:

Any patient having ENL could be treated with thalidomide provided the following requirements had been met:

1) Informed consent.
2) The patient was to be seen at regular intervals (not to exceed 2 months) by the physician requesting "it". *(the criteria is as provided in the protocol, the reference to "it" is unclear).*
3) No more than 60 days of drug was to be dispensed at any one time. It was suggested that the patient keep a drug log (calender to mark the dates thalidomide was taken) to aid record-keeping.
4) An initial 4mm punch biopsy.
5) Required laboratory work.
6) Women of childbearing potential, to be given suitable birth control measures.
7) No significant neuritis was present. Steroids were to be used until the neuritis cleared. Thalidomide could then be used to control ENL, if ENL recurred with attempted discontinuation of the steroids.

Contraindications *(as listed):*

Pregnancy and a history of allergy to the drug are the only contraindications.

Study Treatments:

The initial starting dose was 100 mg of thalidomide 4 times daily. When the ENL had been controlled (usually within 2 days) the dosage of thalidomide was to be tapered as follows:

1) first ENL episode:
100 mg three times daily for 4 days,
100 mg twice daily for 4 days, then
100 mg every other day for 8 days,

Thalidomide was then to be discontinued, since in some cases only one or an occasional course of therapy was thought to be needed to control the problem satisfactorily.

2) Recurrent ENL Episode:

For a recurrence within 30 days, the protocol was as above, and the dose was then to be tapered to a maintenance level. Suggested dose was around 100 mg daily, with a range of alternate day therapy to 100 mg twice daily.

Attempts to discontinue thalidomide were to be made every six months.

3) Maintenance:

Thalidomide should be restarted for an additional 6 months if the reaction recurs.

4) For patients being switched to thalidomide from prolonged ENL therapy (i.e., corticosteroids, chloroquine, etc.), thalidomide (as recommended for the first ENL episode) was to be started if the reaction recurs as the other medication was being tapered.

Tapering to be attempted every 6 months. *(Comment: This most likely refers to tapering of thalidomide, not concomitant medications).*

5) No patient was to receive thalidomide alone if a significant acute reactive neuritis was present. Those cases which had a severe neuritis (severe pain and/or progressive motor or sensory loss) were to be treated with corticosteroids until the neuritis cleared. Thalidomide could then be used to control ENL if it recurred with attempted discontinuation of corticosteroid therapy.

Additional information indicated that the longest required suppressive therapy duration was 4 years.

Possible Thalidomide Failure Rationale:

The following reasons were provided as possible reasons for some cases of thalidomide failure:

1) The reaction was not ENL.
2) ENL was in a dimorphous (borderline) case.
3) The patient was not taking the drug.

Adverse Events (as provided in the background information):

Side-effects listed included:
drowsiness, constipation, peripheral edema, eosinophilia, thrombocytopenia

Newly observed side-effects were to be reported to Carville at once.

Neuritis:
Specific comments regarding peripheral neuritis are as follows:
"Although peripheral neuritis secondary to thalidomide has been reported we have not observed any suspect cases here at Carville. Admittedly such a relationship might be missed in a disease such as leprosy which is itself the most common cause of peripheral neuropathies in the world. It would thus seem advisable to discontinue use of the drug in any patient noting the onset of painful paresthesias or hyperesthsias with no other signs of reaction, particularly after 12 or more months of therapy with thalidomide...."

Reviewer's Comment:

In a 2/97 amendment the sponsor presented a synopsis of patient 2808 from the Hastings' trial at Carville. This synopsis was among those chosen to address thalidomide use in patients with ENL neuritis. In this synopsis, it is recorded that "patient has noted slight loss of full extension of right ring finger. Grossly strength normal but may be very slight early lowering. Will get right ulnar conductions. Will also discontinue thalidomide." (Quotation marks verbatim from the synposis). A follow up progress note is then reported to state that "conduction studies showed no change except questionable right peroneal. Patient however has no evidence of weakness in that nerve distribution. Will just observe for now. Tolerating stopping of thalidomide very well - only very slight ENL (few scattered erythematous nodules)...".

According to this note, it seems that thalidomide was discontinued in response to the nervous system findings. This case preceded the IND database, but occurred at Carville. It is unclear why a case such as this wouldn't be considered "suspect".

Annual Reporting:

Annual reporting was required and, among other information requested, specific examples of some of the requested data included the following:

1) other medical problems.
2) physical findings before thalidomide therapy:

a) gross deformities
b) motor loss
c) sensory loss
d) enlarged nerves
e) eye findings (visual acuity each eye)
f) skin lesions
g) other abnormalities
h) any change in the physical findings since the start of therapy.

Reviewer's Comments:

Response to therapy, listing of other anti-reaction medication, duration of thalidomide, maintenance level, and response (fall in temperature, clearing of skin lesions, etc.) was requested by protocol; however, specific neurological monitoring was not proposed.

The protocol submitted by Celgene with Study L-002, as shown below, appears to be an accurate copy of the original protocol submitted under IND 11,359 in 10/27/75.

Protocol # L-002

Background

L-002 represents a summary of the safety and efficacy findings of the uncontrolled, open-label study of thalidomide for the therapy of erythema nodosum leprosum (ENL) in the United States under IND 11,359 begun in 1975. Parameters regarding safety and efficacy over a 16 year reporting period (1978 - 1994) were provided. According to the sponsor, they were given access to the GWLHDC electronic data base, but not the original case report forms.

The co-investigators were predominately practicing at the U.S.P.H.S.-sponsored Hansen's Disease Centers and other clinics in the United States, U.S. territories and Canada. Participating co-investigators received thalidomide from the GWLHDC, in Carville, Lousianna, and were to submit reports on all patients treated with thalidomide. As previously discussed, included in the original IND 11,359 protocol was a multi-page case report form for use by the investigators. Submitted with the NDA was what appears to be a copy of the original protocol, the original sample report form, and a one page annual report form.

"The sources of drug used under this IND have varied including, most recently, manufacturers in Brazil. Celgene now provides thalidomide to GWLHDC for use in ENL patients, and Celgene is also undertaking controlled clinical trials in order to confirm the safety and efficacy of thalidomide."

Reviewer's Comment:

Sources of thalidomide available to the U.S.P.H.S.G.W.L. Hansen's Disease Center (IND 11,359) have varied, as noted by the Sponsor. These suppliers have included Chemie Grunenthal (Germany) and Tortuga, a Brazilian manufacturer. As noted earlier in the review, PK-001 is the only bioequivalence study between a non-Celgene formulation (Tortuga) and Celgene Corporation's proposed commercial formulation and clinical study formulation. This study has demonstrated that the Tortuga formulation is much less bioavailable than both of the Celgene formulations. The L-002 database ends with 1994. Thus, it is unlikely to include any safety or efficacy data on patients being treated with the Celgene formulations. The sponsor was asked (teleconference with secondary reviewer 7/16/97) whether any patients under the USPHS IND 11,359 (other than those in Celgene's clinical trials) were indeed being treated with Celgene thalidomide and, if so, whether the safety and efficacy data have been submitted to the NDA as an L-002 update. The answer given by Dr. Kook was one of uncertainty about their status as supplier, but it was confirmed that no data have yet been submitted to the NDA from the IND 11,359 database for the time period after 1994.

The clinical significance, if any, of differences in bioequivalence among the thalidomide formulations used under IND 11,359 is unknown. This issue will be discussed under Section 10, as it pertains to safety.

L-002 Title: Summary of the Safety and Efficacy of Thalidomide in the Treatment of Erythema Nodosum Leprosum (IND 11,359)

Objective/Rationale

Not stated.

Sponsor's Summary:

1) Patients were enrolled in the study from a total of 64 centers.
2) In the initial year of treatment, a case report form was provided to the physician. During the following years, a computerized summary format was sent for completion.
3) Original patient records were retained at the individual treatment sites.

GWLHDC Electronic Data Base:

As of April 1995, the database included 1,387 patients treated for a mean duration of 3.46 years.

Table 12 Demographics N=1387

Category	Number (%)
Male	1079 (77.8)
Female	308 (22.2)
Black	54 (3.9)
Caucasian	164 (11.8)
Asian	508 (36.6)
Hispanic	639 (46.1)
Other	22 (1.6)
<18 yrs old	20 (1.4)
18-64 yrs old	1228 (88.5)
>65 yrs old	139 (10.0)
Male yrs old	40.45 (14.97) range 11-91
Female yrs old	48.40 (14.36) range 14-90
disease class: LL	1156 (83.3)
BL	212 (15.3)
BB	11 (0.8)
BT	6 (0.4)
TT	2 (0.1)

Reviewer's Comment: *The information in this table is as presented by the Sponsor.*

Definitions and Procedure (L-002):

1) A treatment course is defined as consecutive years in which patients received a thalidomide dose as reported by the treating physician.
2) For patients with multiple treatment courses, the overall duration was calculated as the sum of the number of years of each treatment course.

Revised Annual Case Report Form (revised in 1978) :

A one page, annual reporting form was submitted with the NDA.

1) The thalidomide dose which was reported annually was the mean dose taken by the patient during the year.
2) Side effects and laboratory abnormalities only due to thalidomide were requested on the Annual Report Form
3) Response to thalidomide therapy was requested; however, only general descriptive terms were provided. Response to treatment categories also included "unknown" and "lost to follow-up" categories in addition to "good", "fair", and "poor".

Reviewer's comments:

1. *The revised annual case report form (CRF) is not as detailed as the CRF of the original submission. It is unclear whether the revised CRF was used in the generation of all the submitted data. For example, line listings for concomitant anti-leprosy medications were often left blank. The submitted "Annual Report to Sponsor" form clearly has an entry for these data. The Sponsor states in volume 2.23 that this discrepency is explained because "Forms that were used for the subsequent years of data collection for a given patient asked only for 'experimental drugs'". Copies of these forms and reporting year(s) of use were not were not provided and so this information has not been verified.*

2. *An annual summary of "mean dosing" for the reporting year does not provide adequate dosing information for the regulatory purposes of establishing a range of effective and safe dosage regimens.*

3. *Dosing, start and stop dates, and response to therapy data were retained by individual investigators. Celgene's access to these data is unclear.*

4. *Investigators were not provided with defined categories for assessment of response to therapy. Furthermore, it is unclear whether the recorded responses (for example "good") referred to the cutaneous lesions of ENL or to the syndrome of ENL.*

5. *Adjunctive therapy could not be extracted by Celgene. Prednisone would not have been listed because it is not "experimental". It is instructive, however, to consider this statement by the Sponsor (Vol 2.23 pg 080778): "Prednisone use is recorded on the CRF for the initial year of treatment...a review of the responses for 1992 indicated that 21 of 55 patients (38%) received prednisone at some time during their initial treatment year. In 1994, 18 of 34 patients (47%) received prednisone concomitantly with thalidomide".*

Adverse Experiences Reported:

1) Physicians were asked to report only those adverse experiences that, in their opinion, were related to thalidomide.

2) A total of 1387 patients have been evaluated for safety over the 17-year reporting period. Adverse experiences were reported in 279 of 1387 (20%) patients. One hundred fifty patients reported only one adverse experience: 129 patients reported two or more adverse experiences during 14 years of treatment with thalidomide.

The most frequently reported adverse experiences were:

somnolence	(11%)
constipation	(4.5%)
peripheral edema	(1.9%)
asthenia	(1.7%)
dry skin	(1.2%)
dizziness	(1.0%)
paresthesia	(0.9%)
depression	(0.6%)
headache	(0.6%)

Leukemias (N = 3): There were three cases of acute leukemia reported under IND 11,359.

1. Patient 261 (diagnosed ?1984), a 61 year old male, treated with thalidomide from 1980-1989; site, San Francisco.

2. Patient 721 (diagnosed 1990) , a 28 y.o. male, treated with thalidomide from 1987-1990, site, San Francisco.

3. Patient E.B., a 28 y.o.female was diagnosed in 1984 with acute undifferentiated leukemia treated with thalidomide from 9/11/81 - 1/7/84; site Staten Island. The reporting physician's impression was that the leukemia was thought to be probably not related to the thalidomide.

Reviewer's comments: *No additional data were provided on the above reported patients.*

Peripheral Neuropathy and Neuritis:

According to the submission, neurological adverse experiences were usually reported after a few years on thalidomide as follows:

1 to 2 years (8 patients)
3 to 4 years (5 patients)
7 to 8 years (5 patients)

The following neurological adverse events were reported:

neuritis reported in 6 patients
neuralgia in 6 patients
neuropathy in 5 patients
causalgia in 1 patient

The Sponsor provided case reviews on 7 of these patients with neuritis and neuropathy whose records were available. These case reviews were done by the treating physician at GWLHDC. Clinical summaries were included in the submission. The submission states the following:

> "A review of the patients reported as having neuropathy, paresthesia, neuritis, peripheral neuritis, or neuralgia showed that the majority of the patients were treated in centers outside of GWLHDC. Detailed information is not available for many of these patients. In only one of the 7 patients did the treating physician at GWLHDC who reviewed the cases conclude that there was evidence of "thalidomide induced neuropathy". In the verbatim reports, some patients had "possible" and "probably" used as a descriptor of the event, and thus, the significance is uncertain. Neuritis from leprosy is relatively common and some clinicians may have reported neuropathy in patients on thalidomide even though it was most likely due to leprosy". In 7 of these patients, the verbatim report stated "nerve pain" or a similar finding and these events were coded as neuralgia or causalgia.

Reviewer's Comments:

1. *An incidence of paraesthesia in 12 (0.9%) patients should not be assumed a result of lepromatous leprosy. The development of neurological AE's during the use of thalidomide should be assessed by careful prospective clinical and electrodiagnostic studies to rule out the development of thalidomide neuropathy.*

2. *The fact that the majority of patients for whom neuropathy was reported were treated "in centers outside of GWLHDC" is consistent with the possibility that these other centers conducted more thorough assessments and/or reporting.*

3. *The incidences noted in the submitted AE table for L-002 are of very limited utility, since investigators were asked to report only those AEs thought to be due to thalidomide and the general consensus seemed to be that ENL patients are not susceptible to thalidomide induced neuropathy (see discussion under Section 10: Neuro Report). The issue of reporting under this IND is further discussed below.*

Discontinuation of Thalidomide Therapy

Thalidomide was reported to have been discontinued in only two patients over the 17-year reporting period.

1) Patient 1036 was a 51-year old female with peripheral neuropathy reported at seven years. She was taking 50 mg of thalidomide every other day.

2) Patient 1145 was a 64-year old female who was taking thalidomide 100 mg daily for the first year; the line listing notes "dizziness-had to discontinue". Thalidomide was restarted during the second year of reporting without any adverse event being reported.

Deaths

The submission states that "One death was reported under the Carville IND that was not related to treatment."

Reviewer's Comments: *This issue is reviewed in section 10, under "Deaths".*

Overall Reviewer's Comments L-002:

1. *Dosing, with start and stop dates, accompanied by a response to therapy, are essential to interpreting Study L-002. Efficacy, dosing, adjunctive therapy, and adverse events as extracted and presented in Study L-002, are of limited value. Data collection from the revised annual case report forms and data entry procedures limited the extraction of needed data. In addition, the coding for response was defined retrospectively by one of the USPHS investigators (San Francisco) who stated that " similar descriptions may have been used by other investigators at USPHS Hospitals in this study". The sponsor then categorized a response of "excellent", "very good", or "good" as a complete response. Note that "good" is defined as "a patient in whom there was a very clear response to thalidomide and the patient was not sick, had no fever, but may have had a few bumps" (Database Information Appendix 7 Vol 2.25) Thus, these data were not reviewed further for efficacy.*

   In an effort to extract additional efficacy information from the IND, patient records were gathered from one of the USPHS sites (LAC/USC) by the Agency, presented to the USPHSGWL (Dr. Leo Yoder), and submitted to the NDA by the Sponsor as a major amendment after it was forwarded to them by the USPHS. At the time of this review, it is undergoing statistical analysis and is not available for review.

2. *As will be documented in detail under Section 10.4 (Neurologic Report), AE reporting under this IND appears to have been extremely limited. Because of the limited adverse event reporting, the assumption cannot be made that, except for teratogenicity, thalidomide is safe. If an adverse event, such as neuropathy, is assumed to be part of the disorder being treated, and only events already assumed to be related to thalidomide are to be reported, drug-related AEs are likely to be under-reported.*

In addition to the review of neuropathy to follow in Section 10, another example of probable under-reporting is the absence of reporting bradycardia: As will be discussed fully in the Section to follow, Dr. Iyers' study (1970) reported "striking bradycardia" associated with the use of thalidomide in ENL as well as irregularities of cardiac rhythm. There are no reports of bradycardia in 1,387 ENL patients treated with thalidomide under IND 11,359 over a 16 year period (1978 -1994, Table 16, Vol 2.1, pg 08 5032). Postural hypotension and bradycardia were noted in PK Study -001 ***despite the small number of subjects.*** *AEs recently reported in a controlled study in HIV related oral aphthous ulcer patients treated with thalidomide (non-Celgene), 200 mg daily vs placebo (29 thalidomide & 28 placebo), included chest pain, irregular heart beat, syncope, and dizziness.*

Conclusion Regarding L-002

There is insufficient evidence from Study L-002 to form a valid conclusion regarding efficacy or safety of thalidomide in the treatment of the ENL syndrome. The annual reporting practices (particularly mean doses, time to response, concomitant anti-reaction medications, lack of standardized efficacy endpoints, etc), the method of adverse event reporting, and neurological monitoring procedures, were inadequate or absent. It appears that assessment of possible thalidomide induced neuropathy, based on clinical or electrophysiological testing, has not been adequately assessed under IND 11,359 as submitted. Therefore, a risk-benefit assessment cannot be made.

Note: See Statistics Review of Study L-002 for further analysis.

Indication **Chronic Erythema Nodosum Leprosum**

8.3.1 **Reviewer's Trial # 3 Sponsor's Protocol # E-001**

Background This open label study of thalidomide in the Treatment of ENL is an ongoing 2-year trial at two U.S. investigational sites. The study was initiated 11/9/95 under IND 48,177.

Title: An Open Label Study of Thalidomide in the Treatment of Erythema Nodosum Leprosum (ENL)

Objective:
This study has multiple objectives. The study is intended to provide evidence of the safety and tolerability of the Celgene Corporation (Celgene) thalidomide drug product in a dose range of 50 to 200 mg/day when administered to patients with ENL for maintenance treatment. The study also will support the efficacy of the drug product when used in the prevention, suppression, and

maintenance treatment of ENL and will provide a basis for instructions for informing the regimen for tapering patients off thalidomide.

Table 13 **Summary of Patient Status by Site in Study E-001** (Through June 12, 1996 as extracted from the Annual Report for the IND March 1997).

Site	Investigator	Number of Patients				
		Enrolled	Completed	D/C* AE	D/C* Other	Ongoing
1	Dr. Leo Yoder	5	0	0	0	5
2	Dr. Thomas Rea	0	0	0	0	0
Total		5	0	0	0	5

*D/C Discontinued

Adverse Events reported are as follows: (5 patients through 6/12/96; 24 AE).

Table 14 Adverse Events E-001

Event	N	Event	N
Rash	2	Brittle nails	1
Head and neck pain	2	Diarrhea	1
Edema	2	Thrush	1
Impotence	2	Constipation	1
Fatigue	1	Stiff neck	1
Malaise	1	Itching	1
Worsening of ENL lesions	1	Bruise	1
Chills	1	Upper gastric pain	1
Yeast infection	1	Dental pain	1
Back pain	2		

Discontinuations/Deaths

There were no serious adverse events or discontinuations reported. There were no deaths reported.

Reviewer's Comment:

The annual report for the IND states that one of the subjects had severe worsening of ENL lesions, coded as continuous and probably related. This patient also had a moderate rash on the face coded likewise. It is unclear why the drug was not discontinued.

Protocol E-002
This single dose pharmacokinetic and dose-proportionality study in ENL patients was proposed; however, according to the submission, with the expansion of the PK studies, there are no plans to initiate this study.

8.4 Indication Acute Erythema Nodosum Leprosum

8.4.1 Reviewer's Trial # 3 Sponsor's Protocol # E-003/P

Background

Protocol(E-003/P), "A controlled dose comparison study of thalidomide in the acute treatment of erythema nodosum leprosum (ENL)", is an ongoing trial conducted in the Philippines by Celgene Corporation. According to Celgene, the study was initiated in the Philippines because of limited patient availability in the United States and because approximately 20% of the U.S. population of patients with ENL are Filipino. If all Asians in the U.S. are included, the proportion increases to 33%. The majority of the remaining patients are Hispanic. The figures were based on patients receiving thalidomide for an initial episode of ENL under the United States Public Health Service Investigational New Drug application (IND) in 1994. It was anticipated that 20 to 30 patients would be enrolled at the Philippine site in one year.

Study E-003/P as submitted with NDA 20-785 represents a summary of nine patients randomized to the study as of October 4, 1996. Study E-003/P under IND 47,188 was initiated on July 16, 1996. The study blind has not been broken.

According to the IND (48,177) for this study, Celgene also intended to initiate Protocol E-003 in the United States. Protocols E-003 and E-003/P were to be identical except for the following:

1. dosing would not occur daily at the Philippines site,
2. the protocol would be open to women of childbearing potential (the Patients' Rights Committee refused the enrollment of women of childbearing potential into the trial to be conducted in the Philippines), and
3. electrophysiological monitoring would not be made available at the study site in the Philippines.

Investigator recruitment for the U.S. study was stated to be ongoing in the July 15, 1996 submission (Celgene stated that they had contacted the Hansen's Disease Clinics identified by the Division). Protocol E-003, "A Controlled Dose Comparison Study of Thalidomide in the Acute Treatment of Erythema Nodosum Leprosum (ENL)", was submitted with NDA 20-785. Principal investigators, Suzanne Bruce, M.D. and Anne Burdick, M.D., were listed with addresses. Additional information was not provided.

Status of Study E-003/P:

(This section was co-authored by the primary and secondary reviewers)

The treatment group assignment for patients (thalidomide at 100 mg/day versus 300 mg/ day) was not made available for this preliminary report, since the blind had not been broken. The data were pooled across treatment groups and differences in efficacy and safety between treatment groups have not been assessed.

According to the submission, response to therapy at day 7 was "complete" in 6 of 9 and "partial" in one due to the presence of occasional acutely inflamed lesions. Two patients were stated by the Sponsor to be treatment failures (01 and 05), one of whom was discontinued after 5 days due to increasing fever and multiple newly inflamed lesions. At the end of the 6-week tapering period, 3 patients continued to have a complete response, according to the Sponsor. Seven of the nine patients were on concomitant medications during the acute treatment period. Patient number 04 was on WHO MB-MDT regimen (dapsone 100mg/day, clofazimine 50 mg/day, and rifampin 600 mg/clofazimine 300 mg once every 4 weeks). One patient (failure) was on paracetamol for the duration; the remaining 3 discontinued use of paracetamol after 1-4 days.

With respect to safety, 15 mild to moderate adverse events were reported in 8 patients. No deaths were reported. There were changes in the laboratory parameters, but none were considered to be clinically significant by the investigators.

According to the NDA, patients continue to be enrolled in the study, and treatment efficacy and safety will be assessed formally when more data become available.

Reviewer's Comment: *In a teleconference on 7/16/97 with the secondary reviewer, Dr. Kook (Celgene) was asked if a safety update had been submitted. She stated that enrollment is around 20 patients at this time, but that no safety update is available at this time.*

Table 15 Summary of Adverse Events E-003/P

Patient Number	Adverse Event	Severity
01	somnolence	mild
01	vertigo	moderate
02	rash	moderate
03	somnolence	mild
04	somnolence	mild
05	somnolence, headache, vertigo	mild
05	rash (3 events)	moderate
05	pruritus	moderate
06	somnolence	mild
07	somnolence	mild
08	rash	mild

As of 10/4/96

Of the 9 patients entered, two patients (22%) were treatment failures and discontinued because of worsening ENL manifestations. In patient 05 (3 events of "rash"), pruritus persisted despite treatment with chlorpheniramine. According to the Sponsor, the other 12 adverse events resolved.

Reviewer's comments:

1. *Patient 02 is noted on Day 7 with anorexia, malaise, and edema. The edema was not present at baseline. It is not noted on the AE table. According to the protocol, the secondary efficacy endpoints include systemic signs and symptoms of ENL, such as anorexia, malaise, and "other" ENL symptoms. This patient is coded as a complete response at day 7.*

2. *Patient 04 is coded with 106 acutely inflamed lesions at baseline, 28 of which were ulcers. The visit timing scale presented by the Sponsor shows the screening visit 5 days prior to the first visit on drug. The chart showing number of acutely inflamed lesions indicates 14 on Day1 (the line listing shows no ulcers). The count the following day was*

zero for all lesions. This patient, as noted above, was taking concomitant clofazimine. His response was coded as "complete". If Day 1 is the first day of dosing, as the protocol implies, it would appear that this patient's ENL was resolving spontaneously on the first day of dosing. Indeed, the listing for ENL assessment comments says "previous ulcers have dried up coalesce forming a scab".

3. *According to the submission, patient 09 had no paresthesia or numbness at baseline, but developed these symptoms at the day 4 visit only. This event is not noted in the above table. In addition, the line listing for this patient shows paracetamol use as an antipyretic starting 7/26, which is baseline. Dosing began the following day. Paracetamol was stopped 7/30 with an axillary temperature of 96.5. The temperature line listings show that the axillary temperatures on 7/27-7/29 ranged from 98.6-98.5F. The day after paracetamol was stopped, the temperature was again 98.6. The protocol states that need for anti-pyretics after 72 hours will result in discontinuation due to treatment failure. This patient is coded as a complete response.*

4. *The line listings indicate that 2 of the 3 subjects with "Complete Response" at the end of the tapering period had persistent elevation of the erythrocyte sedimentation rate (ESR): No. 02: baseline 46, ending 80. No. 06: baseline 125, ending 115. Of the 4 subjects coded by the Sponsor as "Partial Response" at the end of the tapering period, 3 had a higher ESR than at baseline (35 to 82, 114 to 116, and 65 to 82).*

5. *Examination of line listings for "Lesion Assessment" reveal multiple entries of "few", "more", >10, <10, admixed with actual numbers, such as 5, 11, etc. Patient 08, for example, had an entry for >10 resolving pustules on Day 6. On Day 4 he had 1 acutely inflamed pustule. Unless pustules develop from resolving nodules/papules, it is unclear from where the resolving pustules on Day 6 originated. At Day 7 he had a "complete response" with >10 resolving nodules/papules.*

   According to the Sponsor, "The number of lesions for each patient was calculated by adding the number of lesions recorded on the CRF across body region. The number of lesions is an approximate count, since it is difficult for clinic personnel to count the exact number of lesions, particularly when there were many lesions in most body regions. ***In some cases, the clinic recorded approximations that were translated into numbers of lesions using a conservative algorithm (i.e., >10=12, >5=7, <10 =7, few =2, some=4, more=5, and most=7). A more formal scaling approach to these data may have to be developed for the final formal analysis."*** *(bold inserted by reviewer).*

   Thus, the Sponsor's efficacy claims cannot be verified at this time.

6. *It should be noted that the Sponsor states in the Integrated Safety Summary that 57% (8/14) patients enrolled in their ENL trials (E-001 and E-003/P) experienced rash. See Section 10 for discussion.*

Note: See Secondary Review dated 8/8/97 for further information E-003/P KO'C 8/11/97

8.4 Submission of Published Literature Study Report L-003

Medical Officer's Literature Review (this section was co-authored by the primary and secondary reviewers):

Reviewers' Comments:

Study L-003 is a review of the published literature on the efficacy of thalidomide in the management of ENL. It was prepared by Dr. Gelber and appears to encompass papers retrieved as of 11/93. "Articles wherein there was a question were retrieved for review of the complete citation." The publications included 6 controlled clinical trials, 26 open label comparative trials, and 15 case reports. For the purposes of this NDA review, the 6 controlled clinical trials will be reviewed as published, instead of reviewing Dr. Gelber's review. One of these trials is the Hastings study and has been reviewed as Study L-001. It should be noted that these studies, designed and executed in the late 1960s and early 1970s, were not intended to meet current regulatory requirements. The reviews which follow reflect a perspective on the regulatory utility of each study and are not intended as scientific critique.

1. **Thalidomide in the treatment of erythema nodosum leprosum With a note on selected laboratory abnormalities in erythema nodosum leprosum (Hastings et al).**

   The retrospective data collected were reviewed in detail as Study L-001. A valid conclusion could not be drawn regarding the efficacy or safety of thalidomide in the 25 patients studied.

2. **WHO Co-ordinated Short-Term Double-Blind Trial with Thalidomide in the Treatment of Acute Lepra Reactions in Male Lepromatous Patients (Iyer et al., 1971).**

   Summary: This was a double-blind, active control, cross-over, multicenter study of 92 male patients. Acetylsalicylic acid, 400 mg QID, was used instead of a placebo, because of its antipyretic and analgesic activity. The design was a crossover study without a washout period. Each study period was 7 days in duration.

   Author's Conclusions:

   "1) Thalidomide seems to bring about reduction of skin lesions, and a fall in body temperature in a larger number of cases and in a shorter period than acetylsalicylic acid does.

   2) The effect of thalidomide on acute nerve and eye lesions seems to be less pronounced, though more satisfactory than that of acetylsalicylic acid.

3) Both drugs seem to have conferred some benefit on patients with involvement of testes, lymph nodes, liver, and spleen related to lepra reactions; the effect of thalidomide treatment is consistently superior.

4) It appears that acetylsalicylic acid is helpful in the management of certain symptoms of the lepra reaction.

5) In the very short period of treatment, side effects of a serious nature have not been encountered in either group. Thalidomide appears to induce leucopenia and probably a fall in pulse rate."

Author's Risk/Benefit Assessment:

1) Concerning Side Effects:

"...thalidomide is known to cause 3 types of severe adverse reactions: teratogenic. leucopenia, and peripheral neuritis.

Teratogenic effects have been observed after a single dose of 200 mg of thalidomide administered on the fortieth day of pregnancy.

Leucopenia occurred early or later in patients during thalidomide treatment.

Peripheral neuritis has been observed occasionally; this type of adverse reaction may lead to permanent nerve damage."

2) "The early detection and differential diagnosis of drug-induced neuritis has its specific difficulties in leprosy patients because of the neuritis caused by *Mycobacterium leprae*. Thalidomide therapy is, therefore, attended by high risks."

Author's additional observations:

"The influence of thalidomide on the blood pressure and pulse rate is worth noting. It seems that the striking bradycardia in patients of the thalidomide group cannot be attributed entirely to the fall of body temperature. In some instances, irregularities of cardiac rhythm were observed."

Reviewers' Comments:

This published report includes significant amounts of important safety and efficacy data for thalidomide in ENL at a dose of 100 mg QID compared to acetylsalicylic acid (ASA) at 400 mg QID. Despite the considerable merits of the publication, it is insufficient for regulatory purposes

for the following reasons:

1) *The entry criterion was cutaneous ENL, but the extent and/or severity of baseline lesions was not defined. It is unclear how 10% of the subjects were enrolled, since the results tables indicate that these subjects had no skin lesions at baseline.*

2) *The endpoints encompassed the range of body systems affected by ENL, but the assessments were not defined. This is particularly troublesome problem for the endpoint called "nerves", given the known peripheral neurotoxicity of thalidomide. In addition, the final observation was at day 8, which may have been too short to observe effects other than temperature reduction and skin lesion improvement.*

3) *The efficacy data are presented as summations of all subjects and it is not possible to determine the clinical significance of the data without patient tabulations. For example, how many of the "absent" entries for skin lesions meant that one lesion was present and it resolved? It is also noted that there were almost 3 times as many patients in the thalidomide arm with fever >39 degrees at baseline, suggesting a possible blinding problem. This is significant, since the most dramatic effect of thalidomide in this trial was fever reduction. Despite the marked reduction in fever, however, there is little, if any, response for organ systems other than the skin. (Note that the observed "normalization" of leucocytosis is followed by post-treament neutropenia, strongly suggesting a drug toxicity rather than therapeutic effect).*

4) *The safety data are likewise presented as summations and, without tabulations, cannot be used to determine the severity of the AEs listed. For example, the authors refer to "striking" bradycardia and show 8 cases in the thalidomide arm with a pulse less than 60/min by the eighth day. Does this mean that 8 patients had a change in pulse from 60-70 at baseline and then a pulse of 59, or that patients with a baseline pulse of 110 had a decrease to <60, a far more worrisome event? Reference is made to "irregularities of cardiac rhythm" in the discussion. Apparently this is in addition to the bradycardia, but no details are provided.*

   Similarly, the neutrophil counts are expressed as a percent of the differential, and it is impossible to correlate neutropenic cases with results of total WBC counts.

   The table listing side effects indicates that no information was collected for almost half of the entries (for example, drowsiness is coded as present 6, absent 58, and no information 52).

5) *Regarding the authors' comments concerning ASA efficacy, it is noted that the dose used was 40% less than the therapeutic dose for acute inflammation (650 mg*

QID). In addition, the short duration of the trial may have precluded observation of the full benefit of ASA in ENL. As the authors point out, the adverse event profile of ASA in this trial was better than that of thalidomide. They further point out that, because "the early detection and differential diagnosis of drug-induced neuritis has its specific difficulties in leprosy patients...thalidomide therapy is attended by high risks."

6) *The design was a crossover study without a washout period, and there was not an accounting for all patients.*

3. Treatment of Moderately Severe Erythema Nodosum Leprosum with Thalidomide - A Double-blind Control Trial (Pearson & Vedagiri, 1969).

Summary: Patients in this trial were allotted randomly to treatment with thalidomide 100 mg 3 times daily (twice daily if weighing less than 35 kg (77 lbs) or with a placebo identical in appearance. Patient and nursing staff were unaware that a placebo was being used, and the research worker did not know which patient was receiving which treatment at any time. All antileprosy treatment was continued and neither drug nor dosage was altered. After 6 weeks the treatment was switched from active to placebo or placebo to active and continued for an additional 6 weeks.

Selection of patients was as follows:

"All 12 patients admitted to the trial (11 males and one post-menopausal female (case 4) had been suffering from ENL for at least 10 months, and 11 of them for periods of between 1 and 3 1/2 years. They all had frequent courses of antimonials ("stibophen") and some required occasional courses of ACTH or corticosteroids in low dosage." The diagnosis of lepromatous leprosy was confirmed by biopsy in 11 cases. The diagnosis of ENL was made on clinical grounds.

Results:

Table 16: Steroid Requirement

	Steroid Requirement During the Trial Period	
	Total Amount of Prednisolone Prescribed (mg)	
Case No.	Thalidomide Treatment	Placebo Treatment
2	0	35
4	10	135
6	400	630
10	35	0
12	500	345

Authors Conclusion:

Five patients received steriods during the trial; 3 of 5 required less prednisolone when treated with thalidomide.

Table 17: Paracetamol requirements

Parameter	Treatment	Weekly Score (total of all cases) Range	Weekly Score (total of all cases) Average
Paracetamol requirement (no. of tablets)	Thalidomide	114 to 160	142
	Placebo	212 to 282	246

Authors Conclusion:

"There was a most striking difference between the 2 groups, in that the patients took almost twice as many tablets during treatment with placebo."

Table 18: Stibophen treatment

Parameter	**Treatment**	**Weekly Scores** (total of all cases) Range	**Weekly Scores** (total of all cases) Average
Stibophen requirement	Thalidomide	40 to 46	42
	Placebo	26 to 43	31

Author's Conclusion:

"Here the difference between the two groups was very clear cut, as during 5 out of 6 weeks of placebo treatment patients needed more stibophen then the maximum required in any one week of thalidomide treatment."

Author's Summary:

"Twelve patients with long-standing ENL but not usually requiring steroid treatment were subjected to a double-blind control trial of thalidomide in a dosage of 100 mg 3 times daily. Their response was assessed clinically and by the reduction of their requirement for other anti-ENL treatment (stibophen and/or prednisolone). Thalidomide was shown to be superior to placebo, and was preferred by the patients, who consumed less paracetamol during the period of thalidomide treatment."

Reviewers' Comments:

1) *The sample size of 12 patients is too small to draw a valid conclusion for a trial of this design.*

2) *The parameters for prescribing prednisone and stibophen were not provided; paracetamol (acetaminophen) was supplied to the patient to take as they wished.*

3) *Baseline characteristics, order of trial arm entry, and scoring system were inadequately described for regulatory purposes. Also, there was no washout period between treatments.*

4) *Reported clinical assessments consisted of ENL lesions and fever only. No specific assessments of systemic ENL were made.*

5) *Entry criteria and baseline data were not provided, and the baseline characteristics of the patients requiring corticosteroids were not stated.*

6) *No statistical analysis was performed to support the conclusion, and patient preference was extrapolated solely from paracetamol use.*

4. Further Observations with Thalidomide in Lepra Reactions (Sheskin, 1965).

Summary: Twenty-two reactions were treated with 34 assorted therapeutic trials in 13 patients, in the dose range of thalidomide 300-400 mg/day, over approximately seven months. There were five drug combinations:

dapsone + placebo
placebo alone
dapsone + prednisone + thalidomide
dapsone + thalidomide
thalidomide alone

Nine of the patients had active lepromatous leprosy. Clinical assessment was improvement within 48 hours.

Author's Conclusions: In each of 22 tests in which thalidomide was given either alone or in combination with other drugs, there was rapid clinical improvement, both subjective and objective. There was a fall in temperature and cessation of rigors. The patients slept better, nausea disappeared, and the appetite increased. Muscle, joint, nerve, and testicular pains were all relieved, as were headaches. There was resorption of the skin lesions of the lepra reaction and reduction of the size of enlarged lymph nodes...In one patient with severe pains and

thickening of the ulnar nerve, there was relief of pain within 24 hours, and by the ninth day of treatment the ulnar nerve felt normal but still rather tender. A second patient who had severe polyneuritis also experienced relief of nerve pains within 24 hours, and the affected nerves felt normal after 15 days of treatment, although there was tenderness on pressure....Nine of the patients had active lepromatous lesions which also appear to have improved during treatment. In twelve tests the placebo tablet was used; in no case was there any improvement in the patient's condition...In no case was it necessary to stop treatment because of toxic reactions...

Reviewer's comments:

1) This was an unblinded, largely anecdotal report.

2) A definition of clinical response in 48 hours was not provided; however, the responses and treatment assignments were presented. Duration of therapy was not clear.

3) The sample size of 13 patients is too small to draw a valid conclusion for an adjunctive therapy trial.

4) Baseline characteristics and order of trial arm entry are not stated. Also, there was no washout period between treatments.

5) The reported improvement in the leprosy lesions of all 9 active LL patients is puzzling, since there are no data of which we are aware indicating that thalidomide has anti-microbial activity. In fact, the author himself demonstrated 3 years later (1968) that patients treated with thalidomide alone (ie. without antimicrobial therapy) experienced clinical deterioration in their lepromatous leprosy.

5. Results of a Double-blind Study of the Influence of Thalidomide on the Lepra Reaction (Sheskin and Convit, 1969).

This was a double-blind, placebo control, cross-over, one center study of 52 patients (37 males and 15 females) ranging in age from 17 to 56 years. The "essential criteria" appeared to be "clearly demonstrable dermatologic, neurologic or other manifestations of lepra reaction." Duration of the lepra reaction at the time of study entry varied from 3 months to 9 years.

Baseline Characteristics:

ENL Duration:
< 1 year N = 12
> 1 year N= 40
Total N = 42

Reaction Patterns:
Continuous reactions N = 48
Occasional reactions N = 2
Initial reaction N = 2
Total N = 52

Chronic (described as a number of years) corticosteroid use N = 3

Prior to this study all patients had received at different times, singularly or in combination: chaulmooga oil, sulfones, diphenylthiourea, thiosemicarbazone, and antibiotics.

Treatment and Dosage:

1. Each lepra reaction was treated for a total of seven consecutive days (a treatment regimen unit).
2. Patients received thalidomide or placebo QID or TID "with a night pause". Dose was based on weight (6 mg per kg daily) if weight was less than 50 kg. Patients weighed greater than 50 kg, the dose was 100 mg QID.
3. Patients with no clinical improvement after 7 days were considered therapeutic failures and were immediately given a new regimen unit.
4. Even if partial improvement occurred, treatment was discontinued after any therapeutic response until a new skin eruption or neurologic symptom of the lepra reaction appeared.

Seven patients were reincorporated into the study after completion of their four treatment regimens "because their original treatment course did not include a pause after partial improvement". Statistically, they were regarded as new patients and therefore increased the number of subjects to 59.

There were 85 thalidomide regimens and 88 placebo regimens.

Reviewers' Comments:

1) Baseline characteristics cited for the number of ENL reaction durations, listed as N = 42, is inconsistent with the number of 52 or 59 patients.

2) Baseline severity characteristics between the treatment groups were not provided.

3) A table is presented in the published paper entitled "Comparison of the results after thalidomide or placebo". The author calculates the percentage "Complete Improvement" on thalidomide as 91.49%. This is apparently the result of using the total number of complete improvements (thalidomide plus placebo) as denominator rather than the total number of thalidomide trials conducted (n=85). When the data are re-

calculated using the number of responses as the numerator and the total number of trials for each arm as the denominator, the following results emerge:

	Thalidomide (N=85)		Placebo (N=88)	
Category	No.	%	No.	%
Comp. Impr.	*43*	*51*	*4*	*4.5*
Striking Impr.	*13*	*15*	*4*	*4.5*
Partial Impr.	*22*	*26*	*16*	*18*
No change	*7*	*8*	*44*	*50*
Worsening	*0*	*0*	*20*	*23*

This is in contrast to the reported 91% complete improvement with thalidomide and the 100% worsening with placebo.

4) *The re-incorporation of seven patients for efficacy analysis is unacceptable for regulatory purposes without the primary data for review.*

5) *This study did assess systemic manifestations, but provided no parameters for the systemic signs and symptoms of ENL. It is unstated what constituted "improvement", "partial" or "total" for systemic ENL. It is unclear whether baseline and/or follow-up monitoring included any objective neurologic testing (the paper notes only that each patient had a complete history and physical examination; "neuropsychiatry" specialists examined the patients because some of them had "mental disturbances").*

6) *All clinical assessments were subjective. Vital sign assessments were not provided, and there was no presentation of temperature readings.*

7) *Ulnar nerve tenderness was reported as persisting in patients listed under "neuritis" with "total improvement". It is unclear how total improvement exists in the setting of continuing nerve tenderness. This may explain the difference in this conclusion from that reached in the Iyer's study, where neuritis continued unchanged at the seventh day of treatment with thalidomide in 48% of the reactions. The definition of partial improvement was not provided.*

8) *The authors point out that a 7 day trial is insufficient for evaluating thalidomide associated burning sensations in the hands and feet.*

9) *There is no detailed safety assessment.*

6. An Internally Controlled Double-blind Trial of Thalidomide in Severe Erythema Nodosum Leprosum (Waters 1971)

This was a double-blind, internally-controlled clinical trial of thalidomide in severe,

chronic, histopathologically-proven ENL, in 10 adult male patients. Patients received steroids, thalidomide 300 mg with steroids, or placebo with steroids during the 16 or 24 week treatment period. The entry_criterion was a minimum daily requirement of no less than 15 mg of prednisolone or 18 international units of corticotropin. The endpoint was the rate at which steroid dosage could be reduced. Severity grade assessments were based on temperature reduction and skin lesions. These were recorded using a point grading system averaged for each period. The study periods consisted of 4 week rest period, a period of either placebo or thalidomide, and a follow-up rest period. Patient no. 10 was entered only into the second 24-week trial, so that the number of patients in the 16 week trial was 9. Patient no. 9 was omitted from the 24 week trial because his ENL was unstable.

The authors concluded that no dose-for-dose relationship for thalidomide with prednisolone was evident, but that assessments based on clinical signs and symptoms gave confirmatory evidence of the value of thalidomide but "were less decisive".

Reviewers' Comments:

1) *Very low numbers of patients were enrolled for a crossover design trial. Also, there was no washout period between treatments.*

2) *Stibophen use during the initial and final control periods and the free use of antipyretics/anti-inflammatory drugs were confounding variables which were not addressed by the author.*

3) *There was no assessment of neuropathy.*

4) *The criteria for deciding the steroid dosage were not stated (this was the primary endpoint). If one examines the temperature/clinical scores data, it becomes apparent that the efficacy results are indeed not as convincing as the steroid reduction results. Specifically, patients 1, 4, 7, 8, and 9 were worse, as defined by temperature and/or clinical assessment, on thalidomide than at baseline and/or at the final rest period (off thalidomide). Patient 9 was markedly worse on thalidomide and improved when it was stopped (his steroid needs increased by 101% on thalidomide). Patients 2,3,5, and 6 improved on thalidomide, but only patient 3 showed marked improvement.*

Overall Reviewers' Conclusions Regarding the Published Controlled Trials:

The submitted published reports cannot be relied upon to establish the safety and efficacy of thalidomide for regulatory purposes for the following reasons:

1. *The short duration (2, 4, and 7 days) of the controlled trials, including the Hasting's study (4 days), did not allow sufficient time for the natural history of the disease (ENL*

can be episodic and it can vary considerably in severity over short periods of time). The tapering studies of Waters (1971) and Pearson & Vedagiri (1969) were of longer duration; however, the numbers of patients were small and the crossover design did not include a washout period. Additionally, baseline characteristics were not stated and the effects of concomitant medications were not assessed.

2. *There were no clear and adequate descriptions of statistical plans, analytical methods, and study endpoints. It cannot be established that there was a full accounting of all enrolled patients.*

3. *From the assessment of the endpoints, resolution of fever and ENL skin lesions, extrapolation to successful treatment of systemic ENL cannot be made. Neurological assessments were not adequately addressed.*

4. *Documentation of operating procedures for the groups who conducted the submitted studies was not provided.*

5. *Except for the Hastings' study, protocols and other primary supportive data were not available for review.*

The conclusion reached by Dr. Gelber in his review is that "the overwhelming weight of the evidence attests to thalidomide's rapid amelioration of the signs and symptoms of ENL in over 90% of treated patients when used most often in doses of 300 to 400 mg/day, but also, in some patients, in doses of 100 to 200 mg/day." It appears from the published literature that thalidomide, in the doses used, does ameliorate fever and cutaneous lesions in many patients. As documented under the review of the controlled trials, however, it appears that the effects are not as robust as the literature would suggest and that there is an unexplained disagreement regarding the effect of thalidomide on the systemic features of the syndrome. Reduction in fever cannot be assumed to reflect a systemic anti-inflammatory effect because the mechanism of action is, to our knowledge, unknown. It is known that thalidomide is a centrally acting drug, hence, its sedative effects. Its anti-pyretic effects could be analogous to acetaminophen rather than a result of anti-inflammatory activity. Indeed, as discussed in the Comments section for Study E-003/P, the majority of ENL patients coded as complete or partial responders to thalidomide had persistent and significant elevations of the ESR at the final sampling, approximately 8 weeks after initiation of thalidomide therapy.

9 Overview of Efficacy

At the time of this review, information from a major efficacy amendment was not available to the primary reviewer. This amendment will be reviewed by the secondary reviewer, followed by an Overview of Efficacy.

10 Overview of Safety Information

Safety data from the PK studies, Study L-001, L-002, L-003, and E-003/P have been reviewed. This section is a review of the Sponsor's submitted studies L-004, L-005, a neurologist's report, as well as additional information from the Integrated Summary of Safety.

L-004 is a entitled "Safety of Thalidomide in the Treatment of ENL: A Review of the Published Literature". This report was prepared by Robert H. Gelber, M.D. **L-005** is entitled "Safety of Thalidomide in Non-Leprosy Indications: A Review of the Published Literature". It too was prepared by Dr. Gelber. These reports do not specifically address teratogenicity and the reviewer is referred to a separate report on neuropathy. That separate report is authored by Dr. D.R. Cornblath.

10.1 Study L-004 "Safety of Thalidomide in the Treatment of ENL: A review of the Published Literature". This report was prepared by Robert H. Gelber, M.D.

(This Study was reviewed by the secondary reviewer with concurrence of the primary reviewer)

The author states that this report is based on a review of publications identified using "thalidomide" as the search term, updated in November of 1993, with "more recently, targeted searches". *(Rev Comment: "More recently" is not defined, but the study report is dated 12/96. However, the Contents List includes only 2 papers since 1990, the most recent of which is 1993.)* The abstracts and titles were reviewed. A review of the complete article appears to have been undertaken where there was "a question". Thirty-five publications are noted to have addressed the safety of thalidomide in the treatment of ENL and cover 6444 patients. The author of the review notes that no implications regarding the number of patients experiencing events can be drawn from 4769 cases collected in his survey. The adverse event table presented below includes data from 1518 patients in clinical trials or case series where the number of patients with the events was stated in the publication. It is noted that only one study (Dr. Iyer's) presented vital signs.

Attention is also called to reported dose reductions, one for peripheral neuropathy, and discontinuations (4), including one case of exfoliative dermatitis, hypotension with tremors (1 case), intestinal obstruction (1 case). No reported deaths were noted. It is noted that laboratory studies were systematically performed in 15 articles, but that only 2 articles reported abnormalities, mild leukopenia/neutropenia. Examination of the table presented shows that 6 publications looked at liver function and 4 noted serum-based renal function tests. Ten examined WBC counts; platelet counts are not noted.

Table 19 **Overall Summary of Adverse Events in 1518 Patients With ENL Treated With Thalidomide** (as reproduced from the NDA submission)

Adverse Event	Open-label studies N=1483	Double blind studies N=35	All studies N=1518
Cardiovascular System			
Bradycardia	1(<1%)	0	1(<1%)
Hypotension	1(<1%)	0	1(<1%)
Vasodilation	1(<1%)	0	1(<1%)
Digestive System			
Appetite increase	353(24%)	1(3%)	354(23%)
Constipation	48(3%)	10(29%)	58(4%)
Weight gain	33(2%)	13(37%)	46(3%)
Dry mouth	3(<1%)	7(20%)	10(<1%)
Dyspepsia	7(<1%)	0	7(<1%)
Appetite decrease	3(<1%)	0	3(<1%)
Nausea	2(<1%)	0	2(<1%)
Pain, abdominal	2(<1%)	0	2(<1%)
Abdominal distension	1(<1%)	0	1(<1%)
Diarrhea	1(<1%)	0	1(<1%)
Intestinal obstruction	0	1(3%)	1(<1%)
Hemic and Lymphatic System			
Eosinophilia	0	5(14%)	5(<1%)
Leukopenia	2(<1%)	0	2(<1%)
Metabolic & Nutritional Disorders			
Edema	29(2%)	4(11%)	33(2%)
Nervous System			
Somnolence	70(5%)	14(40%)	84(6%)
Dizziness	16(1%)	2(6%)	18(1%)

Neuropathy	4(<1%)	0	4(<1%)
Euphoria	2(<1%)	0	2(<1%)
Excitation	2(<1%)	0	2(<1%)
Tremor	1(<1%)	0	1(<1%)
Skin and Appendages			
Rash	6(<1%)	14(40%)	20(1%)
Pruritus	11(<1%)	0	11(<1%)
"Crazy Pavement"	1(<1%)	0	1(<1%)
Exfoliative Dermatitis	1(<1%)	0	1(<1%)
Ichthyosis	1(<1%)	0	1(<1%)
Perifollicular thickening	0	1(3%)	1(<1%)
Urticaria	1(<1%)	0	1(<1%)
espiratory System			
Cough	1(<1%)	0	1(<1%)
Upper respiratory infection	1(<1%)	0	1(<1%)
Urogenital System			
Impotence	0	4(11%)	4(<1%)
Musculoskeletal System			
Bone tenderness	1(<1%)	0	1(<1%)
Periosteal Disorder	1(<1%)	0	1(<1%)
General Body			
Asthenia	9(<1%)	0	9(<1%)
Headache	3(<1%)	0	3(<1%)
Pain	1(<1%)	0	1(<1%)
"Miscellaneous"	9(<1%)	0	9(<1%)

Reviewer's comments:

1. *This information from published reports, as presented, cannot be verified because primary data or protocols are not available except for Dr. Hastings' study. This study*

only assessed and reported ENL lesions, fever, and selected laboratory monitoring.

2. *Laboratory monitoring and vital signs monitoring were extremely limited.*

3. *An exhaustive review of the summary table will not be presented here; instead, two points are noted to illustrate the limited value of the table as presented:*
   (1) The table lists one bradycardia because Dr. Iyer's paper recorded the event per number of reactions, not patients. Thus, bradycardia is listed in a subsequent table (not reproduced here) as occuring in 8 treatment courses. However, in the text, the author notes that Dr. Iyer's was the only study that presented vital signs. Yet, it appears that the submitted table gives the percentage (3%) as calculated from 229 courses in 3 published studies.

   (2) There is a large discrepancy between the incidence of several adverse events, for example, somnolence and rash, in the double blind studies vs the open label studies.

10.2 L-005 "Safety of Thalidomide in Non-Leprosy Indications: A Review of the Published Literature." Prepared by Dr. Gelber.

(This study was reviewed by the secondary reviewer with concurrence of the primary reviewer).

The methods for retrieval of thalidomide safety data in non-ENL indications was similar to that described in the previous section. There were 93 studies. As noted above, the author refers the reader to other reports regarding teratogenicity and peripheral neuropathy except as it was found coincidentally in those studies he actually reviewed.

The most frequently reported events in non-leprosy patients were somnolence (31%), constipation (10%), skin rashes (6%), weight gain (6%), peripheral neuropathy (4%), dizziness (4%), headache (3%), and nausea (2%). The author notes that significant new side effects not seen in patients treated with thalidomide for ENL were encountered, including myxedema, thrombocytopenia, and single cases of erythroleukemia and Hodgkins disease. It is also noted that some of the reported skin rashes were serious, including erythema multiforme, erythema nodosum, and purpura. Hypotension is likewise noted, as well as 2 cases of syncope/fainting. Laboratory monitoring was presented in only 11 of the articles, with leukopenia/neutropenia ascribed to thalidomide. None of the leukopenia/neutropenia reactions were reported to place the patient a risk of infection. All 3 three cases of thrombocytopenic purpura subjected to rechallenge had a positive result. A patient who developed erythema nodosum 5 days after starting thalidomide for Behcet's also had a positive rechallenge.

There were multiple reports of discontinuations, the most common reasons being rash,

somnolence, peripheral neuropathy, and polyneuritis.

Deaths occurred in 32 patients all of whom had advanced cancer or graft versus host disease. The author noted also a report that 21 of 37 GVHD patients died in another study, but that it was unclear whether they were receiving thalidomide at the time of death.

The author concludes that the available literature suggests that thalidomide is generally safe in the treatment of a wide range of disorders.

Reviewer's Comment:

The previous literature review for ENL covered 35 papers, only 2 of which were published since 1990, the most recent in 1993. However, given that the use of thalidomide for other indications is only recent, it is not unexpected that more of the non-leprosy papers are from the 1990s. The occurrence of side effects not reported in ENL most likely reflects lack of evaluation/reporting in ENL patients, in the much earlier studies, rather than lack of the events.

10.3 "Review of Peripheral Neuropathy in Association with Thalidomide Use Including Hansen's Disease Patients Neuro Report"./Dr. Cornblath

(This section was co-authored by the primary and secondary reviewers).

According to Dr. Cornblath, "The peripheral neuropathy associated with thalidomide use, a central-peripheral distal axonopathy, is well-described and relatively stereotypic. The initial symptoms are paresthesias in the toes and feet, which progress centripetally. If the neuropathy is detected early and the drug is stopped as soon as symptoms develop, the potential for reversibility is high. If the drug is continued after symptoms develop, these symptoms progress and may include dysesthesias, numbness, and muscle cramps. At that point, the potential for reversibility is low. Examinations show reduction in sensory function and reduced/absent ankle reflexes, but weakness only rarely. There is little information on the functional consequences of the neuropathy."

"Electrophysiologic studies are useful in monitoring subjects who take thalidomide. Either the sural or summed sensory response is the most reliable correlate of subjective and objective neuropathy. When electrophysiologic studies are combined with clinical examinations in a prospective manner to identify the development of neuropathy, the incidence and severity of thalidomide-induced neuropathy are dramatically reduced, compared to when such programs are not utilized."

"Many studies have correlated factors related to thalidomide use-daily dose, cumulative dose, age, sex, pre-existing neurologic illness with the development of neuropathy, but no clear relationship has emerged..."

"For unknown reasons, *no patient with leprosy has ever been reported to have developed a thalidomide-induced peripheral neuropathy. (Comment: italics are verbatim)*...However, in both non-leprous dermatologic and non-dermatologic conditions, peripheral neuropathy remains a problem."

Thalidomide and lack of thalidomide-induced neuropathy in leprosy patients.

Gibbels and colleagues (1973) commented on the reported the lack of thalidomide neuropathy in leprosy patients treated with thalidomide, in comparison with the late stage polyneuropathy observed in 30 non-ENL patients who developed a significant sensory polyneuropathy during or immediately after long term thalidomide medication. Of the eleven references cited, J. Sheskin was cited as an author or coauthor in 10 of the 11 articles. Degos and colleagues were also cited in this submission as well as a study by Gibbels; however, the copy of the translation of the Degos article provided, "Quick resolvent effect of thalidomide on outbreaks of leprosy", did not address neuropathy. The Gibbels publication postulated a genetic factor to account for the apparent resistance of leprosy patients to thalidomide induced peripheral neuropathy, but provided no evidence.

Magora, Sheskin, Sahger, and Gonenl (1969 and 1971) conducted motor conduction velocity studies of the ulnar nerve in patients with leprosy reaction under various forms of treatment and follow-up assessment of the effect of thalidomide upon the ulnar nerve. They evaluated 103 leprosy patients (61 males and 42 females) for 6 years, 27 of whom were on thalidomide and dapsone. The usual dose of thalidomide was 300 to 500 mg daily with a maintenance dose of 50 to 100 mg daily. Twenty-one of the 27 took thalidomide for longer than 4 months, 15 for longer than one year, and 7 for longer than 3 years. Four of the 27 patients complained of sensory symptoms; however, these symptoms reportedly disappeared spontaneously. The authors found no evidence of a neurotoxic effect of thalidomide. The ulnar nerve conduction values of the thalidomide patients were reported as slightly better than those of the controls. Lower limb nerve conduction studies were not performed.

Sheskin and Yaar (1981) examined conduction velocity in the ulnar nerves of 26 lepromatous leprosy patients receiving thalidomide for 6-13 years. They reported no adverse effects on electrophysiologic testing or clinical examination.

The submission also cited an unsigned editorial in *The Lancet* in 1985 proclaiming that "in nearly two decades of the clinical use of thalidomide in thousands of lepromatous patients, leprologists have recorded no adverse neurological effects due to the drug." In addition, Awofesco (1992) and Waters (1992), both reported frequent use of thalidomide without any evidence of a toxin-induced neuropathy.

At the end of Dr. Cornblath's review of the literature, he recommends that "Systematic pharmacokinetic and pharmacogenetic studies be undertaken to determine why leprosy patients do not develop thalidomide-induced neuropathy."

Reviewer's comments:

1. *As pointed out by Dr. Cornblath, lower limb nerve conduction studies, which would have strengthened the studies, were not performed in the leprosy patients.*

2. *The nerve conduction studies reviewed by Dr. Cornblath involve 53 ENL patients receiving thalidomide. If it is a comprehensive look at the available published data over the approximately 30 years since thalidomide first came into use in this population, it would appear that the issue of thalidomide induced peripheral neuropathy in ENL has received little investigation since 1981.*

According to the L-002 submission, the following neurological adverse events were reported under the USPHS IND: neuritis reported in 6 patients, neuralgia in 6 patients, neuropathy in 5 patients, and causalgia in 1 patient.

The sponsor provided case reviews on 7 of these patients whose records were available. According to the Sponsor, these case reviews were done by the treating physician at GWLHDC (unnamed). Clinical summaries were included in the submission. The submission states the following:

> "A review of the patients reported as having neuropathy, paresthesia, neuritis, peripheral neuritis, or neuralgia showed that the majority of the patients were treated in centers outside of GWLHDC. Detailed information is not available for many of these patients. In only one of the 7 patients did the treating physician at GWLHDC who reviewed the cases conclude that there was evidence of "thalidomide induced neuropathy". In the verbatim reports, some patients had "possible" and "probably" used as a descriptor of the event, and thus, the significance is uncertain. Neuritis from leprosy is relatively common and some clinicians may have reported neuropathy in patients on thalidomide even though it was most likely due to leprosy. In 7 of these patients, the verbatim report stated "nerve pain" or a similar finding and these events were coded as neuralgia or causalgia. These events were all reported by one clinic and one treating physician. The reviewer stated that these were non-specific findings in the leprosy field and the reports did not suggest that the events were related to thalidomide intake."

A line by line examination of the case tabulations for IND 11,359 was undertaken by the secondary reviewer. Before reviewing the findings, it must be noted that the review by Dr. Cornblath is a literature review, not a review of the material available for our review under Study L-002/IND 11,359.

Assessment of Neurologic Adverse Events Reported Under IND 11,359

(This section was prepared by the secondary reviewer with concurrence of the primary reviewer)

The NDA included tabulated listings for 1,387 ENL patients treated under the IND through 1994. The listing was examined for neurologically related events other than drowsiness/sedation. This was done manually; thus it is possible that a few entries were missed. Thirty six entries

were found. In looking for this information it was noted that there seemed to be a clustering effect of sparse reporting, with large series of entries where almost all the AE/lab abnormalities were coded as "None". The tabulations did not identify the sites. The sites were found by cross-referencing each patient number with an Information Amendment submitted 3/97. The table included in the Appendix shows each patient by tabulation number for whom a neurologic adverse event, other than sedation/drowsiness, was coded. These events are transcribed verbatim, as is the coded "ENL Response". In addition, the dose is shown, but as noted in the review of L-002, the reported doses are mean doses over the reporting year. In cases where the coded AEs seemed particularly relevant, such as paresthesias, multiple years of treatment are noted for the patient to illustrate the temporal relationship.

It should be noted that no conclusions can be drawn regarding reporting frequency by site because the table does not reflect the total number of patients at each site and no statistical analysis was done. However, one site, which the Information Amendment indicated had about 100 of the cases in the database, accounted for approximately 42% of the 36 listings over the 16 year period. In contrast, Carville, which had about 200 of the cases in the database, had no listings in the table. Two sites, each representing approximately 250 cases in the database, had 1 and 4 listings. The cases reviewed in the submission, as described above, are among the 36 entries found. Further information for the remaining cases was not found. However, an amendment (Vol 4) submitted by the sponsor to demonstrate time to response and efficacy of thalidomide in the treatment of ENL neuritis, provided 9 additional narratives. These narratives appear to have been prepared by Celgene from records from Carville and LAC/USC. (The cover letter for the amendment noted that the case narratives were submitted in draft pending review by the investigators. To this reviewer's knowledge, the finalized reviews have not been submitted).

The two cases (LAC/USC) briefly summarized below were coded as "None" under the AE listings in the tabulations:

> Pt 1361 developed abnormal sensation finger and left foot 18 months after starting thalidomide. A burn to the hand at this time is also noted.
>
> Pt 1365 had a normal hand and foot screen on presentation in 1993. Thalidomide was started 5/94. [ ] shows complaint of increasing pain in hands and feet. In [ ] there is c/o "trembling and weakness". The thalidomide response was coded as "fair" and the patient was also on prednisone. In [ ] there was an injury to the shin. The patient died suddenly in [ ] He "had complained of back and chest pain". The cause of death was not given. Nothing in the synopsis suggests that thalidomide had been discontinued. There was a reference to "drinking"early in the synopsis. This patient was born in [ ]
>
> ***Reviewer's Comment:*** *See comment under "deaths" in Section 10.*

These cases are presented to illustrate the difficulty in trying to extract safety data from this

database. Among the possible causes for the uneven reporting patterns are: (1) some sites reported neurologic AEs not thought to be related to thalidomide (recall that only AEs thought by the investigator to be thalidomide related were to be reported), (2) patients at some sites had more thalidomide related neurologic AEs, (3) some sites did not report AEs thought to be thalidomide related, (4) some sites considered all such events not thalidomide related and thus did not report them, and/or (5) the line listings are incorrect. It would seem most likely that the overall reporting patterns reflect the fact that the majority of investigators held the prevailing view that, when neuropathy occurs in these patients, it is due to their underlying disease and unrelated to thalidomide.

Thus, a self-fulfilling prophecy could emerge: Two publications, the most recent 16 years ago, detected no peripheral neuropathy as measured by ulnar nerve motor conduction velocity, not sensory nerve action potentials of the sural nerve. These papers were then widely referenced and may have contributed to the consensus which emerged that thalidomide does not cause peripheral neuropathy in ENL patients. The annual report to the sponsor of the USPHS IND requests only AEs believed to be caused by thalidomide. Since it is "known" that thalidomide induced neuropathy does not occur in ENL patients, possible cases are not reported by the majority of investigators because the neuropathy must be related to the underlying disease or other causes. The belief regarding neuropathy is then continuously strengthened by the reported experience under this IND. The situation is further complicated by the absence of available data regarding pre-treatment and intercurrent electrophysiologic testing in the ENL population.

A cycle such as this could possibly explain the "unknown" in the consultant's statement: "For unknown reasons, *no patient with leprosy has ever been reported to have developed a thalidomide-induced peripheral neuropathy".*

Dr. Cornblath concluded his review of the literature by stating that when thalidomide is given, a prospective monitoring scheme should be utilized to detect the development of peripheral neuropathy.

Reviewers' Comment:

The strategy advocated by Dr. Cornblath should be applied to ENL patients. The risk/benefit ratio of thalidomide in patients with leprosy will remain unknown until it has been objectively demonstrated whether ENL patients are susceptible to thalidomide induced neuropathy, and if so, whether it can be effectively monitored to prevent peripheral nerve damage.

(The safety sections to follow were co-authored by the primary and secondary reviewers)

10.4 Additional Safety Data from the Sponsor's Integrated Summary of Safety

Celgene-Sponsored Clinical Trials in Non-ENL Patients

Reviewer's Comment: *Note that if AEs are reported regardless of supposed relationship to the drug, the most common AEs in different indications may vary due to effects of the underlying disorder, for example, fever in HIV infection. However, looking at the 5 most common AEs presented by Celgene for each indication is instructive, for reasons discussed in the subsequent Comments. Note also that more information is available under the subsequent headings, Discontinuations and Deaths.*

Study W-001 (as of March 1996)

Table 20 Most Common Adverse Events in Patients with HIV-associated Wasting Treated With Thalidomide *or* Placebo (Blind unbroken) N = 64

Event	Number
drowsiness	16
fever	16
rash	16
diarrhea	11
dizziness	11

Study W-002(HIV): See Serious AE/Discontinuations

Study THAL-3 (HIV): 13 patients include 2 cases of rash, significantly decreased platelets judged to be possibly related to treatment, and dyspnea with chest tightness.

Investigator-sponsored INDs

IND [ ] (HIV)
Table 21 Most Common Adverse Events in Patients With Wasting Treated With Thalidomide (N = 21) (Data as of December 1993)

Event	Number
fever	6
skin rash	6
somnolence	5
constipation	3
dry mouth	3

(Chemie.Grunenthal product)

IND [ ] (Rheumatoid arthritis)

Table 22 Most Common Adverse Events in Patients With Rheumatoid Arthritis Treated With Thalidomide (N = 24) (Data as of January 1995)

Event	Number
drowsiness	16
constipation	10
dry mouth	8
rash	7
leg swelling/dizziness	4

(Celgene product)

Table 23 Most Common Adverse Events Emergency Use INDs (N = 217)
(Data as of November 1996)

Event	Number
peripheral neuropathy	7
somnolence	5
asthenia	3
anemia	3
constipation	2

Reviewer's Comment:

As noted earlier in the review of Celgene's on-going clinical trials in ENL (E-001 and E-003/P), the sponsor has reported that 57% of the patients had skin rash (8 of 14). It is not clear why this number is so much higher than the numbers shown above (25 -29%) and in published reports under L-004 (1%). The incidences of rash with Celgene vs Chemie product noted above are similar, which is somewhat reassuring that the difference is not related to some unique characteristic of the Celgene manufactured product. This is of special concern because the PK study demonstrates that the bioavailability of the Celgene product is far greater than that of the Tortuga formulation, which was apparently chosen as a comparator because it represents one of the thalidomide formulations used under the USPHS IND experience. However, it should be noted that the Chemie product was used in a wasting trial (IND [ ]), a population in which rashes are very common due to the underlying disease. In addition, the actual identity of the product source is unclear, since it is stated to be Chemie in the Adverse Experiences section, but as Celgene in the Discontinuations section (clarification by the Sponsor is pending).

Particular attention should be focused on characterizing the cutaneous eruptions as the Celgene ENL trials proceed, especially since thalidomide from various sources has been, as noted in L-004 and L-005, associated with serious cutaneous eruptions such as exfoliative dermatitis, urticaria, and thrombocytopenic purpura. Treating the cutaneous eruption of ENL with a

neurotoxic drug would be particularly problematic if the drug also causes significant cutaneous eruptions in this population already at high risk for peripheral nervous system damage due to their underlying disease.

From a more general perspective regarding the bioequivalence safety issues, it should be noted that the USPHS database experience was reported to the IND only through 1994 and no safety update has been submitted for the subsequent years in which the Celgene product may have been used. ***Thus, it appears that the only confirmed safety data for ENL patients taking Celgene's thalidomide product comes from the 14 reported patients in Celgene's clinical ENL trials (E-001 and E-003/P) plus the 6 ENL patients in pharmacokinetic study 005.***

10.1.1 Deaths

ENL Studies

Celgene Sponsored Studies

According to Celgene, no deaths have been reported in thalidomide-treated patients in Celgene-sponsored studies.

Non-Celgene Sponsored Studies

Carville IND 11,359: Patient No. 99

One death (Pt. No. 99, a 39 y.o. Hispanic female) was reported under the Carville IND which was assessed by the GWLHDC treating physician as not related to thalidomide therapy. The patient had a diagnosis of Lucio leprosy with Lucio phenomenon. She received a total dose of 34.4 gm of thalidomide before her death. Concomitant medications included clofazimine, prednisone and antibiotics. According to the Sponsor, thalidomide dosing was variable during the 6 month period preceding the time of death (other concomitant medications at the time of death were not provided). The cause of death was congestive heart failure. Other contributing causes to her death were sepsis, pneumonia, and pleural effusions.

Reviewer's Comment:

1. *It is unclear from the summary whether this patient received any thalidomide or the dose received at the time of death.*

2. *A review of information submitted by the Sponsor in response to various queries, which were unrelated to death, revealed several more deaths.*

IND 11,359

Patient No. 1365, a 44 y.o. male, site LAC/USC, was treated with thalidomide 200 mg/day initially (5/4/94), restarted 8/3/94 at 100 mg/day, then increased and again tapered to 100 mg/day. In July and September the patient had complaints of pain in the hands and feet and trembling and weakness. Thalidomide was continued, the ENL response being coded as "fair". On 11/9/94, there were no new lesions and steroids were tapered to 20 mg /day then qod, and then decreased to 10 mg qod. It is not stated that thalidomide was discontinued. The patient died on [ ] en route to the hospital. The patient had complained of back and chest pains. No cause of death was given.

L-001

Patient No. 2553, a 65 y.o. Asian male, died of acute myocardial infarction on [ ] prior to treatment with thalidomide; however, "Listing of Patients at the National Hansen's Disease Center in Carville, LA" (Appendix 3) listed "2553 on [ ] (rec'd 4 doses)." The submission dated June 17, 1997, indicates that Pt. No. 2553 did receive four doses of open-label thalidomide on [ ] However, since the patient had not received known treatment from bottle "A", the Sponsor did not discuss the patient further in Study L-001.

Reviewer's Comments:

From the doctors' progress note, doctors' orders, clinical medication and treatment records, and nurses' notes submitted for review, the dosage and administration of thalidomide or trial status of this patient is unclear. However, from the records presented, the patient had perhaps received at least a total of 400 mgs of thalidomide with the last dose being recorded as administered at 8 PM. The patient was seen by the physician at 9:25 PM complaining of chest pains (impressions illegible). Patient 2553 was pronounced dead at 4 AM on [ ]

Patient No. 2274, died suddenly (in [ ], age (approximately) 62. The listed cause of death was myocardial infarction. It is unknown if this patient was taking thalidomide at the time of death. The submission states that attempts to discontinue thalidomide on 7/28/70 resulted in a severe exacerbation of the ENL. (*The last dose recorded in Appendix 3 was 10/3/70. It is unknown if patients were discharged with thalidomide medications in the early 1970s).*

Patient No. 2643, died on [ ] after a complicated course from a right sided cerebrovascular accident in early [ ] Appendix 3 lists thalidomide use 1/15/67 - 9/3/68. This 88 y.o. patient was treated successfully with placebo from 1/19/68 - 1/22/68. The patient received open-labeled placebo from 1/23/68 - 3/1/68 and placebo

bid from 3/16/68 to 3/22/68. It is unknown if the patient was on thalidomide at the time of the CVA which occurred 7 days prior to time of death.

Patient No. 1983, a 69 y.o. female, died [ ]; cause of death was not provided. The patient had been readmitted to Carville on 8/22/69. It is unknown if the patient was on thalidomide during this admission. Appendix 3 indicates: Placebo from 4/17/69 to 5/8/69; however, a progress note entry 7/18/69 indicated "thalidomide as previously done". No other documents were available.

Reviewer's comments:

It must be emphasized that these cases were not found because of a request to the Sponsor related to deaths of subjects taking thalidomide. They were found in the process of reviewing material submitted to support various issues. The death of patient 1365, for example, was noted in an amendment sent to support the time course to response to thalidomide. This case number is coded with "None" under adverse events in the L-002 line listing for 1994. The IND annual report for 1994 and 1995 does not show patient numbers, only names. Line listings for L-002 do not show patient names. However, all entries for the site in the annual reports examined indicate continued treatment with thalidomide for each patient. No death was reported. Such random findings of death in the Sponsor's submission clearly indicate that ***we do not know how many patients under this IND have died.***

With events that occur relatively commonly, such as cardiovascular events, it is difficult to establish a causal relationship. Without a placebo arm or active treatment arm for comparison of rates of deaths, it is especially imperative that the temporal relationship of serious events to the timing of thalidomide dosing be known. There may be a possibility that thalidomide could be a contributing factor in some of these cases, especially given the evidence for effects of the drug on heart rate and blood pressure.

Reports from Published Literature: ENL

According to the Sponsor, there are three reported deaths in the literature (Husser et al., 1991), but none were receiving thalidomide at the time of death.

Non-ENL Indications

According to Study Report L-005, there have been 32 patients who have died while on thalidomide therapy, all of whom had cancer or GVHD. There have been 16 deaths reported to Celgene through 10/31/96. One death occurred under IND [ ], a study in patients with HIV and tuberculosis, and the remainder of the deaths occurred in Celgene-sponsored studies. According to the sponsor, the deaths were associated with the patients' underlying diseases, primarily AIDS (3 are listed as cardiopulmonary arrest).

10.4.2 Overall Summary of Adverse Events Resulting in Discontinuation in Patients with ENL

There have been no dose reductions or discontinuations due to adverse events in Study E-001 or E-003/P. *(See Comment under review of these studies).*

Table 24 **Carville Study (IND 11,359) (N = 1387)**
(1975 to 1994)

Adverse Event	Number
peripheral neuropathy	1 (pt 1036)
dizziness	1 (pt 1145)

Note: According to Celgene, other patients may have discontinued and restarted throughout the study, but there is no indication that any discontinuations were related to the occurrence of an adverse experience.

Reviewer's Comment: *The utility of this information is extremely limited due to the reporting problems already discussed.*

Published Literature

See Section 10.1, Study L-004 and L-005

10.4.3 Non-ENL Clinical Trials

IND [redacted] 6 of 21 patients discontinued this 21 day study due to adverse events, most notably fever/rash. *(Reviewer's Comment: As discussed previously, this was a wasting trial and these are common events in this population. In disagreement with the Adverse Events section of the Integrated Summary, this section states that the study used the Celgene product.)*

IND [redacted] 6 of 24 discontinued this trial in rheumatoid arthritis. Two were due to rash, others to constipation, vertigo with nausea, malaise, and tremor. These are listed as occurring with the Celgene product.

Study W-001: (Celgene sponsored HIV trial) Discontinuations of note include moderate hepatitis (probably), severe liver enzyme abnormalities (possible), life threatening SGPT increase (probable), one severe and one moderate hypersensitivity reaction (both probable). Note that the blind has not been broken for this study at the time of the report.

10.1.5 Other Significant/Potentially Significant Events

Attempted Suicide There was one reported attempted suicide, Pt. No. 2655, Study L-001.

Myxedema See Study L-005, Section 10.2

Edema This adverse event has been associated with thalidomide since the first reports of use in ENL in the 60s. This submission notes an incidence of about 25% in the RA trial, 11% in published studies, 7% in ongoing E-001 and 003, and 1.9% under the USPHS IND 11,359, a figure that most likely represents under reporting for the reasons noted in several previous Comments.

10.2 Overdose Experience

According to Celgene, there have been three reported cases which were cited in a literature review by Koch (1985). The conclusion was that there appears to be an absence of acute toxicity of thalidomide in adult humans.

10.3 ADR Incidence Tables

Reviewer's Comment: *It is not possible to produce a reliable ADR table from the contents of this submission, for the reasons discussed in previous sections of this review.*

10.4 Laboratory Findings, Vital Signs, ECGs

Clinical Laboratory Evaluation

A ENL Patients

1. **Celgene Sponsored Clinical Trial E-003/P (ongoing)**
   According to the Sponsor, the following laboratory values are noted:

   a) Final visit red blood cell count, hemoglobin, and hematocrit values tend to be below normal and below baseline.
   b) WBC count, neutrophil percent and lymphocyte values tended to be above the normal range at baseline and closer to normal at the final visits.
   c) Eosinophil percentage increased above the normal range at the final visit for a few patients.

Reviewer's Comment: *Examination of line listings indicates that 3 subjects had decreases from baseline in hematocrit of 10 or greater, the largest being from 52% to 39%. In addition, 5 of 9 subjects had decrease from baseline in blood glucose. These decreases were: 96 to 56, 98 to 69,*

77 to 62, 80 to 63, and 79 to 66 mg/dl. It should be noted that the follow-up values were measured at the end of the tapering period, approximately 8 weeks following initial dosing.

2. Non-Celgene Sponsored Clinical Trials

IND 11,359 (ENL)

Table 25 Laboratory Abnormalities Reported as AEs Under IND 11,359 (N= 1387)

Event	Number (%)
Leukopenia	117 (8.4%)
Anemia	79 (5.7%)
Eosinophilia	42 (3.0%)
Alkaline phosphatase incr	30 (2.2%)
Anemia hypochrom	27 (1.9%)
SGOT increased	18 (1.3%)
Bilirubin increased	16 (1.2%)
(Other (chemistry)	21 (1.5%)
(Other (hematology)	20 (1.4%)

Additionally; 4 cases of thrombocytopenia had previously been observed (Jacobson , personal communication according to Celgene).

Reviewer's comment:
This information is unreliable for the reasons discussed in previous sections of this review.

Published Literature

Laboratory monitoring extracted from 10 articles representing the treatment of 519 ENL patients (Iyer et al., 1971 and Cazort et al., 1960) described leukopenia/neutropenia. Eosinophilia was noted by Waters (1971). (See Section 10.1 Study L-004).

Sec Study L-005 for laboratory abnormalities in non-ENL indications.

Vital Signs, ECGs

Reviewer's Comment: *As discussed in previous sections, there are very few vital signs data available and the significance of the observations noted below is unknown at this time.*

Celgene Sponsored PK Studies PK-001, PK-004, PK-005: Significant findings related to pulse and blood pressure are discussed at length in the review of these studies.

1) Two cases of hypotension and 2 cases of bradycardia were reported as occurring in Study PK-001. Symptomatic postural hypotension was noted following measurement of standing BPs in PK-001. However, the subsequent PK studies (PK-004 and PK-005), did not measure standing BPs. Multiple recordings of pulses below 50 were seen in PK-004.

2) In study PK-001 temperature spikes above 99.5^0 F (range 99.5^{0}F - 101.0^{0}F) were noted in 12 of the 17 patients after dosing. The significance is unknown. Temperatures other than baseline during the course of the study were not performed in the subsequent PK studies.

3) Bradycardia was noted on post-treatment ECGs in 2 subjects in PK-001. Additional data regarding bradycardia is discussed in detail in the section for PK studies (pgs 13-20). Also, as reviewed previously, Dr. Iyer's published study demonstrated significant thalidomide associated bradycardia and noted irregularities of cardiac rhythm.

Reviewer's Comment:

Adverse events recently reported in a controlled study in HIV related oral aphthous ulcer patients treated with thalidomide (non-Celgene), 200 mg daily vs placebo (29 thalidomide & 28 placebo), included chest pain, irregular heart beat, syncope, and dizziness.

10.5 Drug-Demographic Interactions

According to the Sponsor, there are no gender, age, or racial differences in response or adverse events profile; however, the paucity of data in the pediatric population is acknowledged.

Reviewer's Comments:

To the extent that this conclusion regarding drug-demographic interactions is drawn from the experience under IND 11,359, it is unreliable for the reasons reviewed previously. Refer to the Pharmacokinetics review for further discussion.

10.2.5 Drug-Disease Interactions

The sponsor discusses peripheral neuropathy and leukopenia. The issue of peripheral neuropathy is reviewed under Section 10.3, Neurology Report.

Reviewer's Comment:

In addition to the disorders noted above, alcoholism, diabetes, thyroid dysfunction, and the possible importance of underlying cardiovascular disease should be mentioned. It should also be noted that a recent publication (Jacobson et al NEJM 336:1487, 1997) suggests that

thalidomide enhances the production of HIV. See Biopharmaceutics Review for discussion of possible PK effects in leprosy patients.

10.2.6 Drug-Drug Interactions

The Sponsor notes the following: The published literature indicates that thalidomide enhances the activity of barbiturates, alcohol, chlorpromazine, and reserpine. The sedative action of thalidomide is antagonized by methylphenidate and methylamphetamine. Concomitant use of anti-leprosy medications is discussed in the context of IND 11,359. The use of other medications which have been associated with leukopenia is noted as well. In addition, the sponsor notes that a formal study of PK interaction with oral contraceptives is on-going.

Reviewer's Comment:

1. *The effect of concomitant use of rifampin, common in ENL patients, on hormonal birth control levels is of concern, given the teratogenicity of thalidomide.*

2. *Because concomitant medications were entered into the database for IND 11,359 only if experimental, data from this source is of limited value.*

3. *Because thalidomide appears to be an immunomodulator, the Sponsor should address possible complications in the use of live attenuated vaccines, although we are aware of no evidence that this has occurred.*

4. *See Biopharmaceutics Review for discussion of possible drug or disease effects on the bioavailability of thalidomide.*

10.2.7 Withdrawal Phenomena/Abuse Potential

The proposed label states that "Physical and psychological dependence have not been reported[redacted]

The Integrated Safety Summary submitted by the Sponsor then states, "As with other tranquilizers/hypnotics thalidomide too has been [redacted] to create in patients habituation to its soporific effects,[redacted]
(personal communication, Gelber, 1996)."

Reviewer's Comments:

Withdrawal or abuse potential have not been reported in the literature. Degos et. al. (1966), however, refer to an undeniable euphoria compared to that observed during cortisone treatment. The statement in the submission attributed to Dr. Gelber is difficult to reconcile with the Sponsor's claim under "Drug Abuse and Overdosage" that "[redacted]

[redacted] It is also difficult to reconcile with the statement in the proposed label.

10.2.8 Human Reproduction Data

Thalidomide is a known potent teratogen in humans, which was recognized in 1961 when the link was made between the birth of infants with severe, rare limb defects and mothers who had taken 100 mg or more of thalidomide early during pregnancy. The "sensitive period" for development of embryopathy was based on retrospective analyses and development of a timetable of clinical effects associated with exposure at definitive times during embryogenesis (Newman's review, 1986). This sensitive period is reported as follows:

In the 6th to 7th weeks of pregnancy or 35 to 50 days from the first day of the last menstrual period or 23 to 38 days after conception (Novack, 1965; McBride, 1988).

Days 21 to 36 following conception (days 34 or 35 to 50 postmenses) (Drugs as Teratogens, Chap. 19).

No relationship between the severity of the malformations and the amount of drug taken during the sensitive period was established. Lenz (1962), cited in Drugs as Teratogens, stated that no case was found in which the mother of a normal infant had taken thalidomide between the third and eight week after conception, which implies a risk of teratogenicity of 100%.

The risk of malformation following ingestion of thalidomide is reported as ranging from 2 to 25% with the following references cited (Burly, 1962; Ellenhorn, 1964; and, Tuchmann-Duplessis, 1965). There have been reported "thalidomide-resistant pregnancies" reported (Kajii, 1973; Kohler, 1970; and, Pembrey, 1970).

Limb defects (phocomelia) were the most characteristic abnormality; however, congenital heart disease, ocular, intestinal and renal anomalies, and malformations of the external ears occurred as part of the thalidomide syndrome. The possibility exists of an undetected increase in isolated defects in the absence of the full syndrome (i.e., squint, minor degrees of deafness, and hernias), according to Newman (1986). Cardiovascular, intestinal, and urinary system defects were the most often cited causes of death in the affected children.

11 Labeling Review

Deferred.

12 Primary Reviewer's Conclusion:

Summary

Documentation for clinical studies submitted for review in support of efficacy and safety of thalidomide in the treatment of lepromatous leprosy patients with moderate to severe manifestations of the ENL syndrome were obtained from the following four sources: 1) the Sponsor's review of the published literature, with specific emphasis directed to five controlled studies (including submission of primary data for review from one published controlled study), 2) the Sponsor's summary of a 16-year experience (1975 - 1994) of the ongoing uncontrolled open-label study of thalidomide in ENL (IND 11,359) sponsored by the Public Health Service, 3) three completed Celgene-sponsored PK studies, and 4) two ongoing Celgene-sponsored clinical studies in patients with the ENL syndrome (U.S. and Philippines study sites) with a combined total enrollment of 14 patients at the time of this review.

Extent of Exposure

Thalidomide formulations have varied over the 30-year span from which the Sponsor's source documentation data have been collected. Several times, the suppliers of thalidomide to the GWLHDC have changed over the 16-year span from which data were collected for Study L-002. For example, Chemie Grunenthal supplied thalidomide to the GWLHDC at the initiation of IND 11,359, according to documents under IND 11,359. According to the NDA submission, the Celgene Corporation is the most recent supplier of thalidomide to Carville (GWLHDC), with Tortuga cited as a previous thalidomide supplier; however, dates were not provided delineating the years of thalidomide suppliers. Differences in bioavailability and bioequivalence are unknown variables which may have influences on treatment efficacy and safety outcomes. Celgene's thalidomide formulation has been demonstrated to be more bioavailable than the Tortuga's thalidomide formulation.

Thus, the reviewers do not know how many, if any, ENL patients treated under IND 11,359 are currently being exposed to Celgene thalidomide formulation (excluding five ENL patients enrolled in Study E-001). Data collection for Study L-002 (GWLHDC database for IND 11,359) ended in 1994.

A total of fourteen lepromatous leprosy patients with a diagnosis of ENL have been exposed to Celgene's thalidomide formulation during the conduct of the Celgene-sponsored ongoing clinical studies at the time of this review. Six additional leprosy patients have been exposed to Celgene's thalidomide formulation during the conduct of the Celgene-sponsored completed clinical PK study.

Efficacy

Celgene's thalidomide formulation

Active or placebo controlled clinical trials in support of efficacy in patients with the ENL syndrome conducted with Celgene's thalidomide formulations are not known to be planned. Study E-003/P is a double-blind trial intended to evaluate trends in dose responses and Study E-001 is an open-labeled tapering study for which only descriptive statistics are planned.

Non-Celgene thalidomide formulation

Non-Celgene thalidomide formulations were used in the conduct of the remaining clinical studies submitted for documentation of the efficacy of thalidomide in the treatment of the ENL syndrome. Documentation was not provided for the source of the thalidomide used during the conduct of these clinical studies.

Retrospective Reviews:

One source of documentation was the selected primary data made available, by the Sponsor, for a retrospective review of 25 patients. These patients were identified by the Sponsor as the "original study sample" from the Hastings' et al., Study (1970). Efficacy data were extracted and submitted to the NDA to support the use of thalidomide in control of fever and skin lesions only. The objective, according to the Sponsor, was to corroborate and expand upon these previous efficacy claims for the use of thalidomide in the treatment of the ENL syndrome. The original protocol had been lost; therefore, the published protocol synopsis was used. According to the Sponsor, Dr. Hastings indicated that a complete description of the study protocol was as published.

Incomplete and sometimes inaccurate data sets were presented for assessment by the Sponsor. Without the original randomization code, assignments to active vs placebo arms of the trial were inferred by the Sponsor from review of various source documents. Additionally, "response to treatment" results were also inferred from various source documents by the Sponsor when not recorded on the patient's progress notes. There was also difficulty with validating the study population and thus the blinding status of the sample population presented for review. Study L-001, as presented, did not provide sufficient evidence from which to draw a valid conclusion that thalidomide is effective in the treatment of the ENL syndrome.

A second source of efficacy data was Celgene's summary of a 16-year experience (1978-1994) under IND 11,359, extracted from the Carville (GWLHDC) database (Study L-002). As far as can be discerned from the submission, summary annual reporting to the Sponsor (GWLHDC/Carville) from investigators treating ENL patients with thalidomide under the ongoing, open-label, PHS-sponsored study (IND 11,369) was submitted. Summarized patient data were filed from a total of 64 centers under IND 11,359.

It is unclear whether the protocol submitted with the NDA was followed by participating centers under the Carville IND (IND 11,359) during the 16-year period summarized. Additionally, the revised one page report form, which requested selected data from the investigators, restricted the extractable data needed for regulatory review. Specifically, there were no known uniform definitions of "response to thalidomide therapy" for annual reporting; therefore, these response categories were inferred by the Sponsor for the purposes of the NDA review. It was unclear how to interpret a response to the **mean dose of thalidomide assessed on an annual basis**. The severity of ENL was not requested by Carville of the investigators in the annual reports. Concomitant anti-ENL reaction medications were not requested, and when provided, may not have been entered by Carville into the database because they were not considered experimental.

Study L-002, did not provide adequate evidence to support efficacy of thalidomide in the treatment of an acute episode of the ENL syndrome, nor did it provide adequate evidence to support chronic suppressive therapy of ENL.

Additional data have been submitted by the Sponsor from patients enrolled at the LAC/USC site under IND 11,359. These data were collected by the Agency, submitted to the USPHSGWL, and received by the Division from Celgene Corporation as a Major Amendment, dated 6/18/97. Statistical analysis had not been completed by the Agency at the time of this review and the amendment will be reviewed separately by the secondary reviewer.

Review of the published literature was the third efficacy data source presented. Six published controlled trials were identified by the Sponsor and submitted in addition to uncontrolled studies and anecdotal reports. The Sponsor submitted primary data, in part, for the study by Hastings' et al only. These publications, including the primary data review, did not provide adequate evidence to support the efficacy of thalidomide in the treatment of the ENL syndrome. One study, Iyers' et al. (1971), provided sufficient data to be considered as supportive; however, the limitations of the Iyers' study were previously discussed in this review.

Safety:

Source documentation of safety was provided by the Sponsor from the same sources as efficacy, with the exception of the PK studies which provided additional safety data. The comments to follow are directed specifically to safety source documentation from L-002 (IND 11,359), since this data source included 1,387 patients, and provided more current available documentation potential for data validation than published studies not supported by primary data. Additionally, pharmacokinetic bioavailability study data were available for one of the thalidomide formulations used under IND 11,359.

The original protocol under IND 11,359 did request the reporting of new adverse events at the time of annual reporting. The one page annual report form submitted as part of documentation for Study L-002 was a modified version. Specifically, the modified one page annual report form requested reporting to the sponsor (Carville) only thalidomide-related adverse events and

thalidomide-related abnormal laboratory results. The dates of use of each annual report form or other annual reporting forms are unknown; however, the Sponsor indicated that the one page annual report to the Sponsor submitted with the NDA was modified in 1978.

Thus, the source documentation for safety from L-002 is a summary of adverse events thought to be thalidomide-related. This method of reporting was problematic, since commonly occurring events may have been under-reported.

Unlike the rare form of birth defects caused by thalidomide, which enabled a more rapid association between drug dosing and event, more commonly occurring events in a small population would tend perhaps to go unnoticed for a longer period of time. Additionally, the practice of "only thought to be related adverse event reporting" could systematically lead to under reporting.

First, thalidomide-induced neuropathy occurring in a neurologically intact population has been established as an adverse event and a temporal relationship to the drug established. However, the occurrence of some degree of peripheral neuropathy in leprosy and ENL patients is relatively common, given the unique trophism of M. *leprae* for invasion of the peripheral nervous system and the subsequent degree of pathology resulting mostly from the immunological response of the host. Thus, commonly occurring peripheral neuropathy in leprosy patients would tend to obscure a thalidomide-induced neurological adverse event.

A drug-induced association may have additionally been compromised by the perception that there is a lack of, or rare, occurrence of thalidomide-induced neuropathy in ENL patients, partially based on published results of motor conduction velocity testing on the ulnar nerves. Prospective electrophysiological testing of sensory nerve action potential amplitudes, in addition to clinical neurological assessments, are now considered a more sensitive objective measure of the type of sensory deficit which is characteristic of thalidomide-induced neuropathy. However, no current prospective electrophysiological monitoring and objective clinical data have been presented by the Sponsor. Peripheral neuropathy is one of the most potentially severely debilitating aspects of leprosy and ENL. The issue of thalidomide induced neuropathy in this context has not been adequately addressed by the Sponsor.

During the course of the review, additional examples of relatively common adverse events were noted in which temporal relationships between event and thalidomide dosing might have at least suggested a possible drug relationship (i.e., edema, abnormal glucose regulation, syncopal episodes as a precipitating event of a resultant hip fracture, CVA, MI, deaths, etc.). For example, peripheral edema commonly occurs in the ENL syndrome and as a thalidomide related adverse event. Disease-specific events, as well as commonly occurring events, would be under-reported if assumed to be due to the underlying disease or other causes. In a relatively small number of ENL patients taking thalidomide without all adverse events being systematically assessed, thalidomide dosing, as a factor or cofactor, would not easily be established. Thus systematic under-reporting would continue. Differences in bioavailability of the various thalidomide

formulations used over the 16-year reporting period are unknown contributing variables.

One death, as reported in the NDA, over a 16-year experience in patients with the ENL syndrome treated with thalidomide is unrealistic given the 11 to 91 year old age range reported. The reason for under-reporting of deaths is unknown. However, this under-reporting may again be secondary to the request of reporting thalidomide-related adverse events only. Nonetheless, all known deaths which occurred during the study periods should be reported in the NDA whether related or not.

Based on documentation provided for this NDA review, the following factors should be considered in the safety assessment for the use of thalidomide in ENL patients:

1) Celgene's thalidomide formulation appears to show a greater bioavailability profile than the Tortuga formulation, which according to the Sponsor, was the last known source of thalidomide for patients treated under IND 11,359.

2) The rate of absorption of Celgene's thalidomide formulation was shown to be greater in Hansen's disease patients in PK-005 study than in healthy volunteers. The relationship to the disease process is unknown.

3) Exposure to the Celgene thalidomide formulation is limited to 14 known ENL syndrome patients enrolled in ongoing clinical trials.

4) Differences in bioavailability may have an effect on the safety profile of thalidomide in ENL patients. For example, the prevalence of cardiovascular adverse effects, specifically postural hypotension, in healthy volunteers was 12% with Celgene's thalidomide formulation. However, the prevalence of this cardiovascular adverse effect associated with Celgene's thalidomide formulation in the Hansen's disease patients is unknown, since standing blood pressures were not measured in studies PK-005 and E-003/P.

5) There is insufficient data available to make an adequate risk/benefit assessment in female patients of reproductive potential, especially with the availability of approved therapies. Additional thalidomide/gender and thalidomide/drug interaction effects are needed for assessment of risk/benefit in this population.

6) Documentation of objective neurological monitoring procedures was not provided for studies L-001 and L-002 and objective prospective electrophysiological testing procedures are not known to have been incorporated into the ongoing Philippines study (E-003/P).

Conclusion

The summary safety profile presented by the Sponsor is not adequate. Additional or continued exposure to Celgene formulation thalidomide is assumed to be ongoing for patients enrolled under Celgene-sponsored studies E-001 and E-003/P (IND 48,177); therefore, additional safety data should exist. In addition, no safety update has been provided by Celgene to the NDA submission from IND 11,359 after 1994. Therefore reported exposure to Celgene's thalidomide formulation is limited to **only** 14 known ENL patients in ongoing clinical trials.

The Sponsor did not provide adequate evidence to either define the risks or to establish, at the time of this review, the efficacy of thalidomide in the ENL syndrome. As a result, the Sponsor did not provide sufficient documented data to allow an adequate risk/benefit assessment to be made. At the time of this review, the benefit for lepromatous leprosy patients with manifestations of the ENL syndrome does not appear to outweigh the risks.

13 Primary Reviewer's Recommendation:

It is this reviewer's opinion, based on the material reviewed thus far, that Synovir™ (thalidomide) is Not Approvable.

Brenda Vaughan, M.D. 7/28/97

Brenda Vaughan, M.D.
Primary Reviewer

Kathryn O'Connell MD 7/28/97

Kathryn O'Connell, M.D., Ph.D.
Secondary Reviewer*

(*See subsequent Review of Major Amendment for secondary reviewer's Overview of Efficacy, Conclusions, and Recommendation)

NDA 20,785 cc:
HFD-540
HFD-540/CSO/White
HFD-540/Chem/Decamp
HFD-540/Pharm/Hill/Jacobs
HFD-540/Stats/Gao/Thomson/Srinivasan
HFD-540/MO/Vaughan/OConnell
HFD-540/Biopharm/Bashaw
HFD-540/DivDir/Wilkin

9W 8/13/97

Appendix 1.

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7 PAGE(S) COPYRIGHT MATERIAL - REMOVED FROM THIS SECTION

Robert C. Hastings, M.D., et al., "Thalidomide in The Treatment Of Erythema Nodosum Leprosum," Clinical Pharmacology and Therapeutics, Vol. 11, No. 4, 481-487, July-August 1970.

Appendix 2.

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CLINICAL RECORD

DOCTOR'S ORDERS
(Sign all orders)

DATE AND TIME START	DATE AND TIME STOP	Rx	DRUG ORDERS (Another brand of a generically equivalent product, identical in dosage form and content of active ingredient(s), may be administered UNLESS checked here)	DOCTOR'S SIGNATURE	NURSE'S SIGNATURE
6/6		1.	Admit to infirmary Thursday afternoon (6/8)		
		2.	Diagnosis: Thalidomide trial		
		3.	N. P. O. after midnight Thursday		
		4.	Friday morning (6/7):		
			a) D.C. all anti-reaction treatment, including cortico-steroids		
			b) No ASA or other anti-pyretic		
			c) Continue current anti-leprosy treatment		
			d) Demerol 50- 100 mgm. I.M. q. 3-4 h. PRN pain X 10 days		
			e) Codiene gr. 1 P.O. q. 3-4 h. PRN pain X 10 days		
			f) Seconal gr. iss- iii P.O. h.s. PRN sleep X 10 days		
		5.	BP, P, and Temp. q.i.d. and record		
		6.	Weigh patient daily and record		
		7.	The following lab studies to be done: Friday (6/7), Monday (6/10), Wednesday (6/12), Friday (6/14), and Monday (6/17).		
			a) Hematocrit, Hemoglobin, direct platelet count		
			b) clotting time, clot retraction time, quantitation of clot retraction (by amount of serum expressed), and presence or absence of fibrinolysis		
			c) Qualitative cryoproteins		
			d) Stool for occult blood		
			e) Cholesterol and quantitative urine urobilinogen (2 hour afternoon sample)		
			f) Prothrombin time sp Partial thromboplastin time, Quantitative Fibrinogen		
		8.	Beginning Monday A.M. (6/10) Bottle # A caps 1 q.i.d. P.O. X 4 days, then ask for new orders		
		9.	Please have patient sign two release forms for the use of Thalidomide for the treatment of ENL (one for me, and one for the pasiens's chart).		
			Thank you		

(Continue on reverse side)

PATIENT'S IDENTIFICATION (For typed or written entries give: Name—last, first, middle; name of hospital or medical facility)

REGISTER NO. [ ]

WARD NO. [ ]

DOCTOR'S ORDERS
Standard Form 508
508-107

000445

Appendix 3.

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ANNUAL REPORT TO SPONSOR

THALIDOMIDE PATIENT REPORT FORM

1. Date of report _____

2. Patient's name (Last, First, Middle I.) _____

3. a) Date of birth _____ b) Place of birth _____

4. Race: _____

5. Sex: Male ____ Female ____

If female: Post menopausal Yes ___ No ___. If No - what measures have been taken to prevent pregnancy (hysterectomy, tubal ligation, etc.)?

_____

6. Patient's disease classification (circle one):

a) lepromatous leprosy (LL)
b) borderline-lepromatous (BL)
c) borderline (BB)
d) indeterminate
e) borderline-tuberculoid (BT)
f) tuberculoid (TT)

7. a) Date of diagnosis _____ b) Date ENL began _____

8. Date thalidomide started _____.

9. Mean dose of thalidomide taken during the year _____.

10. Side effects due to thalidomide only. _____

_____ None (other than sedation) _____

11. Laboratory abnormalities due to thalidomide only. _____

_____ None noted _____

12. Other leprosy related drugs taken during the past year only:

Drug	Date Started	Dose
Dapsone (DDS, Avlosulfone)	_____	_____
Clofazimine (B663, Lamprene)	_____	_____
Rifampin (Rimactane®, Rifadin®)	_____	_____
Other _____	_____	_____

13. Response to thalidomide therapy (circle one):

a) Good (complete control of ENL)
b) Fair (partial control of ENL)
c) Poor (no response)
d) Unknown
e) Lost to follow-up

14. Was written informed consent obtained from this patient? Yes ____ No ____
Is it available for inspection if required? Yes ____ No ____

15. Is patient still on therapy? Yes __ (Dose _____) No __ (Date Discont._____)

16. Previous therapy for ENL

Drug	Dose	Duration of Therapy
Corticosteroids	_____	_____
Clofazimine (B663, Lamprene)	_____	_____
Other _____	_____	_____

17. Laboratory data before therapy. Normal _____ Abnormal _____ Not Done _____
List any abnormalities _____
BI on skin scrapings or biopsy(s) before start of therapy _____
_____

18. Has the patient ever been admitted to Carville? Yes ____ No ____
If yes, what dates? _____ Carville # (if known) _____

Clinical Investigator: _____
(Signature)

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Appendix 4.

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Study L-002

Patient#	Treatment Year	Average Daily Thalidomide Dose (mg)	Coded "ENL Response"	Verbatim Neurologic Adverse Events (Other than Drowsiness/Sedation)	Site
401	1	200	fair	none	HAWA
	2	400	fair	none	
	3	100	fair	none	
	4	100	fair	none	
	5	50	excellent	none	
	6	150	excellent	none	
	7	100	excellent	polyneuritis ncv episodic	
444	2	100	good	polyarthritis/polyneuritis ncv	HAWA
495	1,2	200	unknown	left leg weekness	PORT/OHSU#
497	4	100	good	leg cramps & pain	PORT/OHSU#
499	3	100	very good	hand paresthesias/leg cramps	PORT/OHSU#
501	2	100	fair	fatigue arm & leg numbness, pain, cramps	PORT/OHSU#
682	1	100	good	none	SDHC
	2	100	good	neuritis possibly due to thalidomide	
	3	200 to 300	good	none	
	4	100 to 300	good	none	
666	4	100	good	neuritis	SDHC
773	2	100	good	paresthesias, constipation	SFCA
811	5	200	poor	complaining pain in hands & heat in feet	STAT
830	5	50	fair	nerve pain	STAT
839	4	100 to 300	fair	nerve pain	STAT
841	2	100	fair	causalgia in lower extremity	STAT
845	2	50	good	numbness in feet	STAT
851	3	200	fair	nerve pain	STAT
853	3	200	fair	left ulnar pair	STAT
854	6	100 QOD	good	abdominal bloating, slight swelling feet with spasms	STAT

Study L-002

Patient#	Treatment Year	Average Daily Thalidomide Dose (mg)	Coded "ENL Response"	Verbatim Neurologic Adverse Events (Other than Drowsiness/Sedation)	Site
855	2	200	fair	neuritis s/s	STAT
	7	100	good	swelling ankles, leg pains on and off	
	8	100 QOD	fair	leg swelling with pains (burning sensation)	
856	2	50	good	nerve pain	STAT
860	2	50	good	nerve pain secondary to ENL	STAT
869	2	100 QOD	good	increased edema legs, abdominal distention	STAT
	3	100	good	leg swelling, abdominal distention, increased COPD	
	4	100	fair	swelling ankles, leg pain	
873	1,2	100	good	severe headaches, blurry vision	STAT
901	3	100	good	probable neuropathy	UNOM
904	1,3	100	fair	pain in extremities	UNOM
931	1	100	fair	bloating	UOIL
	2	100	very good	questionable bloating	
	3	100 to 150	excellent	pain & weakness both legs	
	4 to 7	100 to 200	good	drowsiness	
936	1	75	unknown	left hand neuritis questionable	UOIL

Study L-002

Patient#	Treatment Year	Average Daily Thalidomide Dose (mg)	Coded "ENL Response"	Verbatim Neurologic Adverse Events (Other than Drowsiness/Sedation)	Site
939	1	150	fair	none	UOIL
	2	200	good	drowsiness	
	3	300	good	drowsiness	
	4	200 to 300	good	drowsiness	
	5	200	good	drowsiness	
	6	200	fair	drowsiness	
	7	200	fair	paresthesias	
	8	200	fair	peripheral neuropathy	
1036	1	200	good	none	USCS
	2	50	good	none	
	3	50	good	none	
	4	50	good	none	
	5	50	good	none	
	6	50QOD	good	none	
	7	50QOD	good	peripheral neuropathy (d/c thalidomide 11/4/87	
1048	1	200	excellent	paresthesias distal extremities	USCS
	2	100QOD	excellent	paresthesias distal extremities	
	3	100QOD	excellent	none	
	4	100	good	none	
1125	1	100	fair	had a transuciant organic psychisis	USCS
		100	poor	none	
1176	1	100	fair	depression, numbness, numbness headache	USCS

Study L-002

Patient#	Treatment Year	Average Daily Thalidomide Dose (mg)	Coded "ENL Response"	Verbatim Neurologic Adverse Events (Other than Drowsiness/Sedation)	Site
1201	1	100	fair	none	UTDA
	2	100	fair	none	
	3	100	excellent	none	
	4	100	poor	none	
	5	100	poor	possible neuropathy - probably weren't treating ENL	
1208	1	100	fair	peripheral neuritis	VANC
	2	100	good	questionable peripheral neuritis	
1254	1	100	good	none	PPNL
	2	100	fair	none	
	3	100	excellent	possible neurologic problems	
1257	1	200	fair	leg pains, penostitis legs	STAT
1315	1	100	unknown	none	STAT
	2	100 TIW	fair	nerve pains	

AUG 13 1997

NDA 20-785

Secondary Medical Officer's Review of NDA 20-785

Major Amendment and Overview of Efficacy/Conclusions/Recommendations

NDA 20-785	Amendment Submission: 6/17/97 Received Agency: 6/18/97 Received Reviewer: 7/27/97 Review Completed: 8/8/97 Revised: 8/13/97
Sponsor:	Celgene Corporation 7 Powder Horn Drive Warren, NJ 07059 (908) 271-1001
Drug:	Thalidomide; Synovir™
Pharmacologic Category:	Immunomodulator
Proposed Indication:	Erythema Nodosum Leprosum (ENL)
Dosage Form:	Thalidomide 50 mg Capsules
Route of Administration:	Oral
NDA Drug Classification:	1P
Related Drugs:	None

2 Table of Contents

3 **Material Reviewed** See Background

4 **Background**

The indication proposed in this NDA is as follows: "Thalidomide is indicated for the acute treatment of moderate to severe erythema nodosum leprosum (ENL) [

] Thalidomide is also indicated as maintenance therapy for prevention and suppression of ENL recurrence."

As noted in the review dated 7/28/97, this submission is somewhat unique in that it is supported by the following sources of clinical data: (1) a retrospective review of a controlled clinical trial conducted in 1968-69 with additional source data; (2) a retrospective review of 16 years experience under an on-going open label IND sponsored by the USPHS; (3) a literature review for safety and efficacy, including 5 controlled clinical trials for which supporting primary data is not available and a consultant's review of peripheral neuropathy; (4) preliminary results from 2 on-going clinical trials, one of which is open-label and the other dose-ranging (14 enrolled patients to date); and (5) the results of 3 completed pharmacokinetic studies.

In an attempt to provide additional efficacy data, patient records were collected by the Agency from one of the USPHS sites under IND 11,359 (LAC/USC). It is this reviewer's understanding that the material to be reviewed here was generated by Agency biostatisticians from an electronic submission of data for 102 ENL patients treated with thalidomide. The sponsor received this data from the USPHS after it was forwarded to the USPHS by the Agency. (The 6/18/97 major amendment also contained hard copy volumes 11.1-11.4, consisting of source documents for Study L001. These documents were utilized in the primary reviewer's analysis of the Hastings' study and will not be addressed here).

The document generated by Biostatistics for review here consists of two parts: summary tabulations based on time periods "on" and "off" thalidomide, and a scatter plot for each patient showing drug usage, as points in time, and the status of up to 3 efficacy parameters for the cutaneous lesions of ENL. Specifically, the plots show available data for thalidomide, prednisone, and clofazimine (no dosages) and for ENL lesions "present/absent", "active/inactive", and "new lesions-yes/no". It is this reviewer's understanding that these parameters were chosen post-hoc by the Agency in an attempt to capture information from the clinic charts of ENL

patients being treated under the USPHS IND at the LAC/USC site, but not enrolled in a clinical trial. Thus, there are numerous missing data points, not unexpected since treatment outside of a trial setting requires no defined endpoints or standardized follow-up intervals. In some cases, these missing data are represented by open circles. More often, there is simply a period of no data along the horizontal time axis (see Introduction to scatter plots in Appendix). In interpreting these data, it is critical to realize that, because this is not a clinical trial, the intervals represented on the x-axes vary widely from patient to patient. Thus, the clinical response can appear to be timely when, in fact, the response is occurring months or even years after the data point for therapy. It is also important to realize that these plots should not be viewed as a contiguous graph because there is no information available other than that recorded at the specific points in time noted. For example, two contiguous points "on" thalidomide may have been separated by weeks, months, or years, and there is no data regarding the treatment or clinical status of the patient in the intervals.

Other limitations of the data will be discussed below; those noted above are presented to illustrate why this review will focus on the scatter plots rather than the summary statistics. Specifically, the summary statistics do not appear to address either of the major limitations noted: the wide variations in time between observations or the lesion response within an 'episode', defined as the time from the start of therapy until an entry indicating a discontinuation. There are multiple examples among the cases illustrating why, in this reviewer's opinion, the summary approach is uninterpretable; two examples are noted here: (1) The plot for Case 194 shows continuous data points for thalidomide "on" until approximately week 65, when the data point for lesions shows none present. Thus, the summary tables would seem to include this case as a success. In fact, the scatter plot indicates that the patient developed new lesions while on thalidomide. (2) The plot for Case 191 indicates 5 episodes of flaring (new lesions) while on thalidomide, but because the drug is "on" continuously over the 5 years represented and the lesions were absent at the end of the summary "episode", this case too would be viewed as a success. The summary statistics are further complicated by the fact that time points "off" drug are extremely limited, which would be expected since this is not a trial, but a clinic experience where patients most likely attend in order to receive treatment for active ENL. In a non-trial setting, it is unlikely that patients will come in if they are doing well off therapy. This is especially problematic for the indication under consideration because the natural history of ENL is to wax and wane.

Before proceeding to interpretation of the scatter plots, the following assumptions and features of the data should be considered:

1) The drug dosages are not shown on the plots. According to the statistics report (appended), 100 mg dosing was utilized in 77% of the first visits and 65% of the final visits. The second most common dosages were 200 mg and 50 mg, respectively (both 19%). (See discussion following data presentation).

2) Use of OTC or prescription anti-inflammatory drugs, other than prednisone and clofazimine, was not captured. As demonstrated almost 30 years ago by Dr. Iyers (see Primary review), aspirin, even in subtherapeutic doses, demonstrated efficacy for the cutaneous lesions of ENL.

3) Characteristics of the lesions relevant to disease severity were not captured. This includes number. Thus, the exact meaning of "new lesions", "yes or no", is undefined, as is the significance of "ENL present/absent". For example, did the patient present with 4 papules which resolved or were there 200 ulcerating nodules that resolved?

4) The first data point is the first visit; as such, it usually shows the treatment drug "on". It will be assumed that this means it was prescribed on this visit, not that the patient is already on the treatment. This is, in itself, an assumption because this is not a trial and there are no entry criteria. Thus, it is unknown whether patients were previously undergoing treatment elsewhere. Moving along the time axis, it is further assumed that subsequent time points noting drug "on" or "off" mean that this is the current situation, extant since the previous visit. However, in many plots there are long temporal gaps (months to years), not surprising given the natural history of the disease being treated. In these cases, the assumption will be made that the data point for the treatment means it is being re-prescribed at that visit. Because no data were presented regarding drug accounting or pharmacy records, it is unknown whether patients received treatment elsewhere in these gaps or whether they used "left-over" medications.

5) The data for review captures only the 3 stated parameters for the cutaneous lesions of ENL. In fact, ENL is a systemic disorder. It is unknown whether the lesion parameters recorded were the sole determinants of the therapeutic decisions reflected along the horizontal axis.

6) It is this reviewer's understanding that the charts utilized for database generation represented all of the patients with ENL treated with thalidomide at the site and were not confined to records of patients currently undergoing

treatment. It is also assumed that the persons who retrospectively transcribed the data from the charts to the CRFs had the background to do so accurately and that audits were performed to measure consistency between transcribers.

7) To this reviewer's knowledge, there is no evidence that any of the patients represented in this database received the Sponsor's formulation of thalidomide. Thus, any efficacy information extracted can only be assumed applicable to the Sponsor's thalidomide formulation. It should be noted, however, that the Sponsor's formulation is more bioavailable than the Tortuga formulation which has been in use by the USPHS.

Despite these considerable limitations, initial examination of the scatter plots indicated that some cases might provide information regarding efficacy in a "de-challenge/re-challenge" context. For this reason, a careful examination of each plot was undertaken. The objective was to identify cases with sufficient follow-up and "off" periods to allow assessment of lesion status relative to the treatment time point, within the limitations noted above. Regarding the issue of follow-up, it is important to note that virtually all published studies and the Sponsor's reported on-going ENL trial results claim that a cutaneous ENL thalidomide response occurs rapidly, with cessation of new lesions within 7 days. Because the data under review here did not derive from a trial setting, the follow-up periods in the vast majority of cases are not measured in days, but in weeks. Thus, an effort was made to concentrate on lesion responses documented within 2 weeks of a dosing point. In reality, however, some cases will be included with longer follow-ups due to the small number available. In any event, the data must be viewed in the context of the issues discussed above, especially the natural history of the disorder and the absence of quantitative or qualitative lesion data.

A second approach to the plots was to look only at the response to the first data point "on" thalidomide because it was noted that follow-up after this initial point seemed to follow more closely. For this purpose, the "new lesions yes/no" parameter was preferred, since this seems most likely to correlate with a "flare" of the cutaneous manifestations.

Finally, an overview of the cases was attempted based on the totality of the "picture" which emerged over the time course available for each case. For this purpose the case was categorized as "success", "failure", "inconclusive", "insufficient data", or "plot missing" (presumably representing patients not entered into the database because the charts indicated a diagnosis other than ENL).

"Success" was coded when there were no obvious flares (new lesions) "on" drug and the patient appeared to improve when thalidomide was started, even if there was adequate data for only one episode. **"Failure"** was coded when the patient appeared to get worse on the drug (new lesions) and/or the lesions persisted for months on the drug. **"Inconclusive"** was used for cases in which concomitant prednisone or clofazimine precluded assessment of the thalidomide response, where the data points were separated by such time that no biologically relevant assessment could be made, or where the patient seemed to experience flares on the drug as well as resolution (for example, Case 231 where there are 2 flares off the drug and 2 flares on the drug). **"Insufficient Data"** was used only when there was so much data missing that no approximation of an assessment could be made; in reality, most of the plots contained insufficient data for a rigorous, valid assessment.

These interpretations of the data are of very limited value. They are unavoidably subjective because clear criteria are not possible, given the non-trial source of the data. In addition, they are derived from painstaking visual examination of over 100 scatter plots and are therefore subject to error. They are offered only to provide some perspective as to what this reviewer saw in the scatter plots, employing the assumptions and allowing for the limitations discussed above.

Despite these problems of interpretation, it is important to consider both approaches to the scatter plots because de-challenge/re-challenge cases, by definition, are dependent on "on/off" episodes and might therefore be biased towards responses; presumably, patients who do not gain timely resolution of their lesions on thalidomide are either maintained chronically or discontinued altogether, neither of which would be captured in "on/off" episodes. (Alternatively, patients could have "on/off" entries because they run out of medication or experience a medication related adverse event. The latter cannot be examined because the information submitted for review did not include safety data. In any event, neither of these would appear to obviously affect the subsequent therapeutic response, except that an adverse event might be followed by a dose reduction. This, however, would lead to possibly false negative responses, not false positive, assuming that thalidomide has a dose response curve).

Results: The scatter plots are arranged in numerical order in the Appendix for cross-referencing to the tables which follow. Some of the scatter plots are labeled "truncated". This means that the case extended over many years, resulting in a horizontal axis with increments representing 10 or more weeks. In an effort to harvest information from such cases, the time frames of interest (more than one "on/off" cycle) were

selected and the remainder truncated in order to impart more useful detail to the x-axis. In a few instances, the cases are presented on 2 or 3 plots.

"De-Challenge/Re-Challenge" Plots

Fourteen case scatter plots were found which met the criteria discussed above for "de-challenge/re-challenge". Three additional cases were found which had "on/off" episodes, but in which follow-up visits were too far apart to meet the criteria stated. These are marked with an (*) in the table which follows.

"De-Challenge/"Re-Challenge Plot Results

Success	Failure	Inconclusive
108**	131	119 (*)
166	137	124
188	171	121 (*)
190**	194 (*)	133
	229	153
		170
		224
		231

**Case 108 had one flare (new lesions) and Case 190 had 3 flare episodes (new lesions) at data point(s) indicating ongoing thalidomide; they are included here because the DC/RC episodes appeared to be a success.

Response to First Episode on Thalidomide

The Case number plots which follow showed no concomitant prednisone or clofazimine during the first 3 weeks after beginning thalidomide (given the assumptions discussed earlier). These cases had "new lesion no" indicated within approximately 3 weeks after a positive baseline lesion data point:

Case No.: 102, 107, 108, 121, 131, 133, 140, 148, 153, 166, 169, 173, 177, 179, 181, 188, 190, 198, 201, 202, 214, 224, 225, 229

As shown in the next table, 14 of these 24 cases did not meet the criteria stated above for overall success.

Reviewer's Overall Interpretation of Scatter Plot Data (Figures represent Case No. on the scatter plots in Appendix; data continues on next page)

Success* (n = 10)	Failure (n = 30)	Inconclusive (n = 45)	Insufficient Data (n = 17)	Plot Missing (n = 27)
102	101	106	103	104
108	107	119	105	109
153	115	122	112	110
166	118	124	120	111
173	121	125	127	113
177	131	126	128	114
188	133	129	134	116
198	137	130	143	117
201	140	135	156	123
202	145	136	161	132
	148	138	162	146
	149	139	165	147
	155	141	168	151
	167	142	184	152
	171	144	187	154
	176	150	197	164
	181	160	233	182
	183	163		185
	189	169		193
	191	172		195
	194	174		205
	196	175		207

Success	Failure	Inconclusive	Insufficient Data	Plot Missing
	199	178		212
	209	179		220
	210	180		222
	211	186		227
	216	190		230
	221	192		
	226	200		
	228	203		
		204		
		206		
		208		
		213		
		214		
		215		
		217		
		218		
		219		
		224		
		225		
		229		
		232		
		233		
		231		

***Note:** Case 102 showed lesional data on thalidomide for only 3 weeks. Case 177 showed *new* lesions occurring approximately 35 weeks after the last thalidomide "on" before the long period with no data. Inclusion of this case as a "success" assumes that the patient was *not* on the drug for this 35 week period, although there is no data to support this (there is no "off" data point). A similar situation is

evident for Case 198, in which *new* lesions are noted twice at two separate episodes 35-40 weeks after the last thalidomide "on" entry with *no* "off" noted. Case 201 is included as a "success" even though the plot shows a flare approximately 9 weeks after resolution and there is *no* data point to suggest that thalidomide was stopped. In addition, this case has no further episodes to confirm the response, the only other new lesion data being accompanied by thalidomide "off".

Dosing

As noted previously, the scatter plots did not capture dosage data, but the Biostatistics summary report indicates that 65% of all visits on thalidomide showed dosages of 100 mg. After the 10 scatter plots above were identified as "successes", the database was re-examined for dosage data on these cases. As shown below, 4 of the 10 cases had doses of 200 mg per day for at least one responding episode. According to the Biostatistics report, 23% of all visits on thalidomide recorded dosages of 200 mg/day.

Case No.	Thalidomide Dose (mg/day)
102	100
108	100
153	100
166	200 decreased to 100
173	200
177	100 increased to 200 2nd episode
188	200
198	50-100
201	100
202	100

Conclusions:

The information received for this review pertains only to the cutaneous lesions of ENL and is thus obviously inadequate to address the Sponsor's proposed indication, which encompasses the systemic syndrome of ENL. From the perspective of the

cutaneous manifestations of ENL, approximately 10 of 102 case plots contained sufficient information to suggest that thalidomide use is associated with overall improvement (no new lesions while on the drug), although as noted above, significant assumptions were required in order to include 3 of these cases. In addition, approximately 24 of 102 case plots had sufficient information to suggest improvement (no new lesions) within the first 2-3 weeks after thalidomide is started.

In considering these "results", it is important to recall that it is not known whether these responses involved a few lesions or hundreds of lesions, small asymptomatic papules or painful ulcerating nodules, or whether they were associated with the use of concomitant NSAIDS or aspirin. As suggested by the large proportion of cases in the "inconclusive" and "insufficient data" categories, it is possible that the data do not adequately reflect either successes or failures, due to missing entries and unknown therapy/responses between data points. In addition, the contribution of a placebo effect, as well as the beneficial therapeutic effect of sedation, cannot be determined. As calculated in the primary review of source documents available for Study L-001, approximately 33% of the ENL patients treated with placebo had a complete response, defined as no new lesions and resolution of fever.

Thus, it is this reviewer's opinion that this database does not provide the evidence required for a regulatory decision.

Addendum: After this review was completed, Biostatistics re-calculated the summary tables using a cut-off for response at 2-3 weeks per "on" or "off" episode. These tables identified 23 episodes characterized by no concomitant clofazimine or prednisone and new lesion status recorded at start and at end. According to the summary table, 18 of these cases resulted in new lesions "yes to no", a number that is very close to the 24 short-term "success" plots identified in this review.

Overview of Efficacy for NDA 20-785

This NDA contained four sources of information pertaining to the efficacy of thalidomide in the treatment of ENL. Each will be summarized, followed by a discussion of their contribution to an overall conclusion regarding the adequacy of evidence in support of the Sponsor's proposed indication.

Study L-001: Retrospective Review of Source Documents for the Hastings' Publication

This publication reported 68% success with 400 mg/day thalidomide in 44 courses involving 22 patients, as compared to no success with placebo. The endpoint at day 4 was no freshly appearing ENL lesions and a temperature $<99.6°$ F. Most of the source documents critical to retrospective analysis of the paper, including the randomization code, were reported to have been lost. Utilizing the information that was available for review and applying very relaxed criteria to its retrospective interpretation, the primary reviewer was able to identify 46% of the thalidomide courses as possibly successful compared to 33% (3 of 13) of the placebo courses. The Sponsor noted 83% treatment success with thalidomide vs. 23% (3 of 9) with placebo. Overall, the available source documentation was found to be inadequate, quantitatively and qualitatively, to support a valid conclusion.

Study L-002: Retrospective Review of 16 Year Experience Under USPHS IND 11,359/Retrospective Analysis of Patient Records from One Site (Major Amendment)

Efficacy information collected under this IND through 1994 was based upon annual reports which indicated mean annual dose and prospectively undefined response categories. In an effort to extract more information from the IND experience, the Agency collected patient records from one of the USPHS sites. The data which was subsequently presented to this reviewer addressed three cutaneous ENL parameters, identified *post hoc* as "activity yes/no", "presence/absence", and "new lesions yes/no". No information was presented regarding previous treatment, lesion counts, lesion severity, use of aspirin or other NSAIDS. In addition, the timing of follow-up visits exceeded, often by weeks to months, the time course for response noted in the Hastings' publication, as would be expected for care in a non-trial setting. Despite these and other significant limitations/assumptions discussed in

detail earlier in this document, an attempt was made to extract information that might be supportive of thalidomide efficacy for the cutaneous manifestations of ENL. As such, it appears that approximately 45% of first visits with "new" lesions are followed by "no new lesions" if the response is examined within 2-3 weeks. Because there is no control group, the contribution of a placebo effect, such as noted above in Study L-001 (possibly up to 33%) is unknown, as is the occurrence of new lesions in the time period between the first visit and the 2-3 week endpoint. It was also noted, from visual inspection of scatter plots along a time axis, that many of the patients experienced episode(s) of new ENL lesions while the data points continued to show on-going thalidomide treatment. Other cases clearly showed long term lesion-free periods off thalidomide, not surprising given the natural history of the disorder. When viewed overall, less than 10 of the 102 case plots clearly suggested consistent effectiveness. Four of these 10 patients received doses of 200 mg/day, while the majority of the represented cases received 100 mg/day. Although a significant number of cases (30) were categorized as "failure, it is important to note that most of the plots led to an "inconclusive" or "insufficient data" classification by this reviewer. It must also be reiterated that the data parameters presented do not distinguish between resolution of a few asymptomatic papules and one hundred painful ulcerated nodules. Overall, the suggestion of efficacy for the cutaneous manifestations of ENL must be viewed within the context of the many pitfalls encountered in retrospective interpretation of data from a non-trial setting for a disease which is highly variable in its course and presentation.

Study L-003: A Review of Published Literature

The Sponsor identified five published studies as controlled trials, in addition to the Hastings' study discussed above. The NDA submission included a review of these papers and the results of a literature search for case reports, open label studies, etc. The five identified controlled studies were reviewed in depth in the primary review; the remainder, for the most part, were assessed as presented in the review submitted with the NDA. The review submitted in the NDA concludes that "the overwhelming weight of the evidence attests to thalidomide's rapid amelioration of the signs and symptoms of ENL in over 90% of treated patients when used most often in doses of 300 to 400 mg/day, but also, in some patients, in doses of 100 to 200 mg/day".

For the most part, the submitted literature specifically addresses fever and the cutaneous lesions of ENL and little information was found regarding alternative

therapies other than prednisone. One notable exception was the 1971 publication by Dr. Iyers involving 92 ENL patients observed over a 7 day period. The thalidomide dosage was 400 mg/day. This study showed that aspirin, in doses of only 400 mg QID, showed significant efficacy, although less than the high dose of thalidomide used, and that the response to both thalidomide and aspirin was far more pronounced for the symptoms of fever and skin lesions than for the systemic manifestations of the disease, even at the high thalidomide dose used.

The discussion of the five in-depth reviews and overview of the literature presented in the primary review will not be reiterated here; it appears from these sources that thalidomide, in the doses reported, does ameliorate fever and cutaneous lesions in many patients, at least over the short follow-up periods generally observed (see discussion at end of this Overview). However, our detailed reviews of the controlled trials suggested that the effects are not as robust as the 90% figure noted in the submission. In addition, multiple sources discussed under the primary review of Study L-002, as well as some cited in Study L003, indicate that the serious systemic manifestations of ENL are not adequately treated by thalidomide and require treatment with prednisone.

Study E-003/P: Preliminary Analysis of the On-Going Celgene Sponsored Clinical Trial for ENL

The NDA submission states that the blind has not been broken for this on-going trial. Nonetheless, the preliminary data submitted for 9 patients provides valuable information because both arms are thalidomide (100 mg/day vs 300 mg/day) and, to our knowledge, this is the only efficacy data available for the Sponsor's thalidomide formulation. For this reason, this study is discussed in detail here.

According to the Sponsor, 6 of the 9 patients showed a complete response (CR) at the Day 7 endpoint, defined as no acutely inflamed lesions and an oral temperature less than 99.7° F. The secondary endpoints consisted of the systemic signs and symptoms of ENL. One patient was reported as a partial response due to new lesions at day 6 with no fever (No. 06). Two (Nos. 01 and 05) were categorized as treatment failures (both patients had worsening of cutaneous lesions, fever, and systemic signs and symptoms). Again, the submission states that the dosing blind has not been broken; therefore, it is not yet known whether these results stratify by dose.

A careful examination of the submitted line listings revealed several problems with this analysis. Before discussing the cases, it should be noted that the protocol specified oral temperature measurements and the endpoint was defined based on this route (fever = >99.7). The submission states that the investigator decided to utilize axillary temperatures. Thus, the temperatures noted are axillary temperatures. It is this reviewer's understanding that normal axillary temperatures are considered to be at least one degree less than normal oral temperatures. The protocol also stated that patients receiving anti-pyretic treatment more than 72 hours after initial dosing were to be discontinued as treatment failures.

In the course of reviewing the tabulations, it was also noted that the discrete lesion counts listed actually represent the results of a "conservative algorithm" apparently appied to the CRF data *post hoc*.: According to the Sponsor, "The number of lesions for each patient was calculated by adding the number of lesions recorded on the CRF across body region. The number of lesions is an approximate count, since it is difficult for clinic personnel to count the exact number of lesions, particularly when there were many lesions in most body regions. **In some cases, the clinic recorded approximations that were translated into numbers of lesions using a conservative algorithm (i.e., >10=12, >5=7, <10 =7, few =2, some=4, more=5, and most=7). A more formal scaling approach to these data may have to be developed for the final formal analysis.**" (bold inserted by reviewer).

This is especially problematic since the endpoint is absence of acutely inflamed lesions with resolving lesions allowed. The distinction between acutely inflamed and resolving is necessarily subjective. The effects of unintentional bias must be considered in the interpretation of results from this trial which consists of only two arms, both of which are thalidomide treatment.

The following points relevant to the efficacy assessment were noted in the tabulations:

1) No. 02 (CR) was coded at baseline with mild fever, chills, anorexia, and malaise, in addition to cutaneous lesions. At the day 7 endpoint, the patient was coded as anorexia, malaise, and edema. Edema, like anorexia and malaise, is a listed systemic manifestation of ENL (ie. a secondary endpoint). Edema has also been reported as an effect of thalidomide, but it was not listed as an adverse event, drug related or otherwise. It was also noted that the Day 4 temperature was listed as 99 degrees. The medication listings do not show any paracetamol prescribed, although paracetamol was prescribed for other patients who had temperatures less than 99 degrees. At the Day 7 endpoint, this patient had 84 lesions listed as resolving. At the 3 week

follow-up there were none, but 84 were again listed 2 weeks later. Thus, while this patient technically fulfills the requirements for a complete response, the actual overall view is less convincing.

2) No. 04 (CR) was coded initially with 28 acutely inflamed ulcers. On days 1 and 2 there were 48 resolving ulcers. On day 3 there were 25 and on day 4, none. On days 5, 6, and 7 (endpoint), there were again 48 resolving ulcers. Unless the natural history of resolving nodules (75 baseline to 36 at Day 7) includes ulceration, it is unclear from where these ulcers arose.

3) No. 07 (CR) listed a temperature of 99.6 on day 6 and 99.0 on Day 7. This patient had received paracetamol for a fever of 99.4 at baseline as well as on day 1 and day 2, when the temperature was 101.1. No paracetamol is shown for day 3, when the temperature was 101.7. If the temperature on Day 6 (higher than baseline) had prompted the same medication order as the baseline temperature, the patient would have been a discontinuation (failure).

4) No. 08 (CR) had a listed temperature of 99.0 on day 7. This patient's medication listing showed paracetamol at baseline for a temperature of 98.6 and at day 1 for a temperature of 99.3. Paracetamol is not listed the following day with a temperature of 99.6.

5) No. 09 (CR) had paracetamol listed for baseline (99.2) and stopped on Day 4 (96.5). The "comments" listing for day 4 states "new ENL lesions appearing, but no associated symptoms". The next comment is day 7: "Most ENL are no longer recognizable". The day 7 lesion listing shows no acute lesions and 8 resolving lesions. At week 3 it shows no acute lesions and 84 resolving lesions. The exact meaning of the day 7 comment is unclear relative to the day 7 listing for acute lesions.

Many of the questions raised by these cases probably arise from protocol deviations regarding temperature monitoring and lesion counts. Nonetheless, this is the only ENL clinical trial data available for the Sponsor's thalidomide formulation and it was reviewed within the context of the submitted protocol. Within the limits of the significant problems identified, it would appear that the drug does decrease the incidence of acute ENL skin lesions in some patients during the 7 day observation period. However, the effects of thalidomide on lesion progression, high fever, and the serious manifestations of ENL (such as orchitis, uveitis, neuritis) are unclear. In addition, the persistence of the effect while continuing therapy is unknown at this time because interpretation of the follow-up tapering period cannot be undertaken until the blind is broken (patients in the 100 mg arm would be off drug by the

second observation point, while those in the 300 mg arm would remain on drug throughout the period). In addition, it must be recalled that this is an uncontrolled trial and the contribution of a placebo effect, as well as the beneficial therapeutic effect of sedation, cannot be determined.

Overall Conclusions Regarding Efficacy

None of the efficacy data submitted for review was derived from well-controlled, blinded trials supported by adequate source documentation and/or details of design and conduct. Nonetheless, viewed "as is", it is this reviewer's impression that thalidomide, in general, reduces the occurrence of new ENL skin lesions in approximately half of the newly treated cases. Given the nature of the efficacy data sources submitted and the significant assumptions required for its analysis, this figure is offered as an impression, not a conclusion, but it seems to be fairly well conserved. Specifically, the revised figure from Study L-001 (published study with primary data) was 46%. The USPHS chart derived data (major amendment) suggests that approximately 45% of new lesion codes went from "yes" to "no" in the first 2-3 weeks after thalidomide was started. The published studies cannot be summarized into a figure, but Dr. Iyer's study showed approximately a 48% "chance" that patients treated with thalidomide would not show any further reaction, "at least during the period of the trial" (7 days). Re-calculation of the Sheskin and Convit paper (1969) yielded a figure of 51% "complete improvement" at the 7 day endpoint (see Primary Review). Finally, the preliminary results from the Sponsor's on-going trial are somewhere between 11% and 67%, depending upon the rigor with which the data are viewed in relationship to the prospectively defined protocol. As noted previously, of these sources, the contribution of a placebo effect can be estimated only from the Hastings' study, where it appeared to be approximately 33% based on available source documents. It is also important to reiterate the fact that all of these figures represent short-term effects and that even the blinded studies were subject to bias introduced by the sedative effects of thalidomide.

The sponsor's proposed indication is as follows: "Thalidomide is indicated for the acute treatment of moderate to severe erythema nodosum leprosum (ENL) [ ] Thalidomide is also indicated as maintenance therapy for prevention and suppression of ENL recurrence."

As discussed in this review and in the primary review, little well-characterized data was submitted regarding the effect of thalidomide on these serious systemic

manifestations of ENL. Specifically, Study L-001, Study L-002 with the major amendment, and the majority of papers reviewed under Study L-003 address fever and/or the cutaneous manifestations of ENL. The Sponsor's on-going trial, E-003/P, as submitted, lists baseline symptoms of malaise (9), anorexia (8), arthralgias (4), chills (7), pain (2), and neuritis (3), all "mild" to moderate except for one case each of severe chills/anorexia. Neuritis was first listed on drug in two subjects (01 and 02); progression is listed for case 01. In another subject (05), "mild" neuritis was present at baseline and then coded as "moderate" on drug. Subject 04 had neuritis listed as "mild" at baseline with no further entry and subject 07 had a moderate listing at baseline with "mild" on day 2 and no further listing. In these last two cases, if the lack of entry is assumed to mean resolution of the symptom, this result is in marked contrast to the vast majority of sources discussed previously which state that thalidomide's effects on neuritis are, at best, delayed.

Reduction in fever alone cannot be assumed to reflect a systemic anti-inflammatory effect because the mechanism of action, to our knowledge, is unknown. It is known that thalidomide is a centrally acting drug, hence its sedative effects. Its anti-pyretic effects could be analogous to acetaminophen rather than a result of systemic anti-inflammatory activity. Indeed, as noted in the primary review of the Sponsor's on-going E-003/P trial, the majority of patients with complete or partial responses to thalidomide had persistent and significant elevations of the ESR at the last visit, approximately 8 weeks after initiation of thalidomide therapy.

The efficacy of thalidomide for the serious systemic manifestations of ENL is a critically important issue, since inadequate treatment could lead to serious disability and disfigurement. It is this reviewer's view that the data submitted do not support the Sponsor's proposed indication.

In addition, it is this reviewer's view that the data submitted do not adequately inform an overall assessment regarding the effects of the drug on the cutaneous manifestations of ENL, specifically: (1) progression of existing cutaneous disease; (2) the persistence of the effect over time while continuing therapy; (3) the lowest effective dosage relative to severity of presentation, an issue of great clinical significance given the drug's adverse events profile; and, (4) whether thalidomide affords unique efficacy, a critical issue given the extremely serious teratogenic effects of the drug.

The last three issues will be addressed in the context of clinical benefit in the risk-benefit section to follow. Regarding the effects of thalidomide on cutaneous ENL over time, the following observations can be made from the submitted material:

(1) The short follow-up periods and/or absence of qualitative lesion characterization in the submitted studies preclude a valid assessment of the effects of thalidomide on the course of existing ENL lesions. As discussed in the primary review (Study L-001 pg 46), there is evidence for progression to ulceration even at dosages of 400 mg/day. Case 04 in Study E-003/P, reviewed above, could also be interpreted as progressing from papules/nodules to ulceration.

(2) As discussed in the review of the major amendment at the beginning of this document, examination of the scatter plot data over time suggests that the effect of continued thalidomide treatment may not be as robust as the initial response. It is unknown whether this impression derives from a biologically based cause or is an artifact of retrospective and incomplete data. It is clearly of significant clinical importance to define the therapeutic effect of thalidomide on ENL over time, since it appears that the well documented neurotoxic effects of thalidomide in other indications may be dependent on the duration of thalidomide treatment. In addition, continued exposure of patients with reproductive potential would logically increase the risk of fetal exposure. These issues will be discussed within the context of ENL in the section which follows.

Secondary Reviewer's Overall Risk-Benefit Assessment

The risk-benefit analysis for thalidomide for any indication obligates consideration of patients with the disease who may benefit from the drug as well as potential patients who may suffer extremely serious birth defects caused by this drug. To be sure, the interests of these two groups overlap in profound ways and are thus inseparable.

In my mind, the pivotal question to be answered here is whether the evidence demonstrates that Synovir™ (thalidomide) confers unique clinical benefit in the treatment of ENL of such severity as to cause significant pain, disability, or disfigurement. The question encompasses the concepts of unique benefit and disease severity because of the extremely serious birth defects caused by the drug. The term unique benefit, as used here, does not refer to the absence of therapeutic options, but to benefit not achievable with a treatment posing less teratogenic risk.

If the application as submitted does not provide an evidence-based "yes" to all aspects of this question, then it is my opinion that Synovir™ (thalidomide) should not be approved. Instead, an aggressive and timely program should be undertaken to generate robust answers, so that if thalidomide does confer clinical benefit, patients suffering from ENL will have an approved alternative to systemic steroids and clofazimine.

If, on the other hand, the application as submitted does provide an evidence-based "yes" to all aspects of the question, then it is my opinion that Synovir™ should be approved without delay after a rigorous program is in place to prevent fetal exposure. However, it is painfully clear from the experience to date with systemic retinoids that even a rigorous program does not prevent the tragedy of devastating birth defects. According to the Sponsor, it is estimated that there are approximately 250-300 patients in the U.S. undergoing treatment with thalidomide for ENL at any one time. In addition, the WHO has recently reiterated its goal of eradicating leprosy by the year 2000 (*The Lancet* 350:347, 1997). Thus, the number of patients for whom the drug would be prescribed in the U.S. is very small and is very likely to decrease dramatically in the foreseeable future. Thus, if Synovir™ (thalidomide) meets the requirements for approval, it is this reviewer's opinion that a program should be instituted to limit distribution of the drug to the indicated population.

I will now offer my view of the answer to the pivotal question, an answer based on my best efforts to accurately and thoughtfully consider all of the information presented for my review.

In order to decide whether thalidomide confers clinical benefit in the treatment of ENL, it is necessary to know the significant adverse effects profile of the drug in the affected population as well as the extent of the therapeutic effect it renders. As discussed at length in the primary review, the adverse events profile of thalidomide in patients with ENL is virtually unknown due to absent or inadequate assessments and/or reporting. The details of possibly serious effects will not be reiterated here, but they include cardiovascular, cutaneous, and neurologic events. The potential for serious adverse neurologic sequelae includes irreversible peripheral nerve damage, a well documented effect in non-ENL indications where prospective, objective monitoring has been done. In short, a valid risk-benefit assessment for patients with ENL is not feasible until it has been determined whether they are likewise at risk, and, if so, whether effective preventative monitoring is possible given the peripheral nerve damage associated with the underlying disease. Underlying this discussion is the unknown imposed by the fact that the available safety data, regardless of its content, appears to include only 20 ENL patients who have received Synovir™, six of whom received only a single dose in a pharmacokinetic study. This is especially problematic since Synovir™ is much more bioavailable than the formulation from another manufacturer to which it was compared, one used in many of the studies submitted by the Sponsor in support of this application.

Efficacy is the second pivotal determinant in the risk-benefit assessment for thalidomide. As discussed earlier, the issues of disease severity and unique benefit are integral to this discussion because thalidomide causes serious birth defects.

There is no doubt that ENL can cause very significant suffering, disability and disfigurement. Likewise, its course can be very mild and self-limiting. As discussed in the Overview of Efficacy, the submitted information does not support the Sponsor's proposed indication. Furthermore, it does not adequately inform an overall assessment regarding the effects of the drug on the cutaneous manifestations of ENL, specifically, progression of existing cutaneous disease, the persistence of the effect over time while continuing therapy, and the lowest effective dosage relative to severity at presentation.

It appears from the submission that thalidomide has essentially become the standard of care in the treatment of ENL patients other than women who might become pregnant. There are two drugs approved for the treatment of ENL, corticosteroids and clofazimine. Neither are known to be teratogenic, but both are attended by risks, particularly when used in high doses for prolonged periods of time. The risks associated with corticosteroids are well known, and suffered by

millions of patients requiring management of a wide variety of chronic diseases. The clofazimine label notes rare reports of serious intestinal complications/death thought to be due to deposits of the drug. Far more commonly, its use causes a long lasting discoloration of the skin and the label notes that depression has been related to this effect, with two suicides reported in patients receiving the drug.

The review of published literature submitted in the NDA included three open-label comparative therapy studies in addition to the study by Dr. Iyers, but publications pertaining to other treatments, not involving thalidomide, were not found. Of the comparative studies, one each compared thalidomide to chloramphenicol, corticosteroids, or thalidomide plus clofazimine. The most recent of these publications was 1981. It is possible that clinical experience with other therapies is very limited, perhaps because thalidomide has gained such widespread acceptance in the treatment of ENL.

Because of this limited database and the teratogenicity of the drug, information very important to ENL patients and to those who provide their treatment would ensue from a well designed comparative trial. For example, thalidomide dosing could be compared to a therapeutic dose of aspirin or a potent non-steroidal anti-inflammatory drug approved for treatment of fever and pain, with and without a concomitant sedative to control for the well known benefit of bed rest in this disease. Initially, only patients with the mildest form of ENL (papular cutaneous lesions and mild fever with no systemic signs or symptoms) would be enrolled. If the comparator was found to be efficacious and safe, enrollment could then proceed to the next most serious presentation of the disease, perhaps painful nodular/ulcerative lesions with higher temperatures. This tiered process could proceed ethically because the study would end when patients do not respond in a timely and clinically meaningful way.

The annals of modern medicine are punctuated with grief and disease caused by the use of well-intentioned but unproven therapies which gained wide acceptance because the underlying concept seemed biologically plausible and published studies, although uncontrolled or inadequately designed, seemed convincing. The tragedy of such errors is compounded when the drug is a teratogen. The teratogenicity of thalidomide demands that approval be based upon clearly demonstrated clinical benefit for suffering patients in whom treatments with less teratogenic potential are ineffective or contraindicated due to adverse effects. It is my opinion that the information presented in the submission does not support approval.

Secondary Reviewer's Recommendation

NDA 20-785 for Synovir™ (thalidomide) is Not Approvable.

Kathryn O'Connell MD. 8/13/97

Kathryn O'Connell, M.D., Ph.D.
Secondary Clinical Reviewer

cc: HFD-540
HFD-540/CSO/White
HFD-540/Chem/Decamp
HFD-540/Pharm/Hill/Jacobs
HFD-725/Stats/Gao/Thomson/Srinivasan/Harkins
HFD-540/MO/Vaughan/OConnell/Walker
HFD-880/Biopharm/Bashaw
HFD-540/DivDir/Wilkin 8/13/97