CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-785

Statistical Review(s)

AUG 4 1997

STATISTICAL REVIEW AND EVALUATION
addendum

NDA: 20-785/1P
Applicant: Celgene Corporation, 7 Powder Horn Drive, Warren, NJ 07059
Name of Drug: Synovir™(Thalidomide)
Route of Administration: Oral
Documents Reviewed: Medical records under IND11,359 from PHS , dated June, 16, 1997.
Indication: Treatment of Erythema Nodosum Leprosum
Related INDs: IND No.48,117; IND [ ] IND No.11,359;
Medical Officer: Brenda Vaughn, M. D. (HFD-540),
Kathy O'Connell , M. D. (HFD-540)

Introduction : This addendum tabulates the dosage frequencies of Thalidomide when neither prednisone nor clofazamine was used in the medical records for patients treated with Thalidomide under IND 11,359 from the Public Health Services.

The dosage frequencies for all visits, for first visits in on-Thalidomide episodes, at visits when favorable responses were recorded have been tabulated in the original review. In this addendum, these frequencies will be tabulated for visits when neither prednisone nor clofazamine was used.

Table 1 lists the frequencies of Thalidomide daily dose for all the available visits in which the patients were taking Thalidomide but were not taking either prednisone or clofazamine.

Table 1 . Daily dose in all visits of on-Thalidomide episodes in which neither prednisone nor clofazamine was used

daily dose (mg)	N(visits)	%
<15	6	0.5%
20	1	0.1%
25	2	0.2%
50	125	11.4%
100	761	69.6%
150	2	0.2%
200	187	17.1%
300	6	0.5%
400	3	0.3%
Total	1093	

Table 2 lists the frequencies of Thalidomide daily dose in the first visits of on-Thalidomide episodes at which neither prednisone nor clofazamine was used. These were the starting doses for the patients in the on-Thalidomide episodes when they were not using either prednisone or clofazamine.

Table 2. Daily dose in first visits of on-Thalidomide episodes at which neither prednisone nor clofazamine was used

daily dose (mg)	N(visits)	%
<15	1	0.6%
20	1	0.6%
50	5	3.1%
100	128	79.0%
200	27	16.7%
Total	162	

Table 3 lists the frequencies of Thalidomide daily dose in the last visits of multiple-visit on-Thalidomide episodes at which neither prednisone nor clofazamine was used. These were the doses for the patients at the end of on-Thalidomide episodes, and were not using either prednisone or clofazamine was.

Table 3. Daily dose in last visits of multiple-visit on-Thalidomide episodes at which neither prednisone nor clofazamine was used

daily dose (mg)	N(visits)	%
25	1	0.7%
50	33	22.4%
100	100	68.0%
200	13	8.8%
Total	147	

In multiple-visit on-Thalidomide episodes, some patients had documented ENL lesion "present" at the beginning of the episode, then the status changed to "absent" in the episode. The daily doses were recorded when "absent " was first documented. The frequencies for all the multiple-visit episodes in which neither prednisone nor clofazamine was used are listed in Table 4.

Table 4. Daily dose at which recorded first change from ENL lesion being "present" to "absent" in episodes where neither prednisone nor clofazamine was used

daily dose (mg)	N(visits)	%
<15	1	1.6%
50	7	11.3%
100	46	74.2%
200	8	12.9%
300	0	0
Total	62	

In multiple-visit on-Thalidomide episodes, some patients had documented "active" ENL at the beginning of the episode, and then the status changed to "inactive" in that episode. The daily doses were recorded when "inactive" was first documented. The frequencies for all the multiple-visit episodes in which neither prednisone nor clofazamine was used are listed in Table 5.

Table 5. Daily doses at which recorded first change from ENL being "active" to "inactive" in episodes where neither prednisone nor clofazamine was used

daily dose (mg)	N(visits)	%
<15	1	1.3%
25	1	1.3%
50	8	10.7%
100	55	73.3%
200	10	13.3%
300	0	0%
Total	75	

In multiple-visit on-Thalidomide episodes, some patients had documented new ENL lesion "yes" at the beginning of the episode, and then the status changed to "no" in that episode. The daily doses were recorded when "no" was first documented. The frequencies for all the multiple-visit episodes in which neither prednisone nor clofazamine was used are listed in Table 6.

Table 6. Daily doses at which recorded change from new ENL lesion being "yes" to "no" in episodes where neither prednisone nor clofazamine was used

daily dose (mg)	N (visits)	%
<15	1	1.3%
50	6	8.0%
100	54	72.0%
200	14	18.7%
300	0	0%
Total	75	

Reviewer's comments : Tables 1 through 6 indicate that when neither prednisone nor clofazamine is used, a starting dosage of 100 mg/day may be the most appropriate dose and that for some patients, titration to 200 mg/day may be required. In between 80% and 90% of the patient visits at which neither prednisone nor clofazamine was used, the dose range of 100mg/day to 200mg/day was used.

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This addendum contains 4 pages.
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JUN 16 1997

Statistical Review an Evaluation

NDA:	20-785/1P
Applicant:	Celgene Corporation, 7 Powder Horn Drive, Warren NJ 07059
Name of Drug:	Synovir™ (Thalidomide)
Route of Administration:	Oral
Documents Reviewed:	NDA 20-785: Vol. 1 (dated Dec. 20, 1996)
Indication:	Treatment of Erythema Nodosum Leprosum in Leprosy Patients
Related INDs:	IND 48,117; IND [ ] and IDA 11,359
Clinical Input:	Brenda Vaughan, M.D. (HFD-540)

Study L001:

This was a retrospective study based on the medical records of patients with active lepromatous leprosy and chronic Erythema Nodosum Leprosum (ENL) reaction who were treated with thalidomide in the late 1960's under an investigator's protocol. The double-blinded, placebo controlled study was conducted by Dr. Robert Hastings of the Public Health Services Hospital in Carville, Louisiana in the inpatient infirmary, which is now the National Hansen's Disease Research Center (NHDRC). Twenty-five patients were identified as having participated in the double blind study. Approximately, one-half of the patients were receiving dapsone as antimicrobial therapy. Twelve patients received thalidomide 400 mg/day and 13 patients received placebo during the 4-day double blind study.

Reviewer's comments:

Study L001, conducted in the late 1960's, can not be considered as adequate or well-controlled. The sample size of this study is small. In addition, there are serious questions about the eligibility of some of the patients (for details, please see medical officer's review of this submission). As a result, these patients were excluded from analysis. The resultant sample size was so small that reliable statistical analysis can not be performed on this data.

Study L002

L002 is an open label study of thalidomide for the treatment of ENL in the United States under IND 11,359. 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 Dr. Leo Yoder (1993 to present) of the Gillis W. Long Hansen's Disease Center (GWLHDC), Carville, Louisiana. Patients enrolled in this study were from 64 centers. The original work began in 1975 and data collection was computerized into a formal database in 1978. As of April 1995, the data base included information recorded in the annual reports on 1387 patients.

Reviewer's comments:

This study failed to capture important information such as the daily dose during treatment, length of treatment, time to response and use of concomitant medication required to evaluate the contribution of Thalidomide in the treatment of ENL. The information contained in the data is deemed to be insufficient for any reliable statistical analysis.

Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):

Data from studies L001 and L002 did not lend sufficient information for reliable statistical analyses on the efficacy/safety claims of Synovir™ in the treatment of Erythema Nodosum Leprosum (ENL) in leprosy patients.

Neither study L001 (due to inadequate sample size) nor study L002 (due to lack of information regarding how thalidomide was actually used) provide data and information required to support the sponsor's proposed claim.

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This review contains ***3*** pages
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STATISTICAL REVIEW AND EVALUATION

AUG 7 1997

NDA: 20-785/1P
Applicant: Celgene Corporation, 7 Powder Horn Drive, Warren, NJ 07059
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Medical Officer: Brenda Vaughn, M. D. (HFD-540),
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Table of Contents:

§ 0. **Introduction** : This review analyzes the data from the medical records for patients treated with Thalidomide under IND 11,359 from the Public Health Services.

Erythema Nodosum Leprosum (ENL) is an immune complex disease reaction occurring in patients with multibacillary subtypes of leprosy. Onset of this inflammatory reaction is often triggered by initial antimicrobial therapy for leprosy. ENL is a systemic disorder with a variety of potential symptoms, i.e., fever, neuritis, iritis, leukocytosis, and anemia. In addition, the most common clinical manifestation is crops of painful erythematous nodules of the skin and subcutaneous tissue.

To investigate the efficacy of Thalidomide in the treatment of ENL, medical records of 131 patients who were treated with Thalidomide (with or without ENL) under IND 11,359 were obtained from Public Health Services. The electronically entered data contains the medical records of 102 patients with documented ENL. These patients were treated from 1973 to 1997, which is a long period of time. Hence, the data generated from these medical records is of varying quality and completeness. No analytical protocol was available from IND11,359. No comparative drug or therapy was used, subjects were not randomized to treatment groups, and there is no fixed dose or duration of dose, no rules of titration up and down. This data set is of inferior quality as compared to the data from an adequate and well-controlled

clinical trial. Hence, statistical modeling analyses will not be performed on this data. Instead, only descriptions of the data structure through summary tables (and scatter plots of individual patient records) will be presented. Therefore, the statistical analyses of this review will not contain any p-values. The whole time period covered in a patient's medical record was broken down to time periods when the patient was under Thalidomide treatment (on-Thalidomide episode) and when the patient was not using Thalidomide (off-Thalidomide episode). Then, the disease progress from the beginning to the end of an on-Thalidomide (off-Thalidomide) episode was tabulated. Many patients had multiple episodes. Due to the high frequency of "No Data" and the wide range of duration of treatment among patients, no meaningful analyses on a per-patient basis could be done. Therefore, in all the tables in this review, each episode was treated as if it had been independent of all other episodes. However, since episodes from a patient were not really independent, the assumption of independence may not be appropriate. Due to these many design problems, the results in this review should be interpreted with great caution. Throughout the course of Thalidomide use under IND 11,359, adverse events were not systematically recorded. Hence, this data does not contain sufficient information for appropriate safety analyses.

In § 1, an overall data description is given. The treatment course of patients was described and information on the efficacy variables (including frequencies of "no data") were tabulated. In § 2, the efficacy variables recorded at the first visit of each episode (on-Thalidomide and off-Thalidomide) were tabulated to compare the "baseline" endpoints for the on-Thalidomide and off-Thalidomide episodes. In § 3, the progress of ENL relative to the efficacy variables in the multiple-visit episodes (on-Thalidomide and off-Thalidomide) were tabulated. In § 4, the progress of ENL relative to the efficacy variables in the prednisone-free and clofazamine-free multiple-visit episodes (on-Thalidomide and off-Thalidomide) were tabulated. In § 5, the "long-on to on " bridges and "long-off to off" bridges were defined, and the progress of ENL relative to the efficacy variables over these bridges were tabulated. In §6, multiple-visit episodes were truncated to no more than 2 weeks and 3 weeks, and the efficacy variables recorded at the first and last visits of the truncated episodes were tabulated. In §7, the efficacy variables recorded at the first and last visits of the prednisone-free and clofazamine-free truncated multiple-visit episodes were tabulated. In § 8, the frequency of dosing regimen was tabulated to find out the most commonly used dosages. In § 9, scatter plots of indications and drug usage of individual patients over time are given.

§ 1. **Overall Data description:**

The data contained medical records of 102 ENL patients who took Thalidomide. All patients had multiple visits to the clinic (min=2,max=61), and there are 1988 visits. The majority of the patients were on and off Thalidomide alternately, thus had multiple "on-Thalidomide episodes" (time periods during which the patients were on Thalidomide) and "off-Thalidomide episodes" (the time periods when the patients discontinued the use of Thalidomide). Since this data is not from an adequate, well-controlled clinical trial, no study treatment group comparison can be made. Instead, the "on-Thalidomide episodes" will be analyzed to compare the "pre-treatment" (first visit of an "on-Thalidomide" episode) ENL symptoms with the "after-treatment" (last visit of an "on-Thalidomide" episode) ENL symptoms. Similarly, the ENL symptoms recorded at the first visit and last visit of an "off-Thalidomide" are compared. Figure 1 illustrates the on and off-Thalidomide episodes.

Figure 1. On and off Thalidomide episodes

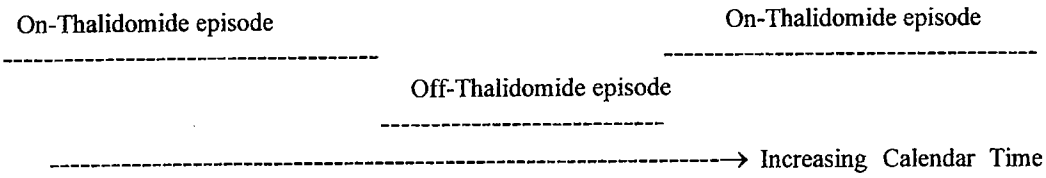


Table 1 lists the patient population by gender and age range.

Table 1. Gender and age range of patients

Total	102
Male	83
Female	19
Age range (at 1st visit)	15-76

As mentioned earlier, patients had multiple visits to the clinic. The number of visits by the patients to the clinic were counted and grouped into ranges. Table 2 lists the groups and the number of patients in each group.

Table 2. Patients by number of visits to physician

	maximum number of visits	number of patients
	2—7	14
	8—15	33
	16-23	21
	24-31	21
	32-61	13
Total	1988	102

The time period between the first and last visit by a patient is calculated in weeks, then grouped according to the length (in weeks) of the period. This is listed in Table 3.

Table 3. Time from first to last visit for patients

weeks covered between first and last visit	number of patients
3—30	8
31—75	12
76—225	22
226—375	27
376---525	16
526--930	17
Total	102

Many of the patients had several "on-Thalidomide" and "off-Thalidomide" episodes. The number of "on-Thalidomide" episodes were counted and grouped into ranges. The frequency distribution of patients in each group is given in Table 4.

Table 4. Patients and number of on-Thalidomide episodes

	maximum number of "on Thalidomide episodes"	number of patients
	1	40
	2	31
	3	20
	4	5
	5—11	6
Total		102
Total number of on-episodes : 221		

Table 5 counts the off-Thalidomide episodes and is similar to Table 4.

Table 5. Patients and number of off-Thalidomide episodes

	maximum number of "off Thalidomide episodes"	number of patients
	1	32
	2	24
	3	20
	4	5
	5—11	7
Total		88
Total number of off-episodes : 203		

As mentioned earlier, comparisons will be made for the ENL symptoms recorded at the first and last visit of an on-Thalidomide and an off-Thalidomide episode to investigate the progress of ENL relative to the efficacy variables. Because of the need of distinguishing between the start and end of an episode, such comparisons are only meaningful for those episodes with more than one visit. Hence, on-Thalidomide and off-Thalidomide episodes with multiple visits are counted and grouped into ranges. Table 6 lists the on-Thalidomide episode groups and the number of patients in each group.

Table 6. Patients with multiple-visit on-Thalidomide episodes

	number of "on Thalidomide episodes" with multiple visits	number of patients
	1	48
	2	32
	3	12
	4	7
	5	2
Total		101
Total number of multiple-visit on-episodes : 186		

Table 7 lists the off-Thalidomide episode groups and the number of patients in each group.

Table 7. Patients with multiple-visit off-Thalidomide episodes

	number of "off Thalidomide episodes" with multiple visits	number of patients
	1	35
	2	9
	3	5
	4	1
Total		50
Total number of off-episodes : 72		

The time period between the first and last visit in an multiple-visit episode (either on or off Thalidomide) is calculated in weeks, then grouped according to the length (in weeks) of the period. The groups and the number of episodes in each group are listed in Table 8.

Table 8. Time from first to last visit in multiple-visit episodes

	off	on
length (weeks) of episodes with multiple visits	N	N
<1	3	1
1	3	3
2	4	11
3	3	3
4—10	9	16
11—20	10	21
21—40	6	25
41—60	7	16
61—80	5	18
81—120	4	24
121—160	2	16
161—876	16	32
Total	72	186

The following Tables 9-15 list frequencies of the categories of the ENL symptoms such as "ENL Lesion", "ENL activity", "New ENL Lesion ", "Erythema", "Lesion Size", "Lesion Number", "Tenderness". Of interest here are the percentages of the "No Data" category, which provide some knowledge of the data quality.

Table 9 lists the frequencies in the ENL lesion categories. This table shows a notable decrease in "No Data" frequencies for the 2nd and later visits of off-Thalidomide episodes from the "All visits" frequencies.

Table 9. ENL Lesion categories

		on Thalidomide		off Thalidomide	
All visits	ENL lesion status	N	%	N	%
	Present	628	40.54%	100	22.78%
	Absent	499	32.21%	195	44.42%
	No data	422	27.24%	144	32.80%
	Total	1549		439	
2nd and later visits in multiple-visit episodes	ENL lesion status	N	%	N	%
	Present	440	33.13%	67	28.39%
	Absent	490	36.90%	119	50.42%
	No data	398	29.97%	50	21.19%
	Total	1328		236	

Table 10 lists the frequencies in the ENL activity categories. This table shows a notable decrease in "No Data" frequencies for the 2nd and later visits of off-Thalidomide episodes from the "All visits" frequencies.

Table 10. ENL activity categories

		on Thalidomide		off Thalidomide	
All visits	ENL activity	N	%	N	%
	Active	491	31.70%	94	21.41%
	Inactive	611	39.44%	174	39.64%
	No data	447	28.86%	171	38.95%
	Total	1549		439	
2nd and later visits in multiple-visit episodes	ENL activity	N	%	N	%
	Active	309	23.27%	62	26.27%
	Inactive	604	45.48%	99	41.95%
	No data	415	31.25%	75	31.78%
	Total	1328		236	

Table 11 lists the frequencies in the new ENL lesion categories. The Table shows a notable decrease in "No Data" frequencies for the 2 nd and later visits of off-Thalidomide episodes from the "All visits" frequencies.

Table 11. New ENL Lesions activity categories

		on Thalidomide		off Thalidomide	
All visits	New Lesions	N	%	N	%
	Yes	278	17.95%	64	14.58%
	No	921	59.46%	216	49.20%
	No data	350	22.60%	159	36.22%
	Total	1549		439	
2nd and later visits in multiple-visit episodes	New Lesions	N	%	N	%
	Yes	135	10.17%	46	19.49%
	No	893	67.24%	127	53.81%
	No data	300	22.59%	63	26.69%
	Total	1328		236	

Tables 12-15 list the frequencies of erythema, lesion size, lesion number, and tenderness. The percentage of "No Data" frequencies are all higher than 86%. Thus, these ENL symptoms can provide very little information for any comparison , and will not be looked at any further.

Table 12. Erythema status by category

	on Thalidomide		off Thalidomide	
Erythema status	N	%	N	%
Increased	56	3.62%	18	4.10%
Decreased	111	7.17%	11	2.51%
Same	19	1.23%	5	1.14%
No data	1363	87.99%	405	92.26%
Total	1549		439	

Table 13. Lesion Size status by category

	on Thalidomide		off Thalidomide	
Lesion Size	N	%	N	%
Smaller	111	7.33%	13	3.26%
Larger	29	1.92%	6	1.50%
Same	50	3.30%	9	2.26%
No data	1324	87.45%	371	92.98%
Total	1549		439	

Table 14. Lesion Number status by category

	on Thalidomide		off Thalidomide	
Lesion Number	N	%	N	%
Increase	59	3.81%	21	4.78%
Decrease	100	6.46%	13	2.96%
Same	51	3.29%	9	2.05%
No data	1339	86.44%	396	90.21%
Total	1549		439	

Table 15. Tenderness categories

	on Thalidomide		off Thalidomide	
Tenderness	N	%	N	%
Yes	55	3.55%	19	4.33%
No	38	2.45%	13	2.96%
No data	1456	94.00%	407	92.71%
Total	1549		439	

§ 2. **"Baseline" data:**

The first visit of an on-Thalidomide (off Thalidomide) episode provides the "baseline" information for this episode. If this visit is not the very first visit for the patient, then this visit follows the last visit of the previous off-Thalidomide (on-Thalidomide) episode. Hence, the symptoms recorded in this visit provide some information of the effect from the previous episode. Tables 16-18 list the frequencies of the categories for ENL lesion, ENL activity, and New lesion status in the first visits in all episodes (including single-visit episodes):

Table 16 shows that the percentage of "on-Thalidomide" episodes (85.07%) starting (first visit) with ENL lesion "present" is higher than that of the "off-Thalidomide" episodes (16.26%).

Table 16. ENL lesions status in the first visit of an episode

		on Thalidomide		off Thalidomide	
1st visit in an episode	ENL lesion status	N	%	N	%
	Present	188	85.07%	33	16.26%
	Absent	9	4.07%	76	37.44%
	No data	24	10.86%	94	46.31%
	Total	221		203	

Table 17 shows that the percentage of "on-Thalidomide" episodes (82.35%) starting (first visit) with "active" ENL is higher than that of the "off-Thalidomide" episodes (15.76%).

Table 17. ENL activity status in the first visit of an episode

		on Thalidomide		off Thalidomide	
1st visit in an episode	ENL activity	N	%	N	%
	Active	182	82.35%	32	15.76%
	Inactive	7	3.17%	75	36.95%
	No data	32	14.48%	96	47.29%
	Total	221		203	

Table 18 shows that the percentage of "on-Thalidomide" episodes (64.71%) starting (first visit) with new ENL lesion is higher than that of the "off-Thalidomide" episodes (8.87%).

Table 18. New Lesions status in the first visit of an episode

		on Thalidomide		off Thalidomide	
1st visit in an episode	New Lesions	N	%	N	%
	Yes	143	64.71%	18	8.87%
	No	28	12.67%	89	42.84%
	No data	50	22.62%	96	47.29%
	Total	221		203	

Reviewer's comments : Tables 16-18 show that the percentages of on-Thalidomide episodes starting (first visits) with ENL lesion "present", ENL "active", and new ENL lesion "yes", were higher than those of the off- Thalidomide episodes.

§ 3. **Change from "baseline": All multiple-visit episodes**

The ENL symptoms recorded at the first and last visits of multiple-visit episodes (both on-Thalidomide and off-Thalidomide) are investigated in detail in this section to compare the change from "pre-treatment" (first visit) to "after treatment" (last visit).

Table 19 shows that 86.56% of the on-Thalidomide episodes started (first visit) with ENL lesion, and 28.49% ended (last visit) with ENL lesion. 3.76% of the on-Thalidomide episodes started (first visit) with documented " ENL lesion absent", and 43.55% ended (last visit) with documented " ENL lesion absent". In contrast, 12.50% of the off-Thalidomide episodes started (first visit) with ENL lesion, and 31.94% ended (last visit) with ENL lesion. 52.78% of the off-Thalidomide episodes started (first visit) with documented " ENL lesion absent", and 47.22% ended (last visit) with documented " ENL lesion absent".

Table 19. ENL Lesion status at the first and last visits of multiple-visit episodes

		1st visit in episode		last visit in episode	
on Thalidomide	ENL lesion status	N	%	N	%
	Present	161	86.56%	53	28.49%
	Absent	7	3.76%	81	43.55%
	No data	18	9.68%%	52	27.96%
	Total	186		186	
off Thalidomide	ENL lesion status	N	%	N	%
	Present	9	12.50%	23	31.94%
	Absent	38	52.78%	34	47.22%
	No data	25	34.72%	15	20.83%
	Total	72		72	

Table 20 gives the frequency distribution of the change in the ENL lesion status from the first visit to the last visit of each episode. "Present-to-absent" happened in 37.63% of the on-Thalidomide episodes, and in 1.39% of the off-Thalidomide episodes. "Absent-to-present" happened in 0% of the on-Thalidomide episodes and in 13.89% of the off-Thalidomide episodes.

Table 20. Change in the ENL lesion status from first to last visit of multiple-visit episode

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL lesion Change	off-episode		on-episode	
	N	%	N	%
present to absent	1	1.39%	70	37.63%
absent to present	10	13.89%	0	0%
present to present	7	9.72%	47	25.27%
absent to absent	25	34.72%	7	3.76%
present to no-data	1	1.39%	44	23.66%
absent to no-data	3	4.17%	0	0%
no-data to present	6	8.33%	6	3.23%
no-data to absent	8	11.11%	4	2.15%
no-data to no-data	11	15.28%	8	4.30%
Total	72		186	

Table 21 shows that 82.80% of the on-Thalidomide episodes started (first visit) with active ENL , and 19.89% ended (last visit) with active ENL . 2.69% of the on-Thalidomide episodes started with documented " ENL inactive", and 49.46% ended with documented " ENL inactive". In contrast, 15.28% of the off-Thalidomide episodes started with active ENL, and 29.17% ended with active ENL. 45.83% of the off-Thalidomide episodes started with documented "ENL inactive", and 43.06% ended with documented "ENL inactive".

Table 21. ENL Activity status at the first and last visits of multiple-visit episodes

		1st visit in episode		last visit in episode	
on Thalidomide	ENL activity	N	%	N	%
	Active	154	82.80%	37	19.89%
	Inactive	5	2.69%	92	49.46%
	No data	27	14.52%	57	30.65%
	Total	186		186	
off Thalidomide	ENL activity	N	%	N	%
	Active	11	15.28%	21	29.17%
	Inactive	33	45.83%	31	43.06%
	No data	28	38.89%	20	27.78%
	Total	72		72	

Table 22 gives the frequency distribution of the change in ENL activity status from the first visit to the last visit of each episode. "Active-to-inactive" happened in 43.01% of the on-Thalidomide episodes, and in 4.17% of the off-Thalidomide episodes. "Inactive-to-active" happened in 0% of the on-Thalidomide episodes and in 8.33% of the off-Thalidomide episodes.

Table 22. Change in ENL activity status from first to last visit of multiple-visit episode

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL activity Change	off-episode		on-episode	
	N	%	N	%
active to inactive	3	4.17%	80	43.01%
inactive to active	6	8.33%	0	0%
active to active	24	33.33%	48	25.81%
inactive to inactive	23	31.94%	4	2.15%
active to no-data	0	0%	41	22.04%
inactive to no-data	4	5.56%	1	0.54%
no-data to active	7	9.72%	4	2.15%
no-data to inactive	5	6.94%	8	4.30%
no-data to no-data	0	0%	0	0%
Total	72		186	

Table 23 shows that 63.98% of the on-Thalidomide episodes started (first visit) with new ENL lesion, and 9.68% ended (last visit) with new ENL lesion. 11.29% of the on-Thalidomide episodes started (first visit) with documented "no new ENL lesion", and 69.89% ended (last visit) with documented "no new ENL lesion". In contrast, 5.56% of the off-Thalidomide episodes started with new ENL lesion, and 20.83% ended with new ENL lesion. 65.28% of the off-Thalidomide episodes started with documented "no new ENL lesion", and 55.56% ended with documented "no new ENL lesion".

Table 23. New ENL lesions status at the first and last visits of multiple-visit episodes

		1st visit in episode		last visit in episode	
on Thalidomide	New Lesions	N	%	N	%
	Yes	119	63.98%	18	9.68%
	No	21	11.29%	130	69.89%
	No data	46	24.73%	38	20.43%
	Total	186		186	
off Thalidomide	New Lesions	N	%	N	%
	Yes	4	5.56%	15	20.83%
	No	47	65.28%	40	55.56%
	No data	21	29.17%	17	23.61%
	Total	72		72	

Table 24 gives the frequency distribution of the change in new ENL lesion status from the first visit to the last visit of each episode. "Yes-to-no" happened in 47.85% of the on-Thalidomide episodes, and in 2.78% of the off-Thalidomide episodes. "No-to-yes" happened in 1.08% of the on-Thalidomide episodes and in 9.72% of the off-Thalidomide episodes.

Table 24. Change in New ENL lesion status from first to last visit of multiple-visit episode

	From the first visit of a multiple-visit episode to the last visit of the same episode			
New lesion status Change	off-episode		on-episode	
	N	%	N	%
yes to no	2	2.78%	89	47.85%
no to yes	7	9.72%	2	1.08%
yes to yes	1	1.39%	11	5.91%
no to no	33	45.83%	17	9.14%
yes to no-data	1	1.39%	19	10.22%
no to no-data	7	9.72%	2	1.08%
no-data to yes	7	9.72%	5	2.69%
no-data to no	5	6.94%	24	12.90%
no-data to no-data	9	12.50%	17	9.14%
Total	72		186	

Reviewer's comments : Tables 19-24 show that multiple-visit on-Thalidomide episodes started (first visit) with higher percentages of ENL lesion "present" (85.56%), ENL "active" (82.80%), and new ENL lesion "yes" (63.98%), whereas, the on-Thalidomide episodes ended (last visit) with much lower percentages of ENL lesion "present" (28.49%), ENL "active" (19.89%), and new ENL lesion "yes" (9.68%). The multiple-visit off-Thalidomide episodes started with lower percentages of ENL lesion "present" (12.50%), ENL "active" (15.28%) , and new ENL lesion "yes" (5.56%) than when they ended (last visit) (31.94%, 29.17%, 20.83%, respectively). The percentage of reported change in ENL lesion from "present-to-absent" is higher for the on-Thalidomide episodes (37.63%) than that for the off-Thalidomide episodes (1.39%). The percentage of reported change in the ENL activity from "active-to-inactive" is higher for the on-Thalidomide episodes (43.01%) than for the off-Thalidomide episodes (4.17%). The percentage of reported change in the new ENL lesion status from "yes-to-no" is higher for the on-Thalidomide episodes (47.85%) than for the off-Thalidomide episodes (2.78%).

§ 4. Change from "baseline": All multiple-visit episodes in which neither prednisone nor clofazamine was used

The ENL symptoms recorded at the first and last visits of a multiple-visit episode (in which neither prednisone nor clofazamine was used) are investigated in detail in this section to compare the changes from "pre-treatment" (first visit) to "after treatment" (last visit) that are not influenced by either prednisone or clofazamine.

Table 25 shows that 86.55% of the on-Thalidomide episodes started (first visit) with ENL lesion, and 27.73% ended (last visit) with ENL lesion. 5.04% of the on-Thalidomide episodes started (first visit) with documented " ENL lesion absent", and 47.06% ended (last visit) with documented " ENL lesion absent". In contrast, 13.21% of the off-Thalidomide episodes started (first visit) with ENL lesion, and 26.42% ended (last visit) with ENL lesion. 56.60% of the off-Thalidomide episodes started (first visit) with documented " ENL lesion absent", and 52.83% ended (last visit) with documented " ENL lesion absent".

Table 25. ENL Lesion status at the first and last visits of multiple-visit episodes during which neither prednisone nor clofazamine was used

		1st visit in episode		last visit in episode	
on Thalidomide	ENL lesion status	N	%	N	%
	Present	103	86.55%	33	27.73%
	Absent	6	5.04%	56	47.06%
	No data	10	8.40%	30	25.21%
	Total	119		119	
off Thalidomide	ENL lesion status	N	%	N	%
	Present	7	13.21%	14	26.42%
	Absent	30	56.60%	28	52.83%
	No data	16	30.19%	11	20.75%
	Total	53		53	

Table 26 gives the frequency distribution of the change in ENL lesion status from the first visit to the last visit of each episode. "Present-to-absent" happened in 38.66% of the on-Thalidomide episodes, and in 0% of the off-Thalidomide episodes. "Absent-to-present" happened in 0% of the on-Thalidomide episodes and in 11.32% of the off-Thalidomide episodes.

Table 26. Change in ENL lesion status from first to last visit of multiple-visit episode during which neither prednisone nor clofazamine was used

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL lesion Change	off-episode		on-episode	
	N	%	N	%
present to absent	0	0%	46	38.66%
absent to present	6	11.32%	0	0%
present to present	6	11.32%	32	26.89%
absent to absent	21	39.62%	6	5.04%
present to no-data	1	1.89%	25	21.01%
absent to no-data	3	5.66%	0	0%
no-data to present	2	3.77%	1	0.84%
no-data to absent	7	13.21%	4	3.36%
no-data to no-data	7	13.21%	5	4.20%
Total	53		119	

Table 27 shows that 83.19% of the on-Thalidomide episodes started (first visit) with active ENL , and 20.17% ended (last visit) with active ENL . 3.36% of the on-Thalidomide episodes started (first visit) with documented " ENL inactive", and 51.26% ended (last visit) with documented " ENL inactive". In contrast, 15.09% of the off-Thalidomide episodes started (first visit) with active ENL, and 20.76% ended (last visit) with active ENL. 50.94% of the off-Thalidomide episodes started with documented "ENL inactive", and 49.06% ended (last visit) with documented "ENL inactive".

Table 27. ENL Activity status at the first and last visits of multiple-visit episodes during which neither prednisone nor clofazamine was used

		1st visit in episode		last visit in episode	
on Thalidomide	ENL activity	N	%	N	%
	Active	99	83.19%	24	20.17%
	Inactive	4	3.36%	61	51.26%
	No data	16	13.45%	34	28.57%
	Total	119		119	
off Thalidomide	ENL activity	N	%	N	%
	Active	8	15.09%	11	20.75%
	Inactive	27	50.94%	26	49.06%
	No data	18	33.96%	16	30.19%
	Total	53		53	

Table 28 gives the frequency distribution of the change in ENL activity status from the first visit to the last visit of each episode. "Active-to-inactive" happened in 43.70% of the on-Thalidomide episodes, and in 3.77% of the off-Thalidomide episodes. "Inactive-to-active" happened in 0% of the on-Thalidomide episodes and in 5.66% of the off-Thalidomide episodes.

Table 28. Change in ENL activity status from first to last visit of multiple-visit episode during which neither prednisone nor clofazamine was used

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL activity Change	off-episode		on-episode	
	N	%	N	%
active to inactive	2	3.77%	52	43.70%
inactive to active	3	5.66%	0	0%
active to active	18	33.96%	32	26.89%
inactive to inactive	20	37.74%	3	2.52%
active to no-data	0	0%	24	20.17%
inactive to no-data	4	7.55%	1	0.84%
no-data to active	2	3.77%	1	0.84%
no-data to inactive	4	7.55%	6	5.04%
no-data to no-data	0	0%	0	0%
Total	53		119	

Table 29 shows that 68.91% of the on-Thalidomide episodes started (first visit) with new ENL lesion, and 8.40% ended (last visit) with new ENL lesion. 12.61% of the on-Thalidomide episodes started (first visit) with documented "no new ENL lesion", and 71.43% ended (last visit) with documented "no new ENL lesion". In contrast, 5.66% of the off-Thalidomide episodes started (first visit) with new ENL lesion, and 13.21% ended (last visit) with new ENL lesion. 66.04% of the off-Thalidomide episodes started (first visit) with documented "no new ENL lesion", and 64.15% ended (last visit) with documented "no new ENL lesion".

Table 29. New ENL lesions status at the first and last visits of multiple-visit episodes during which neither prednisone nor clofazamine was used

		1st visit in episode		last visit in episode	
on Thalidomide	New Lesions	N	%	N	%
	Yes	82	68.91%	10	8.40%
	No	15	12.61%	85	71.43%
	No data	22	18.49%	24	20.17%
	Total	119		119	
off Thalidomide	New Lesions	N	%	N	%
	Yes	3	5.66%	7	13.21%
	No	35	66.04%	34	64.15%
	No data	15	28.30%	12	22.64%
	Total	53		53	

Table 30 gives the frequency distribution of the change in new ENL lesion status from the first visit to the last visit of each episode. "Yes-to-no" happened in 52.10% of the on-Thalidomide episodes, and in 3.77% of the off-Thalidomide episodes. "No-to-yes" happened in 0.84% of the on-Thalidomide episodes and in 7.55% of the off-Thalidomide episodes.

Table 30. Change in New ENL lesion status from first to last visit of multiple-visit episode during which neither prednisone nor clofazamine was used

	From the first visit of a multiple-visit episode to the last visit of the same episode			
New lesion status Change	off-episode		on-episode	
	N	%	N	%
yes to no	2	3.77%	62	52.10%
no to yes	4	7.55%	1	0.84%
yes to yes	1	1.89%	7	5.88%
no to no	27	50.94%	12	10.08%
yes to no-data	0	0%	13	10.92%
no to no-data	4	7.55%	2	1.68%
no-data to yes	2	3.77%	2	1.68%
no-data to no	5	9.44%	11	9.24%
no-data to no-data	8	15.09%	9	7.56%
Total	53		119	

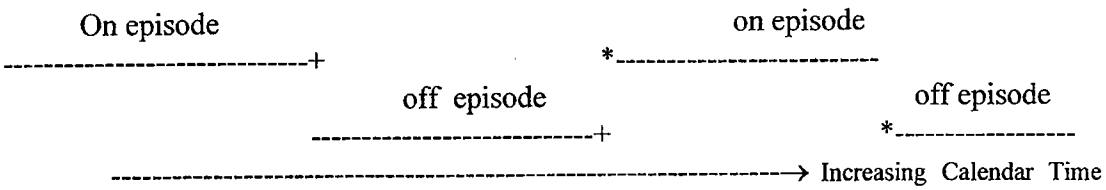
Reviewer's comments : Tables 25-30 show that multiple-visit on-Thalidomide episodes (during which neither prednisone nor clofazamine was used) started (first visit) with higher percentages of ENL lesion "present" (86.55%), ENL "active" (83.19%), and new ENL lesion "yes" (68.91%), whereas, they ended (last visit) with much lower percentages of ENL lesion "present" (27.73%), ENL "active" (20.17%), and new ENL lesion "yes" (8.40%). The multiple-visit off-Thalidomide episodes (during which neither prednisone nor clofazamine was used) started (first visit) with lower percentages of ENL lesion "present" (13.21%), ENL "active" (15.09%), and new ENL lesion "yes" (5.66%) than when they ended (last visit) (26.42%, 20.75%, 13.21%, respectively). The percentage of reported change in ENL lesion from "present-to-absent" is higher for the on-Thalidomide episodes (38.66%) than for the off-Thalidomide episodes (0%). The percentage of reported change in ENL activity from "active-to-inactive" is higher for the on-Thalidomide episodes (43.70%) than for the off-Thalidomide episodes (3.77%). The percentage of reported change in new ENL lesion status from "yes-to-no" is higher for the on-Thalidomide episodes (52.10%) than for the off-Thalidomide episodes (3.77%).

§ 5. Change from the last visit of a multiple-visit on (off)-Thalidomide episode to the first visit of the subsequent on (off)-Thalidomide episode

The changes of ENL efficacy variables from the first visit to the last visit of multiple-visit (on and off-Thalidomide) episodes (for convenience, these multiple-visit on (off)-episodes will be called long-on (off) episodes) have been investigated in § 3 and § 4. In this section, the changes of ENL efficacy variables over the "bridges" (see below) are tabulated to investigate the progress of ENL in episodes (either single-visit or multiple-visit) following a multiple-visit episode (on or off-Thalidomide). As mentioned in § 3 and § 4, the ENL symptoms recorded in the last visit of a multiple-visit on (off)-Thalidomide episode indicated the effect of the patient's being "on-Thalidomide" or "off-Thalidomide" for a period of time. If there were any changes in the following "off (on)-Thalidomide" episode (this episode may be a single-visit or a multiple-visit episode), then these changes might be recorded in the first visit of the subsequent "on (off)-Thalidomide" episode. To analyze these changes, the last visit of a multiple-visit on (off)-Thalidomide episode and the first visit of the subsequent on (off)-Thalidomide episode were paired and called a "long-on to on " bridge ("long-off to off" bridge). The off (on)-Thalidomide episode between

the two on (off)-Thalidomide episodes could be a single-visit episode. Hence, the analyses of the bridges may provide additional information to the results in § 3 and § 4. Figure 2 illustrates these visits.

Figure 2. From the last visit of a multiple on (off) episode to the first visit of the subsequent on (off) episode



+: last visit of a multiple-visit on (off) episode; *: first visit of the subsequent on (off) episode.

There are 27 "long-off to off" bridges. The Thalidomide treatment effect has been investigated by comparing the first and last visits of a multiple-visit on-Thalidomide episode. A "long-off to off" bridge includes an on-Thalidomide episode (single-visit or multiple-visit), and hence, the change over such a bridge provides additional information on the effect of a period of Thalidomide treatment. Since there are only 27 such "long-off to off" bridges and there is a considerable portion of "no data", the additional information provided by the "long-off to off" bridges may be very limited. There are 98 "long-on to on " bridges. A "long-on to on " bridge includes an off-Thalidomide episode (single-visit or multiple-visit), and hence the change over such a bridge provides additional information on the effect of being off-Thalidomide medication for a period. The findings in this section are consistent with those from § 3 and § 4.

Table 31 shows that ENL lesions were documented to be present at 35.71% of the last visits of multiple-visit on-Thalidomide episodes (the entry to the "long-on to on " bridge), and the documented presence of ENL lesion increased to 84.69% of the first visits of the subsequent on-Thalidomide episodes (the exit from the "long-on to on " bridge) after being off Thalidomide for a period of time. ENL lesions were documented to be absent at 39.80% of the last visits of multiple-visit on-Thalidomide episodes (the entry to the "long-on to on " bridge), and the documented absence of ENL lesion decreased to 6.12% of the first visits of the subsequent on-Thalidomide episodes (the exit from the "long-on to on " bridge) after being off Thalidomide for a period of time. The data shows that at the first visits of off-Thalidomide episode following a multiple-visit off-Thalidomide episode(the exit from the "long-off to off" bridge), most of the ENL lesion status were not recorded (70.37%). ENL lesions were documented to be present in 59.26% of the last visits of multiple-visit off-Thalidomide episodes (the entry to the "long-off to off" bridge), and the documented presence of ENL lesion decreased to 7.41% of the first visits of the subsequent off-Thalidomide episodes (the exit from the "long-off to off " bridge) after being on Thalidomide for a period of time. The documented change between the entry and exit of a "long-off to off" bridge in the absence of ENL lesion was less than 5% (25.93% to 22.22%).

Table 31. ENL Lesion status at the last visit of multiple-visit on (off) episodes and the first visit of the subsequent on (off) episodes

		last visit in on (off) episode		1st visit in subsequent on (off) episode	
on-Thalidomide episode to on-Thalidomide episode ("long-on to on " bridge)	ENL lesion status	N	%	N	%
	Present	35	35.71%	83	84.69%
	Absent	39	39.80%	6	6.12%
	No data	24	24.49%	9	9.18%
	Total	98		98	
off -Thalidomide episode to off -Thalidomide episode ("long-off to off " bridge)	ENL lesion status	N	%	N	%
	Present	16	59.26%	2	7.41%
	Absent	7	25.93%	6	22.22%
	No data	4	14.81%	19	70.37%
	Total	27		27	

Table 32 gives the frequency distribution of the change in ENL lesion status from the entry (last visit of the multiple-visit on (off)-Thalidomide episode) to the exit (first visit of the subsequent on (off)-Thalidomide episode) "long-on to on " bridges and "long-off to off" bridges. "Present-to-absent" happened in 1.02% of the "long-on to on " bridges. "Absent-to-present" happened in 33.67% of the "long-on to on " bridges, and "present-to-present" happened in 30.61% of the "long-on to on " bridges.

Table 32. Change in ENL Lesion status from the last visit of multiple-visit on (off) episodes to the first visit of the subsequent on (off) episodes

	From the last visit of a multiple-visit on (off) episode to the first visit of the subsequent on (off) episode			
ENL lesion Change	"long-off to off" bridges		"long-on to on " bridges	
	N	%	N	%
present to absent	2	7.41%	1	1.02%
absent to present	0	0%	33	33.67%
present to present	2	7.41%	30	30.61%
absent to absent	3	11.11%	4	4.08%
present to no-data	12	44.44%	4	4.08%
absent to no-data	4	14.81%	2	2.04%
no-data to present	0	0%	20	20.41%
no-data to absent	1	3.70%	1	1.02%
no-data to no-data	3	11.11%	3	3.06%
Total	27		98	

Table 33 shows that ENL was documented to be active in 21.43% of the entries (last visit of the multiple-visit on-Thalidomide episode) of the "long-on to on " bridges, and increased to 86.73% of the exits (first visit of the subsequent on-Thalidomide episode) of the "long-on to on " bridges after being off Thalidomide for a period of time. ENL was documented to be inactive in 42.86% of the entries (last visit of the multiple-visit on-Thalidomide episode) of the "long-on to on " bridges, and decreased to 4.08% of the exits (first visit of the subsequent on-Thalidomide episode) of the "long-on to on " bridges after being off Thalidomide for a period of time. The data show that in the first visits of off-Thalidomide

episode following a multiple-visit off-Thalidomide episode (the exits of the "long-off to off" bridges), most of the ENL activity status were not recorded (62.96%). ENL was documented to be active in 55.56% of the entries (last visit of the multiple-visit off-Thalidomide episode) of the "long-off to off" bridges, and decreased to 14.81% of the exits (first visit of the subsequent off-Thalidomide episode) of the "long-off to off" bridges after being on Thalidomide for a period of time. The documented difference in the percentage of ENL being "inactive" between the entry and exit of a "long-off to off" bridge was less than 5% (25.93% to 22.22%).

Table 33. ENL activity status in the last visit of multiple-visit on (off) episodes and the first visit of the subsequent on (off) episodes

		last visit in on (off) episode		1st visit in subsequent on (off) episode	
on-Thalidomide episode to on-Thalidomide episode ("long-on to on " bridge)	ENL activity	N	%	N	%
	Active	21	21.43%	85	86.73%
	Inactive	42	42.86%	4	4.08%
	No data	35	35.71%	9	9.18%
	Total	98		98	
off -Thalidomide episode	ENL activity	N	%	N	%
to off -Thalidomide episode ("long-off to off " bridge)	Active	15	55.56%	4	14.81%
	Inactive	7	25.93%	6	22.22%
	No data	5	18.52%	17	62.96%
	Total	27		27	

Table 34 gives the frequency distribution of the change in ENL lesion status from the entries (last visit of the multiple-visit on (off)-Thalidomide episode) to the exits (first visit of the subsequent on (off)-Thalidomide episode) of "long-on to on " bridges and "long-off to off" bridges. "Active-to-inactive" happened in 0% of the "long-on to on " bridges. "Inactive-to-active" happened in 39.80% of the "long-on to on " bridges. "Active-to-active" happened in 25.51% of the "long-on to on " bridges.

Table 34. ENL activity status change from the last visit of multiple-visit on (off) episodes to the first visit of the subsequent on (off) episodes

	From the last visit of a multiple-visit on (off) episode to the first visit of the subsequent on (off) episode			
ENL activity Change	"long-off to off" bridges		"long-on to on " bridges	
	N	%	N	%
active to inactive	4	14.81%	0	0%
inactive to active	1	3.70%	39	39.80%
active to active	8	29.63%	25	25.51%
inactive to inactive	2	7.41%	2	2.04%
active to no-data	8	29.63%	2	2.04%
inactive to no-data	4	14.81%	1	1.02%
no-data to active	0	0%	27	27.55%
no-data to inactive	0	0%	2	2.04%
no-data to no-data	0	0%	0	0%
Total	27		98	

Table 35 shows that new ENL lesions were documented to be present in 10.20% of the entries (last visit of the multiple-visit on-Thalidomide episode) of the "long-on to on " bridges, and increased to 73.47% in the exits (first visit of the subsequent on-Thalidomide episode) of the "long-on to on " bridges after being off Thalidomide for a period of time. 69.39% of the entries (last visit of the multiple-visit on-Thalidomide episode) of the "long-on to on " bridges recorded no new ENL lesions, and 14.29% of the exits of the "long-on to on " bridges recorded no new ENL lesions after being off Thalidomide for a period of time, showing a decrease. The data show that in the first visits of off-Thalidomide episode following a multiple-visit off-Thalidomide episode (exits of the "long-off to off" bridge), most of the new ENL lesions status were not recorded (59.26%). 37.04% of the entries (last visit of the multiple-visit off-Thalidomide episode) of the "long-off to off" bridges recorded new ENL lesions, and 3.70% of the exits (first visit of the subsequent off-Thalidomide episode) of the "long-off to off" bridges recorded new ENL lesions after being on Thalidomide for a period of time, showing a decrease.

Table 35. New ENL lesions status in the last visit of multiple-visit on (off) episodes and the first visit of the subsequent on (off) episodes

		last visit in on (off) episode		1st visit in subsequent on (off) episode	
on-Thalidomide episode to on-Thalidomide episode ("long-on to on " bridge)	New Lesions	N	%	N	%
	Yes	10	10.20%	72	73.47%
	No	68	69.39%	14	14.29%
	No data	20	20.41%	12	12.24%
	Total	98		98	
off -Thalidomide episode to off -Thalidomide episode ("long-off to off" bridge)	New Lesions	N	%	N	%
	Yes	10	37.04%	1	3.70%
	No	12	44.44%	10	37.04%
	No data	5	18.52%	16	59.26%
	Total	27		27	

Table 36 gives the frequency distribution of the change in new ENL lesion status from the entries (last visit of the multiple-visit on (off)-Thalidomide episode) to the exits (first visit of the subsequent on (off)-Thalidomide episode) of "long-on to on " bridges and "long-off to off" bridges. "Yes-to-no" happened in 2.04% of the "long-on to on " bridges. "No-to-yes" happened in 52.04% of the "long-on to on " bridges and 0% of the "long-off to off" bridges.

Table 36. Change in New ENL lesion status from the last visit of multiple-visit on (off) episodes to the first visit of the subsequent on (off) episodes

	From the last visit of a multiple-visit on (off) episode to the first visit of the subsequent on (off) episode			
New lesion status Change	"long-off to off" bridges		"long-on to on " bridges	
	N	%	N	%
yes to no	2	7.41%	2	2.04%
no to yes	0	0%	51	52.04%
yes to yes	1	3.70%	7	7.14%
no to no	6	22.22%	10	10.20%
yes to no-data	7	25.39%	1	1.02%
no to no-data	6	22.22%	7	7.14%
no-data to yes	0	0%	14	14.29%
no-data to no	2	7.41%	2	2.04%
no-data to no-data	3	11.11%	4	4.08%
Total	27		98	

Reviewer's comments : Tables 31-36 show that the "long-on to on " bridges started (last visits of multiple-visit on episodes) with relatively low percentages of ENL lesion "present" (35.71%), ENL "active" (21.43%), and new ENL lesion "yes" (10.20%) and ended with much higher percentages of ENL lesion "present" (84.69%), ENL "active" (86.73%), and new ENL lesion "yes" (73.47%). The change in the percentage of ENL lesion from "present-to-absent" for the "long-on to on " bridges is 1.07%, while the change in the percentage of ENL lesion from "absent-to-present" for the "long-on to on " bridges is 13.67%. The change in the percentage of ENL activity from "active-to-inactive" for the "long-on to on " bridges is 0%, while the change in the percentage of ENL activity from "inactive-to-active" for the "long-on to on " bridges is 39.80%. The change in the percentage of new ENL lesion status from "yes-to-no" for the "long-on to on " bridges is 2.04%, while the change in the percentage of new ENL lesion status from "no-to-yes" for the "long-on to on " bridges is 52.04%.

Thus, Tables 31-36 show that the ENL lesion status, ENL activity status, and new ENL lesion status worsened in the majority of the "long-on to on " bridges, i.e., these ENL symptoms worsened after a discontinuation of Thalidomide.

§ 6. **Change from "baseline" within 2-3 weeks: All "truncated" multiple-visit episodes**

As shown in Table 8, the vast majority of the episodes were longer than 4 weeks, and about half of the on-Thalidomide episodes were longer than 60 weeks. Because of the nature of ENL, the efficacy variables recorded after the patients had been on Thalidomide for more than 60 weeks do not provide useful information on the efficacy of Thalidomide in the treatment of ENL. Therefore, at the suggestion of the reviewing medical officer, Dr. O'Connell (HFD-540), efficacy variables recorded 2-3 weeks after the first visit of an on (off)-Thalidomide episode are tabulated in § 6 and § 7 to compare the changes of the efficacy variables in more biologically meaningful time periods.

To analyze the efficacy variables at no more than two weeks after a patient started Thalidomide, multiple-visit episodes (on and off) were selected. Then all visits at two weeks or longer from the first visit in the episode were deleted, and only those visits which were less than two weeks from the first visit in the episode were retained. Thus, the multiple-visit episodes are truncated to be no more than two weeks long.

Then the efficacy variables recorded at the first and last visit of the truncated episodes were tabulated. The results of the analyses are listed in Tables 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, and 59. To analyze the efficacy variables at no more than 3 weeks after a patient started Thalidomide, multiple-visit episodes (on and off) were truncated to no more than 3 weeks long. The results of the analyses are listed in Tables 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, and 60.

The number of truncated off-Thalidomide episodes is too small (there are 15 such episodes if truncated to no more than 2 weeks, and 22 if truncated to no more than 3 weeks) to provide a meaningful comparison with the truncated on-Thalidomide episodes. Nevertheless, the efficacy variables recorded in the truncated off-Thalidomide episodes are tabulated to reflect the limited information from this data set.

Tables 37 and 38 show that the percentage of reported "present" of ENL lesion reduced from 84.38% to 70.31% of the on-Thalidomide episodes after no more than two weeks (Table 37), and from 84.4% to 66.06% of the on-Thalidomide episodes after no more than 3 weeks. The percentage of reported "absent" of ENL lesion increased from 3.13% to 14.06% of the on-Thalidomide episodes after no more than two weeks (Table 37), and from 2.75% to 15.60% of the on-Thalidomide episodes after no more than 3 weeks. The percentage of reported "present" of ENL lesion increased from 13.33% to 40.00% of the off-Thalidomide episodes after no more than two weeks (Table 37), and from 13.64% to 31.82% of the off-Thalidomide episodes after no more than 3 weeks.

Table 37. ENL Lesion status at the first and last visits of truncated multiple-visit episodes (truncated to at most 2 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	ENL lesion status	N	%	N	%
	Present	54	84.38%	45	70.31%
	Absent	2	3.13%	9	14.06%
	No data	8	12.50%	10	15.63%
	Total	64		64	
off Thalidomide	ENL lesion status	N	%	N	%
	Present	2	13.33%	6	40.00%
	Absent	6	40.00%	8	53.33%
	No data	7	46.67%	1	6.67%
	Total	15		15	

Table 38. ENL Lesion status at the first and last visits of truncated multiple-visit episodes (truncated to at most 3 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	ENL lesion status	N	%	N	%
	Present	92	84.40%	72	66.06%
	Absent	3	2.75%	17	15.60%
	No data	14	12.84%	20	18.35%
	Total	109		109	
off Thalidomide	ENL lesion status	N	%	N	%
	Present	3	13.64%	7	31.82%
	Absent	10	45.45%	12	54.55%
	No data	9	40.91%	3	13.64%
	Total	22		22	

Tables 39 and 40 show that the ENL lesion status of 12.50% of the on-Thalidomide episodes changed from present to absent in no more than 2 weeks (Table 39). The ENL lesion status of 13.76% of the on-Thalidomide episodes changed from present to absent in no more than 3 weeks (Table 40).

Table 39. Change in the ENL lesion status from first to last visit of truncated multiple-visit episode (truncated to at most 2 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL lesion Change	off-episode		on-episode	
	N	%	N	%
present to absent	0	0.00%	8	12.50%
absent to present	0	0.00%	0	0.00%
present to present	2	13.33%	41	64.04%
absent to absent	6	40.00%	1	1.56%
present to no-data	0	0.00%	5	7.81%
absent to no-data	0	0.00%	1	1.56%
no-data to present	4	26.67%	4	6.25%
no-data to absent	2	13.33%	0	0.00%
no-data to no-data	1	6.67%	4	6.25%
Total	15		64	

Table 40. Change in the ENL lesion status from first to last visit of truncated multiple-visit episodes (truncated to at most 3 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL lesion Change	off-episode		on-episode	
	N	%	N	%
present to absent	0	0.00%	15	13.76%
absent to present	0	0.00%	0	0.00%
present to present	3	13.64%	67	61.47%
absent to absent	10	45.45%	2	1.83%
present to no-data	0	0.00%	10	9.17%
absent to no-data	0	0.00%	1	0.92%
no-data to present	4	18.18%	5	4.59%
no-data to absent	2	9.09%	0	0.00%
no-data to no-data	3	13.64%	9	8.26%
Total	22		109	

Tables 41 and 42 show that the percentage of reported "active" of ENL activity status reduced from 82.81% to 42.19% of the on-Thalidomide episodes after no more than two weeks (Table 41), and from 85.32 % to 41.28% of the on-Thalidomide episodes after no more than 3 weeks (Table 42). The percentage of reported "inactive" of ENL activity status increased from 1.56% to 23.44% of the on-Thalidomide episodes after no more than two weeks (Table 41), and from 0.92% to 23.85% of the on-Thalidomide episodes after no more than 3 weeks (Table 42). The percentage of reported "active" of ENL activity increased from 20.00% to 26.67% of the off-Thalidomide episodes after no more than two weeks (Table 41), and from 18.18% to 22.73% of the on-Thalidomide episodes after no more than 3 weeks (Table 42).

Table 41. ENL Activity status at the first and last visits of truncated multiple-visit episodes (truncated to at most 2 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	ENL activity	N	%	N	%
	Active	53	82.81%	27	42.19%
	Inactive	1	1.56%	15	23.44%
	No data	10	15.63%	22	34.38%
	Total	64		64	
off Thalidomide	ENL activity	N	%	N	%
	Active	3	20.00%	4	26.67%
	Inactive	2	13.33%	5	33.33%
	No data	10	66.67%	6	40.00%
	Total	15		15	

Table 42. ENL Activity status at the first and last visits of truncated multiple-visit episodes (truncated to at most 3 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	ENL activity	N	%	N	%
	Active	93	85.32%	45	41.28%
	Inactive	1	0.92%	26	23.85%
	No data	15	13.76%	38	34.86%
	Total	109		109	
off Thalidomide	ENL activity	N	%	N	%
	Active	4	18.18%	5	22.73%
	Inactive	5	22.73%	9	40.91%
	No data	13	59.09%	8	36.36%
	Total	22		22	

Tables 43 and 44 show that the ENL activity status of 20.31% of the on-Thalidomide episodes changed from "active" to "inactive" in no more than 2 weeks (Table 43). The ENL activity status of 22.94% of the on-Thalidomide episodes changed from "active" to "inactive" in no more than 3 weeks (Table 44).

Table 43. Change in ENL activity status from first to last visit of truncated multiple-visit episode (truncated to at most 2 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL activity Change	off-episode		on-episode	
	N	%	N	%
active to inactive	0	0.00%	13	20.31%
inactive to active	0	0.00%	0	0.00%
active to active	9	60.00%	27	42.19%
inactive to inactive	2	13.33%	0	0.00%
active to no-data	0	0.00%	17	26.56%
inactive to no-data	0	0.00%	1	1.56%
no-data to active	1	6.67%	4	6.25%
no-data to inactive	3	20.00%	2	3.13%
no-data to no-data	0	0.00%	0	0.00%
Total	15		64	

Table 44. Change in ENL activity status from first to last visit of truncated multiple-visit episode (truncated to at most 3 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL activity Change	off-episode		on-episode	
	N	%	N	%
active to inactive	0	0.00%	25	22.94%
inactive to active	0	0.00%	0	0.00%
active to active	12	54.55%	49	44.95%
inactive to inactive	5	22.73%	0	0.00%
active to no-data	0	0.00%	28	25.69%
inactive to no-data	0	0.00%	1	0.92%
no-data to active	1	4.55%	5	4.59%
no-data to inactive	4	18.18%	1	0.92%
no-data to no-data	0	0.00%	0	0.00%
Total	22		109	

Tables 45 and 46 show that the percentage of reported "yes" of new ENL lesion status reduced from 68.75% to 7.81% of the on-Thalidomide episodes after no more than two weeks (Table 45), and from 66.06 % to 11.93% of the on-Thalidomide episodes after no more than 3 weeks (Table 46). The percentage of reported "no" of new ENL lesion status increased from 6.2 5% to 70.31% of the on-Thalidomide episodes after no more than two weeks (Table 45), and from 9.17% to 64.22% of the on-Thalidomide episodes after no more than 3 weeks (Table 46). The percentage of reported "yes" of new ENL lesion status increased from 6.67% to 13.33% of the off-Thalidomide episodes after no more than two weeks (Table 45), and from 4.55% to 9.09% of the on-Thalidomide episodes after no more than 3 weeks (Table 46).

Table 45. New ENL lesions status at the first and last visits of truncated multiple-visit episodes (truncated to at most 2 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	New Lesions	N	%	N	%
	Yes	44	68.75%	5	7.81%
	No	4	6.25%	45	70.31%
	No data	16	25.00%	14	21.88%
	Total	64		64	
off Thalidomide	New Lesions	N	%	N	%
	Yes	1	6.67%	2	13.33%
	No	4	26.67%	7	46.67%
	No data	10	66.67%	6	40.00%
	Total	15		15	

Table 46. New ENL lesions status at the first and last visits of truncated multiple-visit episodes (truncated to at most 3 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	New Lesions	N	%	N	%
	Yes	72	66.06%	13	11.93%
	No	10	9.17%	70	64.22%
	No data	27	24.77%	26	23.85%
	Total	109		109	
off Thalidomide	New Lesions	N	%	N	%
	Yes	1	4.55%	2	9.09%
	No	10	45.45%	14	63.64%
	No data	11	50.00%	6	27.27%
	Total	22		22	

Tables 47 and 48 show that the new ENL lesion status of 48.44% of the on-Thalidomide episodes changed from "yes" to "no" in no more than 2 weeks (Table 47). The new ENL lesion status of 46.79% of the on-Thalidomide episodes changed from "yes" to "no" in no more than 3 weeks (Table 48).

Table 47. Change in New ENL lesion status from first to last visit of truncated multiple-visit episode (truncated to at most 2 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
New lesion status Change	off-episode		on-episode	
	N	%	N	%
yes to no	0	0.00%	31	48.44%
no to yes	0	0.00%	0	0.00%
yes to yes	0	0.00%	4	6.25%
no to no	4	26.67%	3	4.69%
yes to no-data	1	6.67%	9	14.06%
no to no-data	0	0.00%	1	1.56%
no-data to yes	2	13.33%	1	1.56%
no-data to no	3	20.00%	11	17.19%
no-data to no-data	5	33.33%	4	6.25%
Total	15		64	

Table 48. Change in New ENL lesion status from first to last visit of multiple-visit episode (truncated to at most 3 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
New lesion status Change	off-episode		on-episode	
	N	%	N	%
yes to no	0	0.00%	51	46.79%
no to yes	0	0.00%	2	1.83%
yes to yes	0	0.00%	7	6.42%
no to no	10	45.45%	7	6.42%
yes to no-data	1	4.55%	14	12.84%
no to no-data	0	0.00%	1	0.92%
no-data to yes	2	9.09%	4	3.67%
no-data to no	4	18.18%	12	11.01%
no-data to no-data	5	22.73%	11	10.09%
Total	22		109	

Reviewer's comments : Tables 37-48 show that the truncated multiple-visit on-Thalidomide episodes started (first visit) with higher percentages of ENL lesion "present" , ENL "active" , and new ENL lesion "yes" , whereas, the truncated on-Thalidomide episodes ended (last visit) with lower percentages of ENL lesion "present", ENL "active" , and new ENL lesion "yes" . The multiple-visit off-Thalidomide episodes started with lower percentages of ENL lesion "present" , ENL "active" , and new ENL lesion "yes" than when they ended (last visit) . The ENL lesion status of 12.5% of the truncated on-thalidomide changed from "present" to "absent" after no more than 2 weeks , and 13.76% changed from "present" to "absent" after no more than 3 weeks. The ENL activity status of 20.31% of the truncated on-thalidomide changed from "active" to "inactive" after no more than 2 weeks , and 22.94% changed from "active" to "inactive" after no more than 3 weeks. The new ENL lesion status of 48.44% of the truncated on-thalidomide changed from "yes" to "no" after no more than 2 weeks , and 46.79% changed from "yes" to "no" after no more than 3 weeks.

§ 7. Change from "baseline": All truncated multiple-visit episodes in which neither prednisone nor clofazamine was used

In this section, the truncated multiple-visit episodes in which neither prednisone nor clofazamine was used are selected, and the efficacy variables recorded at the first and last visits of the truncated episodes are tabulated.

Tables 49 and 50 show that the percentage of reported "present" of ENL lesion did not change for the on-Thalidomide episodes after no more than two weeks (Table 49), and reduced from 85.37% to 78.05% of the on-Thalidomide episodes after no more than 3 weeks. The percentage of reported "absent" of ENL lesion increased from 0% to 6.25% of the on-Thalidomide episodes after no more than two weeks (Table 49), and from 2.44% to 9.76% of the on-Thalidomide episodes after no more than 3 weeks.

Table 49. ENL Lesion status at the first and last visits of multiple-visit episodes during which neither prednisone nor clofazamine was used (truncated to at most 2 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	ENL lesion status	N	%	N	%
	Present	28	87.50%	28	87.50%
	Absent	0	0.00%	2	6.25%
	No data	4	12.50%	2	6.25%
	Total	32		32	
off Thalidomide	ENL lesion status	N	%	N	%
	Present	1	25.00%	2	50.00%
	Absent	1	25.00%	1	25.00%
	No data	2	50.00%	1	25.00%
	Total	4		4	

Table 50. ENL Lesion status at the first and last visits of multiple-visit episodes during which neither prednisone nor clofazamine was used (truncated to at most 3 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	ENL lesion status	N	%	N	%
	Present	35	85.37%	32	78.05%
	Absent	1	2.44%	4	9.76%
	No data	5	12.20%	5	12.20%
	Total	41		41	
off Thalidomide	ENL lesion status	N	%	N	%
	Present	1	12.50%	2	25.00%
	Absent	5	62.50%	5	62.50%
	No data	2	25.00%	1	12.50%
	Total	8		8	

Tables 51 and 52 show that the ENL lesion status of 6.25% of the on-Thalidomide episodes changed from "present" to "absent" in no more than 2 weeks (Table 51). The ENL lesion status of 7.32% of the on-Thalidomide episodes changed from present to absent in no more than 3 weeks (Table 52).

Table 51. Change in ENL lesion status from first to last visit of multiple-visit episode during which neither prednisone nor clofazamine was used (truncated to at most 2 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL lesion Change	off-episode		on-episode	
	N	%	N	%
present to absent	0	0.00%	2	6.25%
absent to present	0	0.00%	0	0.00%
present to present	1	25.00%	25	78.13%
absent to absent	1	25.00%	0	0.00%
present to no-data	0	0.00%	1	3.13%
absent to no-data	0	0.00%	0	0.00%
no-data to present	1	25.00%	3	9.38%
no-data to absent	0	0.00%	0	0.00%
no-data to no-data	1	25.00%	1	3.13%
Total	4		32	

Table 52. Change in ENL lesion status from first to last visit of truncated multiple-visit episode during which neither prednisone nor clofazamine was used (truncated to at most 3 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL lesion Change	off-episode		on-episode	
	N	%	N	%
present to absent	0	0.00%	3	7.32%
absent to present	0	0.00%	0	0.00%
present to present	1	12.50%	30	73.17%
absent to absent	5	62.50%	1	2.44%
present to no-data	0	0.00%	2	4.88%
absent to no-data	0	0.00%	0	0.00%
no-data to present	1	12.50%	2	4.88%
no-data to absent	0	0.00%	0	0.00%
no-data to no-data	1	12.50%	3	7.32%
Total	8		41	

Tables 53 and 54 show that the percentage of reported "active" of ENL activity reduced from 87.50% to 40.63% of the on-Thalidomide episodes after no more than two weeks (Table 53), and from 87.80 % to 48.78% of the on-Thalidomide episodes after no more than 3 weeks (Table 54). The percentage of reported "inactive" of ENL activity increased from 3.13% to 18.75% of the on-Thalidomide episodes after no more than two weeks (Table 53), and from 2.44% to 17.07% of the on-Thalidomide episodes after no more than 3 weeks (Table 54).

Table 53. ENL Activity status at the first and last visits of truncated multiple-visit episodes during which neither prednisone nor clofazamine was used (truncated to at most 2 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	ENL activity	N	%	N	%
	Active	28	87.50%	13	40.63%
	Inactive	1	3.13%	6	18.75%
	No data	3	9.38%	13	40.63%
	Total	32		32	
off Thalidomide	ENL activity	N	%	N	%
	Active	2	50.00%	2	50.00%
	Inactive	0	0.00%	0	0.00%
	No data	2	50.00%	2	50.00%
	Total	4		4	

Table 54. ENL Activity status at the first and last visits of truncated multiple-visit episodes during which neither prednisone nor clofazamine was used (truncated to at most 3 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	ENL activity	N	%	N	%
	Active	36	87.80%	20	48.78%
	Inactive	1	2.44%	7	17.07%
	No data	4	9.76%	14	34.15%
	Total	41		41	
off Thalidomide	ENL activity	N	%	N	%
	Active	2	25.00%	2	25.00%
	Inactive	3	37.50%	3	37.50%
	No data	3	37.50%	3	37.50%
	Total	8		8	

Tables 55 and 56 show that the ENL activity status of 15.63% of the on-Thalidomide episodes changed from "active" to "inactive" in no more than 2 weeks (Table 55). The ENL activity status of 14.63% of the on-Thalidomide episodes changed from "active" to "inactive" in no more than 3 weeks (Table 56).

Table 55. Change in ENL activity status from first to last visit of multiple-visit episode during which neither prednisone nor clofazamine was used (truncated to at most 2 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL activity Change	off-episode		on-episode	
	N	%	N	%
active to inactive	0	0.00%	5	15.63%
inactive to active	0	0.00%	0	0.00%
active to active	4	100.00%	11	34.38%
inactive to inactive	0	0.00%	0	0.00%
active to no-data	0	0.00%	12	37.50%
inactive to no-data	0	0.00%	1	3.13%
no-data to active	0	0.00%	2	6.25%
no-data to inactive	0	0.00%	1	3.13%
no-data to no-data	0	0.00%	0	0.00%
Total	4		32	

Table 56. Change in ENL activity status from first to last visit of multiple-visit episode during which neither prednisone nor clofazamine was used (truncated to at most 3 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
ENL activity Change	off-episode		on-episode	
	N	%	N	%
active to inactive	0	0.00%	6	14.63%
inactive to active	0	0.00%	0	0.00%
active to active	5	62.50%	19	46.34%
inactive to inactive	3	37.50%	0	0.00%
active to no-data	0	0.00%	12	29.27%
inactive to no-data	0	0.00%	1	2.44%
no-data to active	0	0.00%	2	4.88%
no-data to inactive	0	0.00%	1	2.44%
no-data to no-data	0	0.00%	0	0.00%
Total	8		41	

Tables 57 and 58 show that the percentage of reported "yes" of new ENL lesion status reduced from 75.00% to 12.50% of the on-Thalidomide episodes after no more than two weeks (Table 57), and from 65.85 % to 19.51% of the on-Thalidomide episodes after no more than 3 weeks (Table 58). The percentage of reported "no" of new ENL lesion status increased from 3.13% to 62.50% of the on-Thalidomide episodes after no more than two weeks (Table 57), and from 9.76% to 58.54% of the on-Thalidomide episodes after no more than 3 weeks (Table 58).

Table 57. New ENL lesions status at the first and last visits of truncated multiple-visit episodes during which neither prednisone nor clofazamine was used (truncated to at most 2 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	New Lesions	N	%	N	%
	Yes	24	75.00%	4	12.50%
	No	1	3.13%	20	62.50%
	No data	7	21.88%	8	25.00%
	Total	32		32	
off Thalidomide	New Lesions	N	%	N	%
	Yes	1	25.00%	1	25.00%
	No	1	25.00%	1	25.00%
	No data	2	50.00%	2	50.00%
	Total	4		4	

Table 58. New ENL lesions status at the first and last visits of truncated multiple-visit episodes during which neither prednisone nor clofazamine was used (truncated to at most 3 weeks)

		1st visit in episode		last visit in episode	
on Thalidomide	New Lesions	N	%	N	%
	Yes	27	65.85%	8	19.51%
	No	4	9.76%	24	58.54%
	No data	10	24.39%	9	21.95%
	Total	41		41	
off Thalidomide	New Lesions	N	%	N	%
	Yes	1	12.50%	1	12.50%
	No	5	62.50%	5	62.50%
	No data	2	25.00%	2	25.00%
	Total	8		8	

Tables 59 and 60 show that the new ENL lesion status of 46.88% of the on-Thalidomide episodes changed from "yes" to "no" in no more than 2 weeks (Table 59). The new ENL lesion status of 43.90% of the on-Thalidomide episodes changed from "yes" to "no" in no more than 3 weeks (Table 60).

Table 59. Change in New ENL lesion status from first to last visit of truncated multiple-visit episode during which neither prednisone nor clofazamine was used (truncated to at most 2 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
New lesion status Change	off-episode		on-episode	
	N	%	N	%
yes to no	0	0.00%	15	46.88%
no to yes	0	0.00%	0	0.00%
yes to yes	0	0.00%	4	12.50%
no to no	1	25.00%	1	3.13%
yes to no-data	1	25.00%	5	15.63%
no to no-data	0	0.00%	0	0.00%
no-data to yes	1	25.00%	0	0.00%
no-data to no	0	0.00%	4	12.50%
no-data to no-data	1	25.00%	3	9.38%
Total	4		32	

Table 60. Change in New ENL lesion status from first to last visit of multiple-visit episode during which neither prednisone nor clofazamine was used (truncated to at most 3 weeks)

	From the first visit of a multiple-visit episode to the last visit of the same episode			
New lesion status Change	off-episode		on-episode	
	N	%	N	%
yes to no	0	0.00%	18	43.90%
no to yes	0	0.00%	1	2.44%
yes to yes	0	0.00%	5	12.20%
no to no	5	62.50%	3	7.32%
yes to no-data	1	12.50%	4	9.76%
no to no-data	0	0.00%	0	0.00%
no-data to yes	1	12.50%	2	4.88%
no-data to no	0	0.00%	3	7.32%
no-data to no-data	1	12.50%	5	12.20%
Total	8		41	

Reviewer's comments : Tables 49-60 show that the truncated multiple-visit on-Thalidomide episodes (during which neither prednisone nor clofazamine being used) started (first visit) with higher percentages of ENL lesion "present", ENL "active", and new ENL lesion "yes", whereas, the truncated on-Thalidomide episodes ended (last visit) with lower percentages of ENL lesion "present", ENL "active", and new ENL lesion "yes". The multiple-visit off-Thalidomide episodes started with lower percentages of ENL lesion "present", ENL "active", and new ENL lesion "yes" than when they ended (last visit). The ENL lesion status of 6.25% of the truncated on-thalidomide changed from "present" to "absent" after no more than 2 weeks, and 7.32% changed from "present" to "absent" after no more than 3 weeks. The ENL activity status of 15.63% of the truncated on-thalidomide changed from "active" to "inactive" after no more than 2 weeks, and 14.63% changed from "active" to "inactive" after no more than 3 weeks.

The new ENL lesion status of 46.88% of the truncated on-thalidomide changed from "yes" to "no" after no more than 2 weeks , and 43.90% changed from "yes" to "no" after no more than 3 weeks.

§ 8. **Dosage:**

Since this data came from medical records under IND11,359, and not from an adequate and well-controlled clinical trial, patients were not using fixed dosage of Thalidomide. However, for labeling purposes, a recommended dosage is required. In an effort to determine a recommended starting dose, the most frequently used dosage(s) were examined. The following tables list the frequencies of Thalidomide daily doses for all the visits (overall), first visit in an episode (starting dose), last visit in an episode (ending dose), doses at which patients recorded first change from ENL lesion being "present" to "absent" (doses at which patients recorded change for the better), doses at which patients recorded first change from ENL being "active" to "inactive" (doses at which patients recorded change for the better), and doses at which patients recorded first change from New ENL lesion status being "yes" to "no" (doses at which patients recorded change for the better). In all the tables, 100mg/day is the most frequently used dosage.

Table 61 lists the frequencies of Thalidomide daily dose for all the available visits in which the patients were taking Thalidomide.

Table 61 . Daily dose in all visits of on-Thalidomide episodes

daily dose (mg)	N(visits)	%
<15	6	0.4%
20	1	0.1%
25	2	0.1%
50	138	9.1%
100	989	65.3%
150	2	0.1%
200	347	22.9%
300	25	1.7%
400	5	0.3%
Total	1515	

Table 62 lists the frequencies of Thalidomide daily dose in the first visits of on-Thalidomide episodes. These were the starting doses for the patients in the on-Thalidomide episodes.

Table 62 . Daily dose in first visits of on-Thalidomide episodes

daily dose (mg)	N(visits)	%
<15	1	0.5%
20	1	0.5%
50	6	2.8%
100	165	76.7%
200	42	19.5%
Total	215	

Table 63 lists the frequencies of Thalidomide daily dose in the last visits of multiple-visit on-Thalidomide episodes. These were the doses for the patients at the end of on-Thalidomide episodes.

Table 63 . Daily dose in last visits of multiple-visit on-Thalidomide episodes

daily dose (mg)	N(visits)	%
25	1	0.6%
50	34	19.4%
100	114	65.1%
200	26	14.9%
Total	175	

In multiple-visit on-Thalidomide episodes, some patients had documented ENL lesion "present" at the beginning of the episode, then the status changed to "absent" in the episode. The daily dose were recorded when "absent " was first documented. The frequencies are listed in Table 64.

Table 64 . Daily dose at which recorded first change from ENL lesion being "present" to "absent"

daily dose (mg)	N(visits)	%
<15	1	0.6%
50	14	8.9%
100	107	68.2%
200	34	21.7%
300	1	0.6%
Total	157	

In multiple-visit on-Thalidomide episodes, some patients had documented "active" ENL at the beginning of the episode, and then the status changed to "inactive" in that episode. The daily dose was recorded when "inactive" was first documented. The frequencies are listed in Table 65.

Table 65 . Daily dose at which recorded first change from ENL being "active" to "inactive"

daily dose (mg)	N(visits)	%
<15	1	0.7%
25	1	0.7%
50	13	8.6%
100	103	68.2%
200	32	21.2%
300	1	0.7%
Total	151	

In multiple-visit on-Thalidomide episodes, some patients had documented new ENL lesion "yes" at the beginning of the episode, and then the status changed to "no" in that episode. The daily dose was recorded when "no" was first documented. The frequencies are listed in Table 66.

Table 66 . Daily dose at which recorded change from new ENL lesion being "yes" to "no"

daily dose (mg)	N (visits)	%
<15	1	0.9%
50	7	6.0%
100	81	69.8%
200	25	21.6%
300	2	1.7%
Total	116	

Reviewer's comments : Tables 61 through 66 indicate a starting dosage of 100 mg/day may be the most appropriate dose and that for some patients, titration to 200 mg/day may be required. This dose range included between 80% and 90% of the patient visits.

§ 9. **Scatter Plots of Indications and Drug Usage Over Time**

Scatter plots of the medical records for each patient are displayed and attached to this review as an appendix. At each point where drug use was recorded, these plots display the presence of three ENL indications (i.e., whether or not there are new lesions, whether ENL is present or not, and whether or not ENL is active) versus usage of three potentially useful drugs (thalidomide, clofazamine, and prednisone). There is one plot for each subject. The horizontal axis indicates the weeks since the start of the study, beginning with week one for that patient. A data point is indicated by a solid dot, and missing data is indicated by a circle. Drug usage is indicated by whether the patient is on or off the designated drug according to the medical records.

§ 10. **Reviewer's Summary and Conclusions (which may be conveyed to the sponsor):**

This data set is not from an adequate and well-controlled clinical trial. There was no control group for comparison, which seriously impacts the efficacy evaluation and risk associated with use of Thalidomide. The duration of Thalidomide treatment varied from 3 weeks to 18 years among patients. There was not only a serious problem due to missing data, especially in recording the severity of the disease such as lesion size, erythema status, tenderness and number of lesions, but also in recording advent events and safety associated with drug use. Virtually no adverse event data was collected. The percentage of missing data in these categories ranged from 86% to 94%. Less than 50% of the patients had multiple on and off Thalidomide episodes. Based on the above considerations, it was decided that summary statistics using patient as an observational unit could not be meaningfully performed.

Nevertheless, every effort was made to extract optimal information relative to dose versus benefit from these data set. The approach of treatment (on or off) episode as an observational unit was used. Statistical testing of hypotheses was not performed because of the nature of the data. Great caution should be exercised in the interpretation of these summary statistics. Taken at face value, these summary evaluations show that higher percentages of improvement in ENL based on lesion status, ENL activity status and new ENL lesion occurred during on- Thalidomide episodes than during off-Thalidomide episodes. Similarly, higher percentages of worsening in ENL based on the same variables occurred during off-Thalidomide episodes than during on-Thalidomide episodes. It is not known how much of these differences are due to concurrent medications such as prednisone and clofazamine, the waxing and waning of the disease, or to the massive amount of missing data. It should be noted that this analysis is

very likely to mask the fact that ENL could be present or active during the on-Thalidomide episodes even though it may not be present at the last visit. For this reason, another analysis was performed in which the change of ENL status was examined for a period of 2 to 3 weeks after the first visit of an on(off)-episode. The results showed some reduction in the percentage of reported "active" in ENL activity status and in the percentage of "yes" in new ENL lesion status (the magnitude of the reductions were less than those for the un-truncated episodes), and minimal change in the reported ENL lesion status for the truncated on-Thalidomide episodes. The sample size for the truncated off-Thalidomide episodes was too small to provide a meaningful comparison with the truncated on-Thalidomide episodes.

These data seem to indicate the use of Thalidomide may make a positive contribution to the treatment of ENL in terms of cutaneous lesions. Further, approximately 70% of the episodes in which favorable responses were recorded appeared to do so at a dose of 100 mg/day and an increase to 150 mg/day or 200 mg/day includes 80% to 90% of the episodes in which favorable responses were recorded. However, due to the total absence of any safety and adverse event data, no benefit to risk evaluation can be made. In the absence of safety information, the lowest possible dose should be used until more definitive safety information is provided.

Ping Gao Aug 7. 97

Ping Gao, Ph.D.
Mathematical Statistician, DOB IV

Aug 7, '97

Concur: Rajagopalan Srinivasan, Ph.D.
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8/7/97

Concur: Ralph Harkins, Ph.D.
Director, DOB IV

HFD 540
NDA 20-785
HFD-105/Dr. Weintraub
HFD-105/Ms Walling
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Dr. Vaughn
HFD-540/Dr. O'Connell
HFD-540/Mr. White
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-725/Dr. Gao

HFD-344/Dr. Carreras
Chron.

This review contains 38 pages of text and an appendix of graphs.
MS word/d: \nda\20-785\20-785.doc\Aug. 7, 97; Ping Gao /(301)-827-2083

121 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

STATISTICAL REVIEW AND EVALUATION.

NDA# 20-785

Applicant: Celgene Corporation

Name of Drug: Synovir (Thalidemide)

Documents Reviewed: Volume BZ dated April 1, 1997.

Type of Report: Stability review.

Chemistry Input: Wilson DeCamp, Ph.D. (HFD-830)

I. Introduction

The law requires an expiration dating period to be indicated on the container label for every drug on the market. The expiration dating period is defined as the time interval that a drug is expected to remain within the approved specifications after manufacture. Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic, and toxicological specifications. Assurances that the product in its container will be suitably stable for an anticipated shelf life must come from an accumulation of data on the packaged drug. These stability data involve selected parameters which, taken together, form the stability profile.

Usually, the degradation curve of a product characteristic can be adequately represented by a linear function of time. If the drug characteristic is expected to decrease (or increase) with time, the shelf life is estimated as the time period at which the lower (upper) 95% one sided confidence bound for the mean degradation curve intersects the acceptable lower (upper) specification limit. The confidence bound is obtained by using the ordinary least square method.

MODEL SELECTION: TESTS FOR POOLING STABILITY DATA.

Since different batches of a drug may have different degradation pattern, at least three batches are required to estimate batch-to-batch variability and to test the hypotheses that a single expiration dating period is justifiable for all batches. Batch similarity of the degradation curves is assessed by fitting linear regression models to the data of the individual batches and applying statistical tests for equality of slopes and/or intercepts to these models. If the degradation curves are

similar, it is preferable to pool the data to get a more accurate estimate of the expiration period. If batch-to-batch variability is small, the data from individual batches are combined into one overall estimate, which usually resulted in a longer expiration dating period. One of the following models is selected based on the results of the poolability tests:

Model 1. Common intercept, common slope;

Model 2. Common slope, separate intercept;

Model 3. Common intercept, separate slope;

Model 4. Separate intercept, separate slope.

Under Models 2-4, the final expiration dating period of the drug product is estimated by the minimum of the expiration dating periods of the individual batches.

EXTRAPOLATION BEYOND THE OBSERVED DATA

In the estimation of an expiration dating period, the observed data are used to fit a regression line and construct 95% bounds around the mean degradation line. The estimate of the expiration dating period is the point of the earliest intersection of the confidence interval with the upper or lower product specification limit. This estimate of an expiration period is simply forecasting of a time point when the mean drug characteristic is likely to be still within the prescribed range. For example, if the sponsor submitted data for 60 months, the assumption is made that the degradation pattern seen within 60 months will continue throughout the estimated expiry period. This assumption can only be verified by the collection of data over the total range of the requested expiration period and is not satisfied by the fact that the extrapolation provided for a long expiration period.

COMPUTATIONAL METHOD

Statistical analyses of the stability data were performed by the reviewer using 'Drug Stability Analysis Programs' created at CDER, FDA, revision of March 26, 1996. Two programs were used. The first program, STABEST.SAS, analyzes the stability data by fitting simple linear regression to the each batch data. Then the program runs tests for pooling data from several batches. Based on the tests, one of the Models 1-4 is chosen. The results of the program are presented for each batch in the form of the regression equation and estimated expiration period.

The second program, STABPLOT.SAS, plots the 95% confidence limits for the

selected characteristics of the drug.

II. Results.

The sponsor submitted data for the stability analysis for Thalidomide Capsules, 50mg. There are 3 batches: DEV2195, DEV2117, and DEV 2400. Each batch has 3 bottle sizes : 10 count, 100 count, 450 count. The trial (storage) conditions were: 40C/75% RH and 25C/60%RH .

This reviewer analyzed the data from the three batches in three bottle sizes and under two conditions using the FDA programs STABEST.SAS and STABPLOT.SAS. The following is the result of the stability analysis by the reviewer.

The poolability test for the three batches in three bottle sizes was not significant i.e. the three batches in three bottle sizes in the trial condition of 25 C/60% RH are poolable. Therefore, one regression line for the three batches in three bottle sizes in the trial condition of 25 C/60% RH with the same intercept and common slope were analyzed . In this case, the estimated expiry period for the drug is equal to — **months** .

Figure 1. Poolability test under 25C/60% RH

Drug Stability Analysis

NDA 20-785
Drug Name: Synovir
Storage Condition: 25 C/60% RH
Subset Data: thal25

Test of Batch Poolability (p-value cutpoint used: 0.25)

BY VARIABLE	SOURCE	SS	DF	MS	F	P
ASSAY	Com Int Com Slo	23.49	16	1.47	0.27	0.9898
	Sep Int Com Slo	17.51	8	2.19	0.40	0.8968
	Sep Int Sep Slo	5.97	8	0.75	0.14	0.9951
	Residual	49.78	9	5.53		

Note: 3 batches and 3 bottle sizes
Source:

Figure 2. Expiry period under 25C/60% RH

Drug Stability Analysis

NDA 20-785
Drug Name: Synovir
Storage Condition: 25 C/60% RH
Subset Data: thal25

Estimate of Expiry Period

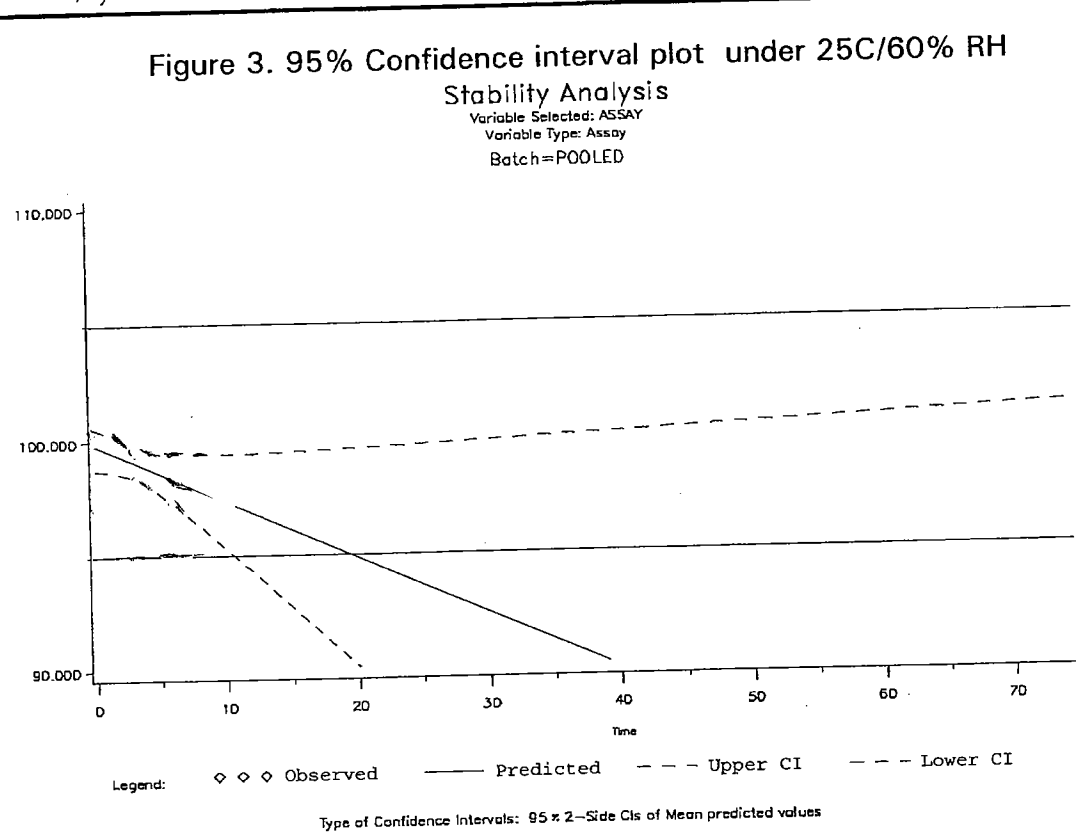
A (D) indicates that the parameter represents the dissolution activities
An (A) indicates that the parameter represents the assay values

By Variable	------- Fitted Line -------	Batch	Estimated Expiry Period
ASSAY(A)	C		1

Note: 3 batches and 3 bottle sizes
Source:

The plot of the regression line with their 95% confidence bounds is shown in Figure 3.

Figure 3. 95% Confidence interval plot under 25C/60% RH



The poolability test for the three batches in three bottle sizes in the trial condition of 40 C/75% RH was not significant i.e. the three batches in three bottle sizes in the trial condition of 40 C/75% RH are poolable. Therefore, one regression line for the three batches in three bottle sizes in the trial condition of 40 C/75% RH with the same intercept and common slope were analyzed . In this case, the estimated expiry period for the drug is equal to — **months** .

Figure 4. Poolability test under 40C/75% RH

Drug Stability Analysis

NDA 20-785
Drug Name: Synovir
Storage Condition: 40 C/75% RH
Subset Data: thal40

Test of Batch Poolability (p-value cutpoint used: 0.25)

BY VARIABLE	SOURCE	SS	DF	MS	F	P
ASSAY	Com Int Com Slo	30.32	16	1.90	0.77	0.6980
	Sep Int Com Slo	10.78	8	1.35	0.55	0.8071
	Sep Int Sep Slo	19.54	8	2.44	1.00	0.4630
	Residual	58.78	24	2.45		

Note: 3 batches in 3 bottle sizes
Source:

Figure 5. Expiry period under 40C/75% RH

Drug Stability Analysis

NDA 20-785
Drug Name: Synovir
Storage Condition: 40 C/75% RH
Subset Data: thal40

Estimate of Expiry Period

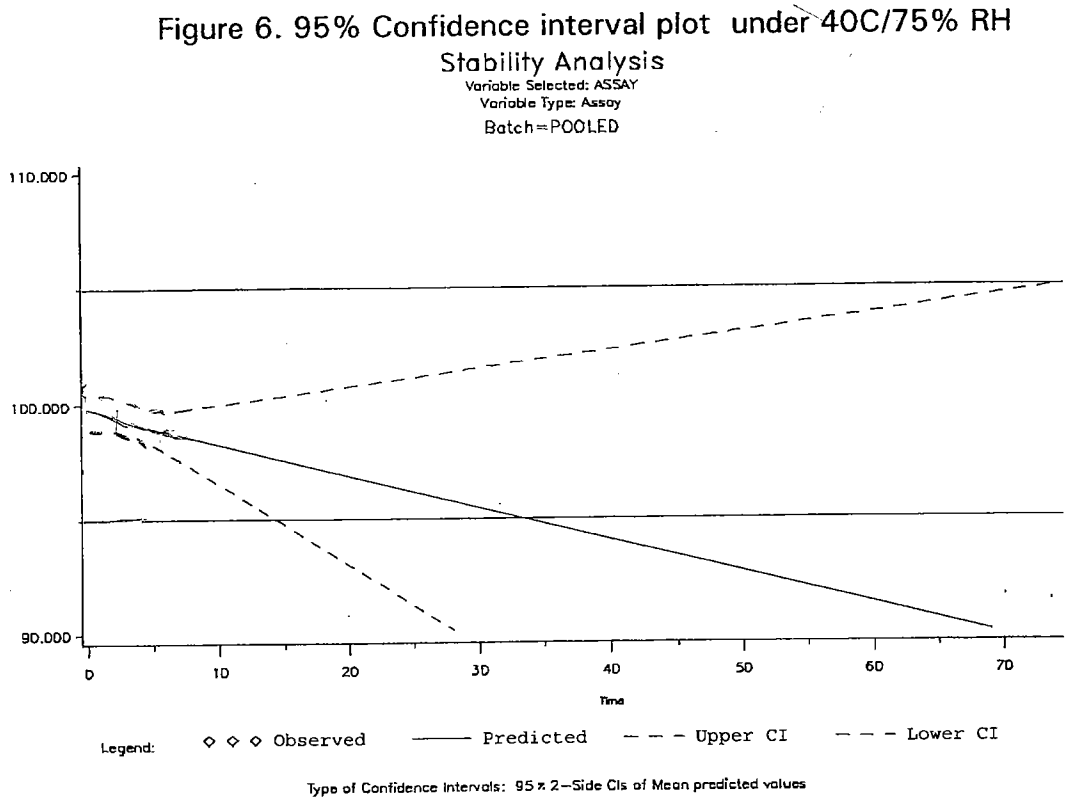
A (D) indicates that the parameter represents the dissolution activities
An (A) indicates that the parameter represents the assay values

By Variable	------- Fitted Line -------	Batch	Estimated Expiry Period
ASSAY(A)	[		]

Note: 3 batches in 3 bottle sizes
Source:

The plot of the regression line with their 95% confidence bounds is shown in Figure 6.

Figure 6. 95% Confidence interval plot under 40C/75% RH



Reviewer's Conclusion: ***Data from three batches (dev2117, dev2195, dev2400) in three bottle sizes (10, 100, 450) under trial condition 25C/60% RH were pooled by the reviewer. The expiry period is — months.***

Data from three batches (dev2117, dev2195, dev2400) in three bottle sizes (10, 100, 450) under trial condition 40C/75% RH were pooled by the reviewer. The expiry period is — months.

Ping Gao Aug 6, 97

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Archival NDA 20-785
HFD-540
HFD-540/Mr. White
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HFD-540/Dr. Walker
HFD-540/Dr. Vaughn
HFD-540/Dr. O'Connell
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-725/Dr. Gao
HFD-830/Dr. DeCamp
HFD-344/Dr. Carreras
Chron.
This review contains 9 pages.
MS Word/ d:\nda\20-785\stabilty\20-785st.doc\Aug. 6, 1997; Ping Gao (301)-827-2083