CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-785

Clinical Pharmacology and Biopharmaceutics Review

MEMO

To: Michael Weintraub, M.D., ODE-V Director

From: E. Dennis Bashaw, Pharm.D., HFD-540 PK Team Leader

Date: Thursday, April 23, 1998

Subject: Thalidomide and Semen

At the present time it is not known whether or not thalidomide is present in the ejaculate of males and what risk, if any, it poses. To address this issue the sponsor has incorporated language in the current package insert warning against sexual activity in males being treated with thalidomide unless barrier methods of contraception are used. Reproduced below is a verbatim copy of the statement addressing this issue from the Warnings section of the current label:

> *Because it is not known whether or not thalidomide is present in the ejaculate of males receiving the drug, males should use a condom when engaging in sexual activity which could possibly lead to pregnancy.*

Similar warnings are also incorporated in the opening "*Black Box*", in the warnings section and in the information for patients section.

From a pharmacokinetic standpoint the distribution of any drug into semen (to include the sperm itself and seminal fluid) is a distinct possibility. What is unknown is to what extent, if any, thalidomide may be concentrated in these fluids and the degree of risk posed to either conception or to a developing fetus.

While the absolute amount of thalidomide present in the semen may be small, it is still a risk and as there is no known safe level of thalidomide exposure it should be investigated. This could easily be done by obtaining semen samples from males in ongoing phase IV clinical trials of thalidomide. Provided that the subjects have reached steady-state plasma levels, the subjects could be asked to provide a semen sample during a routine clinic visit. It should be relatively easy to obtain a suitable number of samples for analysis which could then lead to clarification of the label in this matter.

CC: NDA 20-785   (ORIG),
HFD-540/DIV File
HFD-540/CSO/Walling
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy
HFD-344(Viswanathan)

Clinical Pharmacology/Biopharmaceutics Review

Thalidomide Capsules 50mg

Celgene, Inc.
Warren, NJ

NDA 20-785 SN-25, 32, &36
IND [   ]
Reviewer:E.D. Bashaw, Pharm.D.
APW

Submission Dates:
Sept. 22, 1997-SN-25
Dec. 23, 1997-SN-32
Jan. 7, 1998-SN-36
Jan. 14, 1998-N-136

Combined Review of an IND/NDA Amendments

I. Background

Thalidomide was found by the Agency to be approvable for use in the treatment of the cutaneous manifestations of Hansen's Disease in late 1997. Since then, there has been additional dialog between the Agency and the sponsor regarding the development of appropriate labeling for the product that will balance the usefulness of the compound with its known toxicity. Since the completion of the original NDA review, additional in vivo biopharmaceutic studies have been completed and their results have been submitted to the NDA and IND files for thalidomide. This review contains the results of three such trials: a drug interaction trial between thalidomide and oral contraceptives in women, a combined food-fasting/bioequivalency study, and a study in HIV-seropositive patients. As each of these studies contributes a piece of information to the final labeling, it was decided to review them together rather than separately.

II. Recommendation

The information contained in the trials that were submitted under the various supplemental applications and amendments has greatly added to the pharmacokinetic database present in this NDA. The lack of a pharmacokinetic drug interaction with oral contraceptives (while not ruling out the possibility of a pharmacodynamic interaction) is a key element to the contraceptive approach being developed for use in the "STEPS" monitoring program for thalidomide use. The labeling recommendations made in section IX of this review should be forwarded to both the thalidomide review team and to the sponsor for consideration and implementation. Two comments are also being provided to the sponsor for additional consideration.

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III.   Overview of Studies

As noted above this review combines a number of submissions into one review for purposes of both review efficiency and so as to make a single labeling recommendation. At the time of the original NDA approval for thalidomide a total of six pharmacokinetic studies were either in the planning stages or were still underway. With the completion of these three studies the only remaining unfinished pharmacokinetic studies are two long term studies in chronic ENL patients and a relative
bioavailability study using the marketed product and a to be developed oral solution formulation.

While this review does contain data from HIV-Seropositive patients, it should be remembered that thalidomide is not approved for use in these patients (the only approved indication is Erythema Nodosum Leprosum or ENL). Given that clinical studies in HIV patients on thalidomide revealed that the subjects HIV viral titer increases, i ᘡ

ᘡ As it is all of the studies contained in this review do add to the overall pharmacokinetic knowledge base of thalidomide in important areas and relevant portions of them should be included in the labeling.

IV.   Analytical Methods

In regards to the analytical validation, a total of three analytical methods were used during these trials by two different contractors. For thalidomide a high pressure liquid chromatography (HPLC) system was used by ᘡ   ᘡ for all three studies, while both the estrogen and progesterone samples in study PK-003 were analyzed by ᘡ   ᘡ via a gas chromatography/mass spectroscopy system (GC/MS). While sufficient analytical information

was submitted in the application to indicate that all of the assays were acceptable throughout the period of analysis, the different analytical reports varied greatly in quality.

The validation report for the thalidomide assay, while detailed, lacked tabulations of both the linearity and QC sample values across the entire assay run. Examination of the individual analytical runs yielded relevant QC data, but it was not properly collated and analyzed either from an intra- or inter-day perspective. In comparison the [   ] report was much better organized and provided the reviewer with data that were easily accessible for both the ethinyl estradiol and norethindrone components. Ultimately it was possible to evaluate the individual run data for the thalidomide assay, however, it required time and additional effort that should not have been needed (see Comment #1).

Representative validation data for the ethinyl estradiol and norethindrone components are attached as part of the study summary sheet for study PK-003. The corresponding data for thalidomide are interspersed throughout vol. 2 of the 9/22/97 submission. The analytical method and procedure used for each component of the oral contraceptive was properly validated. As for thalidomide while the assay was ultimately validatable, the data were not generally accessible.

V.   General Pharmacokinetics (In Vivo)
A. Submitted to NDA 20-785

Study Title: A pharmacokinetic evaluation of the effects of thalidomide on combination estrogen/progesterone hormones in premenopausal healthy women volunteers.

Objective: This study had one primary objective and two secondary objectives. The primary objective of this study was to evaluate the potential for thalidomide to interact with the metabolism of a combined estrogen/progesterone contraceptive. The secondary objectives were to evaluate the pharmacokinetics of thalidomide in healthy females and to evaluate the effect of chronic administration on thalidomide pharmacokinetics.

Study Methods

This study was designed primarily as a drug interaction protocol between thalidomide and oral contraceptives. A total of 12 healthy female subjects were enrolled in the trial and 10 subjects completed all phases of the trial (2 subjects, 1 in each group failed to return for the second phase of the trial and were excluded from the data analysis). Attached in Appendix I (page 2) is a patient demographic summary for all subjects. The trial itself was designed as a two period randomized crossover trial. Upon randomization the subjects received the following treatments in a random order:

Trt. 1 200mg of thalidomide as 4x50mg capsules everyday at bedtime for 20 days. On the morning of day 20 a single two tablet dose of Ortho-Novum 1/35 was taken.[1]

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[1]   The two tablet dose was done to simulate "pseudo" steady-state levels of the oral contraceptive and to ensure adequate plasma levels.

Trt. 2 On the morning of day 20 a single two tablet dose of Ortho-Novum 1/35 was taken.

The specific treatments and dosing pattern along with the associated plasma sampling strategy is somewhat complicated and is best summarized in the attached study summary sheet (Appendix I, page 3). The dosing is confusing because the sponsor continually shifts between a number of different numbering schemes when referring to the last day of the trial. The following may be helpful in understanding what was done during the thalidomide treatment arm:

Day 1-Confined to clinic PK samples collected after first bedtime thalidomide dose.
Day 2-Confined to clinic
Day 3-18-Outpatient dosing
Day 18-Confined to clinic, PK sample taken after 10pm dosing
Day 19-PK samples taken after dosing at 10pm
Day 20-Dosed with Ortho-Novum 1/35 at 8am
Day 22-Last PK sample taken subjects released for 9 1/2 day washout period

For Trt. 2, subjects were instructed to take nothing for the first 19 days of the trial and then to repeat the 2 tablet dose of Ortho-Novum 1/25 at 8am of day 20

The confusion comes in with the fact that the final collection of pk samples is sometimes called day 18 sampling and day 20 sampling. Attached as page 1 in Appendix I is a study summary sheet that provides additional details on dosing and treatments used.

Study Results

The primary objective of this study was to assess the impact of thalidomide at steady-state on the plasma levels of a combined oral contraceptive agent (Ortho-Novum 1/35). Attached as pages 3-17 in Appendix I are the mean and individual results and calculated pharmacokinetic parameter for both species. Reproduced below is a summary data table of pharmacokinetic parameters for both ethinyl estradiol and norethindrone.
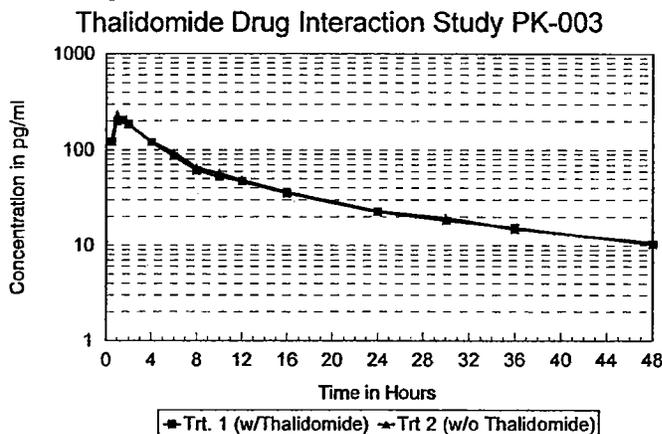
Mean Values +/- S.D.

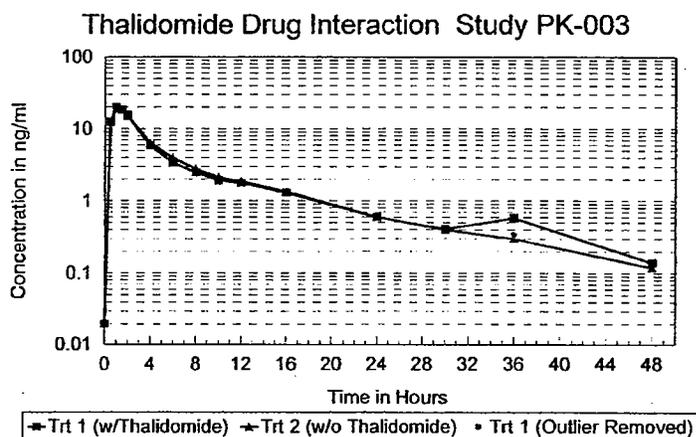| Parameters	Ethinyl Estradiol			Norethindrone		
	Trt 1	Trt 2	Ratio 1:2	Trt 1	Trt 2	Ratio 1:2
AUC_{0-t}*	1951+/-709	2033+/-787	0.96	94.8+/-35.5	97.5+/-32.5	0.973
AUC_{0-inf}*	2238+/-912	2365+/-1207	0.947	97.5+/-37.1	99.6+/-32.7	0.978
Cmax*	210+/-77	245+/-146	0.860	21.2+/-6	19.8+/-6.63	1.069
Tmax(hr)	1.3+/-0.26	1.2+/-2.6	1.076	1.2+/-0.35	1.3+/-0.35	0.920
Cl/F(L/hr)	18+/-6.87	17.7+/-7	1.019	12.6+/-7.91	11.7+/-6.38	1.078
MRT(hr)	20+/-4.38	19.4+/-7.65	1.028	8.55+/-2.98	8.63+/-2.57	0.99

*units for ethinyl estradiol are in ng/ml and ng*hr/ml
for norethindrone units are in pg/ml and pg*hr/ml.

Initial inspection of the parameter values and their associated variance suggests that co-administration of thalidomide to steady-state in Trt 1 did not significantly impact the metabolism or absorption of either the estrogen or progesterone component of the oral contraceptive. A graphical representation of the data is provided below:

Ethinyl Estradiol Mean Concentrations
Thalidomide Drug Interaction Study PK-003

Trt. 1 (w/Thalidomide) — Trt 2 (w/o Thalidomide)

Norethindrone Mean Concentrations
Thalidomide Drug Interaction Study PK-003

Trt 1 (w/Thalidomide) — Trt 2 (w/o Thalidomide) • Trt 1 (Outlier Removed)

Examination of the mean plots for either component reveals an almost 1:1 degree of super-imposition in the results, clearly suggesting the lack of a significant interaction. In examining the data for norethindrone, there did appear to be one point that was an outlier. At the 36hr sample for subject 8 the plasma sample was reported out as 2.7ng/ml (page 8, Appendix I). The previous sample for this subject at 30hrs was 0.1ng/ml and the following sample at 48hrs was 0.2ng/ml. This aberrant point could be due to analytical error (although the validation was acceptable) or due to a mishandling/mislabeling of samples. In any event this value clearly appears to be at odds with the rest of the data and if this value is removed and a new mean value

calculated for the 32hr timepoint a value of 0.34ng/ml is obtained. As this value is more in keeping with the observed trend in the data, it should be included in the final evaluation.

As to the statistical basis for an interaction, the sponsor a priori decided that a significant difference would be defined as a 35% change in the mean AUC values for either component. The basis for such a deviation from the normal 20% change allowed for bioequivalency determinations under OCPB policy was not provided by the sponsor. In order tô establish whether or not the tighter bioequivalency standards would be passed this, reviewer re-calculated the ln transformed 90% confidence intervals.

Ln Transformed 90% Confidence Intervals

Component	AUC_{0-t}	AUC_{0-inf}
Ethinyl Estradiol	89-101%	89.5-102.4%
Norethindrone	92.2-100.5%	92-102.2%

As can be seen from the table, even if one applies the stricter bioequivalency standards, there is not a significant difference between the resulting levels of either component of the oral contraceptive after steady-state dosing with thalidomide.

In terms of thalidomide, the results of this trial clearly indicate that there is minimal change in the observed pharmacokinetics of thalidomide in women following once daily dosing at bedtime. Attached as pages 11-17 in Appendix I are the mean and individual results and calculated pharmacokinetic parameter for thalidomide. A summary table of results from day 1 to day 18 is reproduced below from this data.

Mean Data +/- S.D.

Parameters	Compartmental Analysis		Non-Compartmental Analysis	
	Day 1	Day 18	Day 1	Day 18
AUC_{0-inf}(ug*hr/ml)	23+/-5.56	22.8+/-4.35	23.3+/-5.79	n.a.
AUC_{0-tau} (ug*hr/ml)	n.a.	n.a.	n.a.	22.6+/-4.48
Cmax (ug/ml)	n.a.	n.a.	2.3+/-5.1	2.3+/-0.33
Tmax (hr)	n.a.	n.a.	5.8+/-2	5.1+/-1.7
Cl/F (L/hr)	9.16+/-2.26	9.04+/-1.56	9.09+/-2.26	9.15+/-1.67
T1/2 (hr)	3.03+/-0.676	3.35+/-1.01	4.12+/-0.796	4.45+/-1.15

Examination of the mean parameter values indicates that over the 18 days of dosing in the trial there was no significant accumulation of thalidomide in women. This is in keeping with thalidomide's relatively short half-life of ~3.5-4.5hrs which would allow for from 6 to 7 half-lifes per 24hr dosing cycle (depending on the half-life estimate used). This lack of accumulation is also reflected in the unchanged values for AUC and Cmax from this trial across the period of dosing. Reproduced below is a graphical representation of the overlap or "super-imposition" of the day 1 and 18 plasma level time curves.

Thalidomide Mean Data
Day 1 vs. Day 18
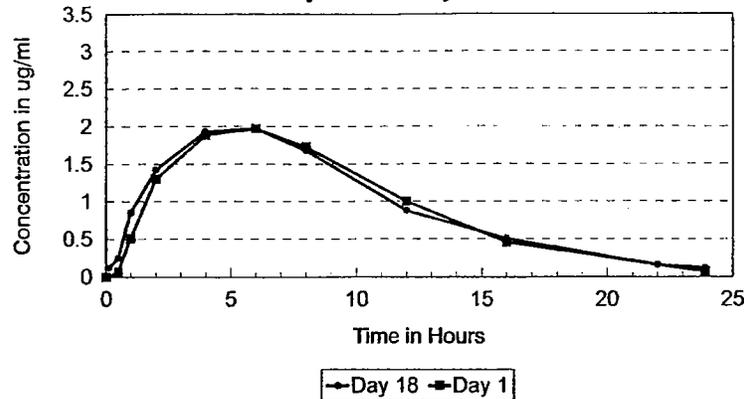
In terms of the "general" pharmacokinetics of thalidomide there is minimal drug accumulation associated with multiple-day dosing and the resulting absorption profile of thalidomide is variable and associated with a relatively late attainment of peak plasma concentrations. Whether or not this is due to the poor solubility of thalidomide in gastric fluid or is a formulation effect will require additional in vivo pharmacokinetic studies with a solubilized dosage form of thalidomide.

Study Title: A Single-Dose, Three-Way, Crossover Study of Two Formulations of Thalidomide and Relative Bioequivalence of Thalidomide With & Without Food When Administered Orally to Healthy Volunteers.

Objective: This study was in fact a combined study with two primary objectives. The first objective was to evaluate the effect of a high fat meal on the pharmacokinetics of thalidomide from the Celgene capsule. The second primary objective was to evaluate the degree of bioequivalence between Celgene's product and another form of thalidomide from Serral, S.A.

Study Methods

As mentioned in the study objectives section above this study is in fact two studies combined into one. In this study the sponsor is doing a classical fed vs. fasting evaluation of their dosage form. In addition to this they are then comparing the fasted treatment leg to another brand of thalidomide given in the fasted state. A total of 13 healthy male and female subjects were enrolled in the trial and successfully completed all treatment legs. Upon enrollment the subjects were randomized to receive the following treatments in a random order:

Trt. A   200mg of Celgene's thalidomide as 4x50mg capsules-fasted
Trt. B   200mg of Celgene'e thalidomide as 4x50mg capsules-fed
Trt. C   200mg of Serral, S.A.'s thalidomide as 2x100mg tablets-fasted

There was a 1 week washout between each phase of the study and for the fasted treatment legs the subjects were fasted for 10hrs. prior to dosing and for 4hrs. post-dosing. During the fed leg the subjects were required to consume the FDA High Fat Breakfast immediately prior to dosing. Attached in Appendix I as page 18 is the study summary sheet for this trial which provides additional detail regarding dosing, demographics, and pharmacokinetic sampling.

Study Results

The results of this study will be presented separately to keep the conclusions from each primary objective separate. Attached in Appendix I as pages 19-21 are the detailed results of the fed/fasted portion of the trial. A summary data table extracted from these results is reproduced below.

Mean Values +/- S.D.

Parameters	Celgene's Product Fasted	Celgene's Product Fed	ln Transformed 90% Confidence Intervals
AUC_{0-t} (ug*hr/ml)	23+/-5.11	22.1+/-4.29	87.7-103.1%
AUC_{0-inf} (ug*hr/ml)	24.7+/-5.13	23.5+/-3.73	88.8-102.3%
Cmax (ug/ml)	1.99+/-0.41	2.17+/-0.509	95.7-121.6%
Tmax (hrs.)	4+/-1.13	6.08+/-2.33	--
MRT (hrs.)	10.4+/-2.34	10.9+/-1.96	--

A graphical representation of these data is attached (Appendix 1, pg. 19). While this type of study is descriptive in nature only (i.e. passing a confidence interval is not required), the fact that one can demonstrate bioequivalency between the products is re-assuring. What is surprising from this analysis is the wide disparity seen in Tmax (4hrs. vs. 6hrs.). One does not usually associate this type of difference with bioequivalent drug products or treatments unless there is a lag time associated with absorption (as is the case with thalidomide). Reproduced below is a graphical representation of the Tmax distribution for each treatment leg.

Box and Whisker Plot of Tmax

CFASTED=Celgene Fasted, CFED=Celgene Fed

25 cases 1 missing cases
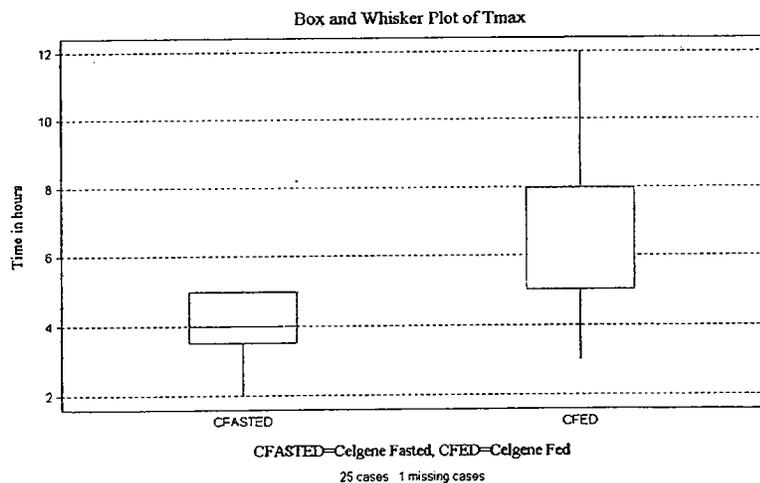
Examination of these data clearly shows that there is a definite shift in time to peak concentration (i.e. Tmax) caused by food. The clinical significance of this is questionable given that the two treatments are "bioequivalent" to each other in "rate and extent of absorption" and that the magnitude of the difference (1hr) relative to the dosing interval (q24hr) is a very small one. For completeness this shift in time should be noted in the package insert.

As for the bioequivalency determination between the Celgene product and the Serral, S.A. product, the following summary table drawn from the data contained in Appendix I (pages 22-25) provides sufficient information to find the products to be bioinequivalent.

Mean Values +/- S.D.

Parameters	Celgene's Product Fasted	Serral's Product Fasted	ln Transformed 90% Confidence Intervals
AUC_{0-t} (ug*hr/ml)	23+/-5.11	19.05+/-4.26	112.7-132.51%
AUC_{0-inf} (ug*hr/ml)	24.7+/-5.13	22.66+/-4.45	102.5-117.5%
Cmax (ug/ml)	1.99+/-0.41	1.05+/-0.31	170.3-210.1%
Tmax (hrs.)	4+/-1.13	6.23+/-1.88	--
MRT (hrs.)	10.4+/-2.34	21.37+/-8.17	--

What is interesting in these data is the finding of bioinequivalence at AUC0-t and equivalence at AUC0-inf. This suggests that absorption of thalidomide from the Serral, S.A. product is slow and prolonged. In an effort to look at this issue further the reviewer took advantage of the fact that thalidomide follows one-compartment pharmacokinetics and conducted a mean Wagner-Nelson analysis (fractional absorption over time) for all three treatments in this study. The graphical results of the analysis are presented below.

Thalidomide Bioequivalency
Mean Wagner-Nelson Analysis

-●-Celgene Fasted -■-Celgene Fed -▲-Serral Fasted
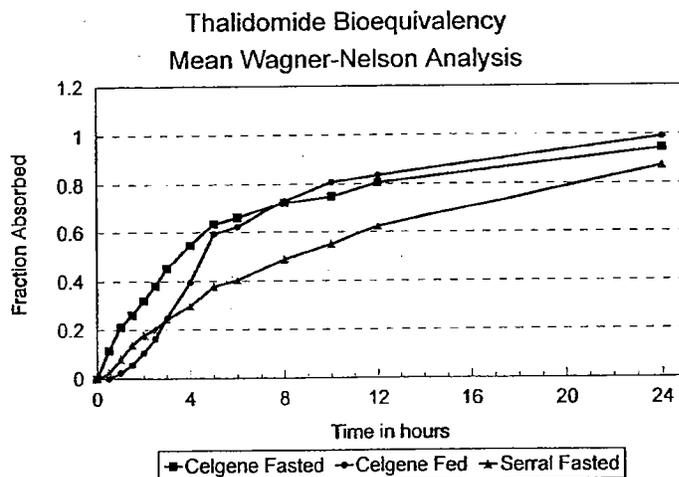
The results of this analysis clearly show that the Serral, S.A. product is absorbed much slower than either the fed or fasted Celgene legs. This accounts for the lower Cmax, the long MRT, and the long "apparent" half-life of elimination (13.5hrs vs. 5.8hrs. for Celgene's fasted leg). In regards to Celgene's fed and fasted legs, this analysis clearly shows a significant lag in absorption over the first 2-3hrs of the fed leg that is eventually made up for by 5 hrs. This rapid

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absorption during the fed leg at the very time that the fasted leg is peaking explains the finding of bioequivalency for Cmax between the products even though there is a difference in time to peak levels.

B. Submitted to IND · L   ⅃

Study Title: A Single-Dose, Two-Way, Crossover Study of Thalidomide 100mg and 200mg (as 50mg capsules) Administered Orally to Fasting Male Volunteers Who are HIV-Seropositive.

Objective: The primary objective of this study was to evaluate the pharmacokinetic profile of thalidomide in HIV-Seropositive patients following single 100 and 200mg doses.

Study Methods:

This study was designed as a straight-forward demonstration of dose-proportionalitiy in an HIV-Seropositive patient population. Patients enrolled in this trial had to be otherwise healthy HIV-Seropositive males. Even with the requirement that the subjects be "healthy" the 16 subjects enrolled in this trial were on a total of 16 different medications at enrollment ranging from anti-retroviral therapy to asthma inhalers. Attached as pages 26-28 are the study summary sheets describing the design, dosing, and sampling features of this trial and a more detailed table of demographics and concomitant medication usage.

Upon enrollment in the trial, the subjects were randomized to receive the following treatments in a random order with a 1 week washout period between doses:

Trt. A Thalidomide 100mg as 2x50mg capsules.
Trt. B Thalidomide 200mg as 4x50mg capsules.

Study Results

The individual and mean data and derived pharmacokinetic parameters from this study are attached in Appendix I as pages 29-34. A summary table of the results extracted from these tables is reproduced below:

Parameters	Treatment A 2x50mg Caps.	Treatment B 4x50mg Caps. *	log Transformed 90% Confidence Intervals
AUC_{0-t} (ug*hr/ml)	8.76+/-1.67	9.12+/-0.23	101-108%
AUC_{0-inf} (ug*hr/ml)	9.76+/-1.62	9.69+/-1.77	97-102%
Cmax (ug/ml)	1.15+/-0.24	0.963+/-0.23	74.77-91.3%
Tmax (hrs.)	2.5+/-1.5	3.3+/-1.4	--
MRT (hrs.)	8.23+/-2.0	8.99+/-1.84	--

*normalized to a 100mg dose

The results of this study are very much in keeping with what was seen in the original dose proportionality study in the NDA (PK-004). PK-004 looked at dose proportionality over a range of doses from 50-400mg in 14 healthy subjects. In that study, a dose-related decrease in Cmax was seen. At the time that PK-004 was reviewed this decline in Cmax was attributed to the poor aqueous solubility of thalidomide and the attendant solubility problems associated with giving multiple dosage units of a poorly soluble drug. If one plots the Cmax/dose data from this study along with those original results one would get the following figure.

Thalidomide Cross-Study Comparison
Cmax/Dose vs. Dose
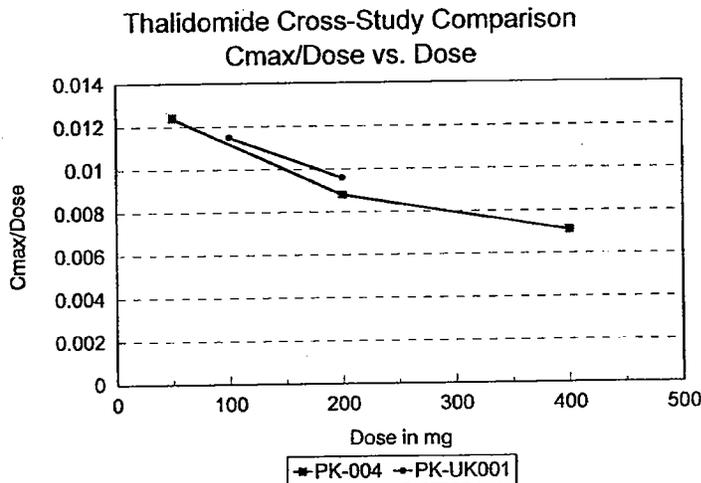
While the two lines do not overlap each other, the high degree of association between the lines suggests that the same mechanism is in play here. When one considers that this plot makes no correction for volume or body weight factors it makes the likelihood even higher. This suggests that the lack of dose proportionality for Cmax seen in HIV-Seropositive patients is most likely due to solubility issues related to thalidomide and not a physiologic or disease based change in absorption.

VI.   Secondary Cross-Study Analysis

With the completion of these three studies, the pharmacokinetic database for thalidomide becomes extensive enought to consider use of the data to answer secondary pharmacokinetic questions. To that end in their submissions the sponsor (Celgene) has introduced a number of pharmacokinetic issues that it believes can be answered from this data. Specifically, in their submissions they refer to gender, diurnal variation, and smoking status as "co-variates" that can be addressed through examination of the data in a cross study manner. Each of these issues and the supporting data will be considered in turn.

Gender

As part of the enrollment scheme of study PK-006 (fed vs. fasted) both male and female subjects were enrolled in the trial. A total of 5 males and 8 females were enrolled in the trial. Using the data from the fasted Celgene treatment leg the following results were obtained:

Mean Values +/-S.D.

Parameters	Males N=5	Females N=8
AUC_{0-t} (ug*hr/ml)	22.2+/-8.05	23.6+/-2.61
AUC_{0-inf} (ug*hr/ml)	23.4+/-5.35	25.5+/-2.32
Cmax (ug/ml)	1.81+/-0.38	2.1+/-0.41
Tmax (hrs.)	4.5+/-0.58	3.75+/-1.28
MRT (hrs.)	10.9+/-2.28	10.1+/-2.48
T1/2 (hrs.)	5.35+/-0.86	6.09+/-2.1

A statistical analysis was not undertaken on the data due to both the small numbers of subjects involved and the unbalanced nature of the study. Even so, there does not appear to be a significant deviation in the pharmacokinetics of thalidomide between males and females. Unfortunately the study report did not report individual weights for each subject so it was not possible to attempt any normalization for parameters such as Cmax in which volume (which is highly correlated with body weight) plays a major role in determining the parameter value.

Acknowledging the lack of sufficient numbers to make a definitive determination, it appears that if there is a statistically significant difference in pharmacokinetics between gender, it does not appear to be very large.

Diurnal Variation

One of the unusual features of thalidomide is that it is being used in many different areas for indications that it was never inititally developed for. One of the dose limiting toxicities of thalidomide is that it is a sedative. The consistent finding in all of the PK studies in terms of adverse events is feelings of drowsiness, sleepiness, fuzzy thinking, etc.. Ideally the way to dose thalidomide would be at bedtime to minimize the impact of this "side effect" and to harness it as a positive. Up until the oral contraceptive trial (PK-003) all dosing with thalidomide was done in the morning and the patients were in a sitting position. In PK-003 the patients took their dose two hours prior to bedtime. By comparing the data in these women with the data from women in PK-006 it should be possible to assess the degree of impact of diurnal variation albeit in a parallel, cross-study manner.

Mean Values +/-S.D.

Parameters	Females N=10 PK-003	Females N=8 PK-006
AUC_{0-t} (ug*hr/ml)	21.4+/-5.51	23.6+/-2.61
AUC_{0-inf} (ug*hr/ml)	23.3+/-5.79	25.5+/-2.32
Cmax (ug/ml)	2.3+/-5.1	2.1+/-0.41
Tmax (hrs.)	5.8+/-2	3.75+/-1.28
MRT (hrs.)	8.98+/-1.54	10.1+/-2.48
T1/2 (hrs.)	4.12+/-0.796	6.09+/-2.1

Examination of these data suggests that administration of thalidomide within two hours of bedtime is associated with a small reduction in bioavailability and a prolongation of time to peak concentrations. Like in the instance of co-administration of food the actual peak concentrations do not seem to be affected, only the time to achieve them. The impact of these changes in regards to the effect of thalidomide is unknown. The use of thalidomide in this manner is an issue to be considered given its known sedative properties.

Smoking

Unlike the other two issues (gender and diurnal variation) smoking is not an issue that has much pharmacokinetic interest with thalidomide. This lack of interest is due in part to the results of in vitro testing which revealed at the time of NDA approval the lack of thalidomide participation in CYP450 mediated metabolism and the theory that the primary route of metabolism is via non-enzymatically mediated hydrolysis. Even so in study PK-UK001, 9 of the 14 subjects who were enrolled in the trial smoked cigarettes (amount per day unknown). When the data in this trial are parsed along the lines of smoker vs. non-smoker, the following table can be developed:

Mean Value +/- S.D.

Parameters	100mg Dose Level		200mg Dose Level	
	Non-Smoker	Smoker	Non-Smoker	Smoker
$AUC_{0\text{-inf}}$ (ug*hr/ml)	10.4+/-1.21	9.39+/-1.76	20.1+/-2.85	19+/-4.01
Cmax (ug/ml)	1.17+/-0.26	1.15+/-0.25	1.95+/-0.38	1.91+/-0.53
Tmax (hrs.)	2.7+/-2.1	2.4+/-1.2	4.2+/-0.84	2.7+/-1.5
MRT (hrs.)	9.25+/-3.02	7.66+/-1.2	9.36+/-1.22	8.78+/-2.16
T1/2 (hrs.)	5.35+/-1.52	4.58+/-0.68	5.46+/-0.37	5.1+/-1.52
Cl/F (L/hr.)	9.7+/-1.17	10.9+/-1.6	10.1+/-1.38	10.8+/-1.68

The data themselves and the sponsor's use of them raises more questions than it answers. While there does not appear (again) to be a significant difference between the smokers and non-smokers, the sponsor's analysis of the data stops with the construction of a table. The sponsor does not identify the individual subject in either group nor do they provide the means to identify the patients. No statistical analysis of the data is attempted by the sponsor and the information itself is poorly documented.

The lack of detail in all of these "secondary" comparisons severely limits the ability of this reviewer to make a definitive finding one way or the other for any of these "secondary analysis" isues raised by the sponsor (see Comment #2).

VII.   Conclusions

1.   The pharmacokinetics of a combined estrogen/progesterone oral contraceptive are not altered by pre-treatment for 20 days with thalidomide.

2. Following 20 days of dosing in women, the pharmacokinetic profile of thalidomide is unchanged.

3. Administration of Celgene's product with a high fat meal causes a significant delay in the time required to attain peak plasma concentrations but does not affect the peak concentrations themselves. Food has no affect on the extent of absorption of thalidomide.

4. Serral, S.A.'s brand of thalidomide tablets is bioinequivalent to Celgene's capsules.

5. HIV-Seropositive males display similar pharmacokinetics to those seen in other healthy populations. The lack of Cmax dose-proportionality between 100 and 200mg is in keeping with the data from the original NDA submission.

6. Secondary analysis in a cross-study fashion suggests that there is not a significant gender difference in the pharmacokinetics between males and females.

7. The utility of cross-study comparisons in terms of smoking status and diurna variation needs additional analysis.

VIII. Review Comments

1.) The analytical reports prepared for thalidomide lacked an overall summary of the QC samples run before and after each subjects samples. Although the results for each run were interspersed throughout the report, the lack of either an inter-day assessment of the QC results or the variance seen in the intra-day samples across runs was needlessly wasteful of review time. In future submissions the contract lab should be required to provide such results as part of their validation report.

2.) The sponsor has provided some preliminary cross-study analysis of data related to gender, diurnal variation, and smoking status on the pharmacokinetics of thalidomide. At the present time an insufficient level of detail has been provided to address these issues directly. The sponsor should re-visit these issues by clearly identifying which individuals in each study belong to the appropriate sub-group and then provide additional statistical analysis (box-whisker plots, distribution plots, etc.) to support their conclusions.

IX. Labeling Comments

Using as our internal standard the Oct. 14, 1997 proposed thalidomide label, most if not all of the information contained in the studies reviewed here has already been added to the proposed label. The sponsor did this by adapting the FDA's version to incorporate the new material. In fact, very few changes/edits were proposed by the sponsor in this version of the label. Using that label as a numbering guide the following revisions are proposed:

line 106 (part of Table I)

add "%" sign to 44.1 and 52.6, also close parentheses at end of row
(i.e. last row in table should read) 400mg 46.6 (44.1%) 3.44(52.6%) 5.7 (27%) 6.86 (17%)

<u>lines 129-132</u>

should be replaced with the following text:

Special Populations

There is no apparent significant difference in measured pharmacokinetic parameters between healthy human C   J and HIV-seropositive subjects following the single dose administration of THALOMID (thalidomide capsules).

<u>ADD as a sub-category of special populations</u>

Hansen's Disease: Analysis of data from a small study in Hansen's patients suggested that these patients, relative to healthy subjects, may have an increased bioavailabilty for thalidomide. This increase C   J is reflected both in an increased area under the curve and in increased peak plasma levels C   J The significance of this increase is unknown.

lines 273-276 REVISE as indicated

Oral Contraceptive: C

J

[This revision attempts to convey that while thalidomide was at steady-state, only a single OC dose was given. Also while 12 females were enrolled in the study, only 10 successfully completed it.]

4/5/98

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-540)
Division of Pharmaceutical Evaluation-III

Secondary Review, John Lazor, Pharm.D.   *Janice Barnett Jenkins*
Peer Review
4-13-98

CC: NDA 20-785 (ORIG),
HFD-550/DIV File
HFD-550/CSO/Walling/White
HFD-880(Bashaw)
HFD-880(DIV File)
CDR. ATTN: B. Murphy
HFD-344(Viswanathan)

APPENDIX I

**Appears This Way
On Original**

NDA/IND# 20-785   Suppl/Amend.#   25 Submission Date: 9/22/97   Volume: n.a.

Study Type: Drug Interaction   Study #   PK-003

Study Title: A pharmacokinetic evaluation of the effects of thalidomide on combination estrogen/ progesterone hormones in premenopausal healthy women volunteers

Clinical Investigator Site ⌐   ⌐   Analytical Species Site ⌐   Thalidomide ⌐   Norethindrone & Ethinyl Estradiol

Single Dose: Y   Multiple Dose: Y   Washout Period: 9 1/2 days

Cross-Over Y   Parallel ___   Other Design: Drug Interaction

Fasted Y   Food Study N   FDA High Fat Breakfast n.a.

If fasted, how long (hrs.)? 4hrs

Subject Breakdown

Normal Y   Patients N   Young Y   Elderly N   Renal N   Hepatic N

	Subject Type	Females	Group All	N= 12	M= 0	F= 12
Weight	Mean 63 Range	48.6-77.6kg	Group	N=	M=	F=
Age	Mean 33 Range	22-44yrs.	Group	N=	M=	F=

Treatment Group	Dosing Period	Dose	Dosage Form	Strength	Lot#	Lot Size
A. (Thalidomide)	Days 1-21qhs	200mg	capsule	4x50mg	DEV2400	[ ]
(Ortho-Novum)	Day 20 (8am)	1/35	tablet	1mg norethindrone 35mcg ethinyl estradiol	26C503ABC	Unknown
B. (Ortho-Novum)	Day 20 (8am)	1/35	tablet		26C503ABC	Unknown

Plasma Sampling Times

Thalidomide	Prior to dose and at 0.5, 1, 2, 4, 6, 8, 12, 16, and 24hours on days 1 and 20. Trough samples were also collected 2 hours prior to the 19th, 20th, and 21st doses. (during Trt 1, only)
Norethindrone & Ethinyl Estradiol	Prior to dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48hrs after dosing. (during Trt 1 & 2 Day 20 only)

Assay	Thalidomide	Norethindrone	Ethinyl Estradiol
Method:	HPLC	GC/MS	GC/MS
Sensitivity	0.1ug/ml	0.050ng/ml	2pg/ml
Accuracy*	see text	|0.15ng|0.16ng|4.1%|,|1ng|1.06ng|3.5%|, |10ng|10.6ng|5.5%|	|6pg|5.9pg|7.1%|,|40pg|39.9pg|3.2%|, |400pg|398pg|4.6%|

Labeling Claims From Study   Following 20 days of dosing with thalidomide there was no evidence of a drug interaction between thalidomide or either component of a combined estrogen/progesterone oral contraceptive. In addition there was no alteration in the pharmacokinetics of thalidomide over 20 days of once daily dosing.

*Assay Accuracy Data= |QC Target|Detected|%CV|

01

Table 1   Summary of Demographic Information

Variable	Summary Statistic		All Subjects
Age (years)	Mean		33.2
	S.D.		7.4
	Minimum		22.0
	Maximum		44.0
	Number		12.0
Height (inches)	Mean		65.3
	S.D.		2.2
	Minimum		60.0
	Maximum		60.5
	Number		12.0
Weight (pounds)	Mean		139.0
	S.D.		23.0
	Minimum		107.0
	Maximum		194.0
	Number		12.0
Gender	Number	Female	12.0
Race	Number	Caucasian	10.0
	Number	Hispanic	2.0
Frame Size	Number	Large	1.0
	Number	Medium	5.0
	Number	Small	6.0

= 63 kg

22

0.2

Ethinyl Estradiol Mean Concentrations
Thalidomide Drug Interaction Study PK-003

Concentration in pg/ml

Time in Hours

- Trt. 1 (w/Thalidomide) - Trt 2 (w/o Thalidomide)

03
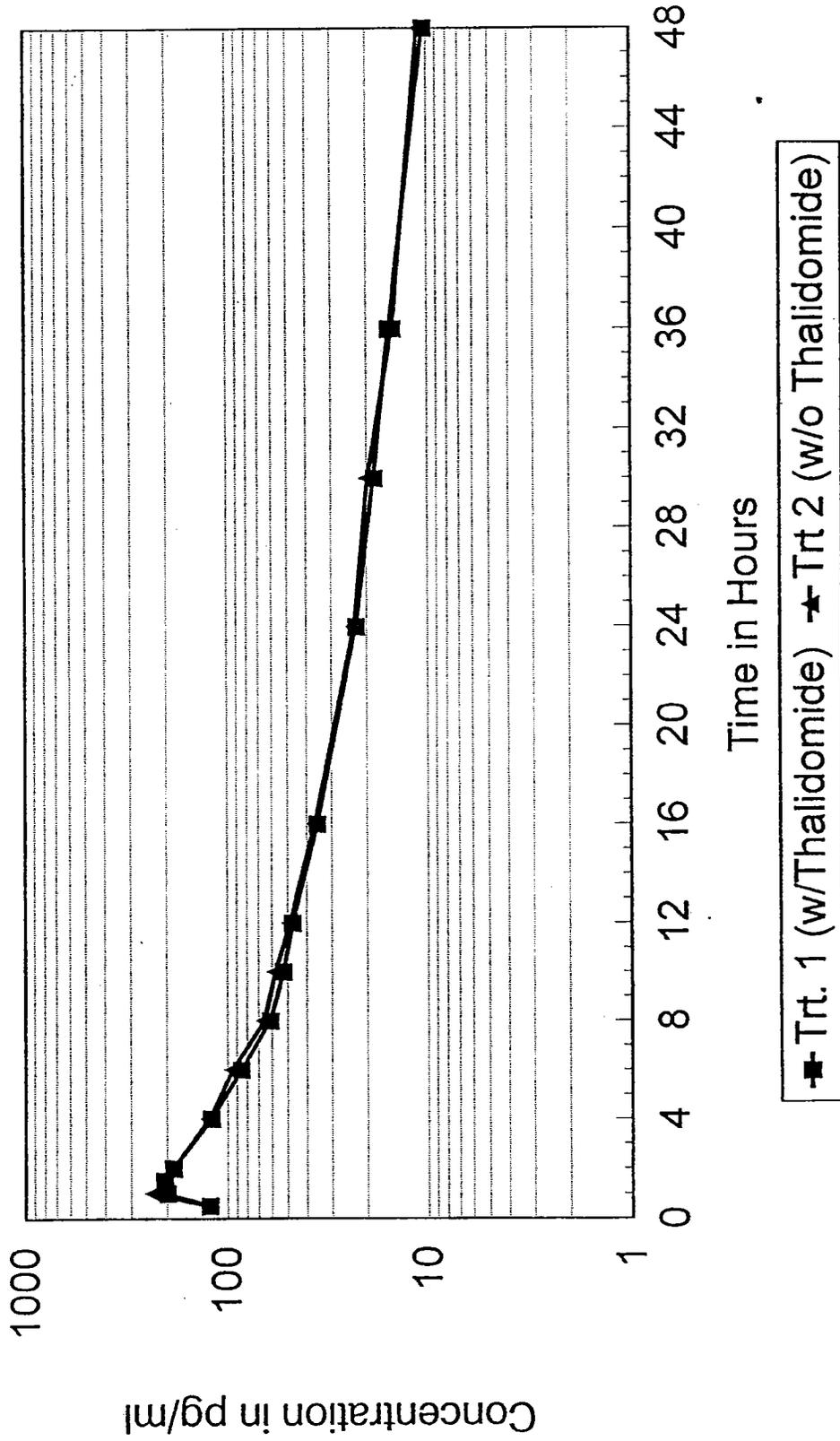
Individual and Mean Serum Ethinyl Estradiol Concentrations (pg/mL) Following Thalidomide 200 mg/day Given for 21 days (Days 20 and 21)

Treatment A

Subject Number	Treatment Sequence	Study Period	441.9	442.5	443.0	443.5	444.0	446.0	448.0	450.0	452.0	454.0	458.0	466.0	472.0	478.0	490.0
2	AB	1															
3	BA	2															
4	AB	1															
5	BA	2															
6	AB	1															
8	BA	2															
9	AB	1															
10	AB	1															
11	BA	2															
12	BA	2															
Mean			0.00	122	198	206	186	120	85.3	61.0	52.4	47.0	35.4	22.5	18.3	15.4	10.3
S.D.			0.00	74.9	72.2	74.9	70.7	42.9	28.9	19.1	14.9	14.9	12.5	9.71	8.54	7.85	5.75
C.V.(%)			.	61.4	36.4	36.4	38.0	35.7	33.9	31.2	28.3	31.6	35.4	43.1	46.7	51.1	56.0
S.E.M.			0.00	23.7	22.8	23.7	22.4	13.6	9.15	6.03	4.70	4.70	3.97	3.07	2.70	2.48	1.82
N			10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum																	
Maximum																	

. = sample value not reportable or missing.
Samples below the quantifiable limit of 2.0 are reported as 0.00.
Hours 432, 456 and 480 correspond to 19th - 21st dose of Thalidomide
Hour 442 corresponds to dose of Ortho-Novum

Individual and Mean Serum Ethinyl Estradiol Concentrations (pg/mL) in the Absence of Treatment with Thalidomide (Days 20 and 21)

Subject Number	Treatment Sequence	Study Period	441.9	442.5	443.0	443.5	444.0	446.0	448.0	450.0	452.0	454.0	458.0	466.0	472.0	478.0	490.0
1	B	1															
2	AB	2															
3	BA	1															
4	AB	2															
5	BA	1															
6	AB	2															
8	BA	1															
9	AB	2															
10	AB	2															
11	BA	1															
12	BA	1															
Mean			0.00	125	234	204	185	123	94.1	65.2	57.4	48.5	36.4	23.0	19.7	14.8	10.9
S.D.			0.00	69.0	150	91.8	79.9	46.1	33.0	20.3	18.5	17.1	12.2	9.80	9.14	7.57	10.3
C.V.(%)			.	55.1	64.1	45.0	43.1	37.6	35.1	31.1	32.3	35.4	33.4	42.6	46.5	51.3	94.5
S.E.M.			0.00	21.8	47.3	29.0	25.3	14.6	10.4	6.41	5.86	5.42	3.85	3.10	2.89	2.39	3.27
N			10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum																	
Maximum																	

. = sample value not reportable or missing.
Samples below the quantifiable limit of 2.0 are reported as 0.00.
* = Subject was not included in summary statistics.
Hour 442 corresponds to dose of Ortho-Novum

04

Individual and Mean Pharmacokinetic Parameter Values from Serum Ethinyl Estradiol Concentrations Following Thalidomide 200 mg/day

Given for 20 days (Day 20) - Treatment A

							Parameters				
Subject Number	Treatment Sequence	Study Period	Cmax pg/mL	Tmax hr	AUC(0-inf) pg*hr/mL	AUC(0-t) pg*hr/mL	Kel 1/hr	T 1/2el hr	Cl/F L/hr	Varea/F L	MRT hr
2	AB	1									
3	BA	2									
4	AB	1									
5	BA	2									
6	AB	1									
8	BA	2									
9	AB	1									
10	AB	1									
11	BA	2									
12	BA	2									
Mean			210	1.3	2238	1951	0.0407	17.7	18.0	441	20.0
S.D.			77.3	0.26	911.5	709.1	0.00821	3.66	6.87	151	4.38
C.V.(%)			36.8	20	40.72	36.34	20.2	20.7	38.1	34.3	21.9
S.E.M.			24.5	0.082	288.2	224.2	0.00260	1.16	2.17	47.8	1.38
N			10.0	10	10.00	10.00	10.0	10.0	10.0	10.0	10.0
Minimum											
Maximum											

Individual and Mean Pharmacokinetic Parameter Values from Serum Ethinyl Estradiol Concentrations in the Absence of Tretment with

Thalidomide (Day 20) - Treatment B

							Parameters				
Subject Number	Treatment Sequence	Study Period	Cmax pg/mL	Tmax hr	AUC(0-inf) pg*hr/mL	AUC(0-t) pg*hr/mL	Kel 1/hr	T 1/2el hr	Cl/F L/hr	Varea/F L	MRT hr
1	B	1									
2	AB	2									
3	BA	1									
4	AB	2									
5	BA	1									
6	AB	2									
8	BA	1									
9	AB	2									
10	AB	2									
11	BA	1									
12	BA	1									
Mean			245	1.2	2365	2033	0.0453	16.6	17.7	389	19.4
S.D.			146	0.26	1207	787.3	0.0117	5.59	7.00	123	7.65
C.V.(%)			59.6	22	51.05	38.72	25.8	33.8	39.6	31.7	39.4
S.E.M.			46.1	0.082	381.7	249.0	0.00369	1.77	2.21	39.0	2.42
N			10.0	10	10.00	10.00	10.0	10.0	10.0	10.0	10.0
Minimum											
Maximum											

• = Subject was not included in summary statistics.

Table 16 Statistical Comparisons of Serum Ethinyl Estradiol Pharmacokinetic Parameters Treatment A versus Treatment B

Parameter	Treatment ..... LSMEANS ..... A	B	Pct Difference	Mean Ratio	One Sided T-test P_values A - .65B < 0	A - 1.35B > 0
Cmax	210.400	244.570	-13.97	0.860	0.9300	0.9867
Tmax	1.300	1.208	7.63	1.076	1.0000	0.9991
AUC(0-t)	1951.259	2033.290	-4.03	0.960	1.0000	1.0000
AUC(0-inf)	2238.493	2364.634	-5.33	0.947	1.0000	0.9999
T 1/2el	17.677	16.540	6.87	1.069	1.0000	0.9995
Kel	0.041	0.045	-10.06	0.899	1.0000	1.0000
Cl/F	18.017	17.686	1.87	1.019	1.0000	1.0000
Varea/F	440.622	389.369	13.16	1.132	1.0000	0.9993
MRT	19.954	19.427	2.77	1.028	1.0000	0.9990
LN[AUC(0-t)]	7.514	7.552	-0.50	0.995	1.0000	1.0000
LN[AUC(0-inf)]	7.641	7.672	-0.40	0.996	1.0000	1.0000

Treatment A = Thalidomide 200 mg/day (Day 20)
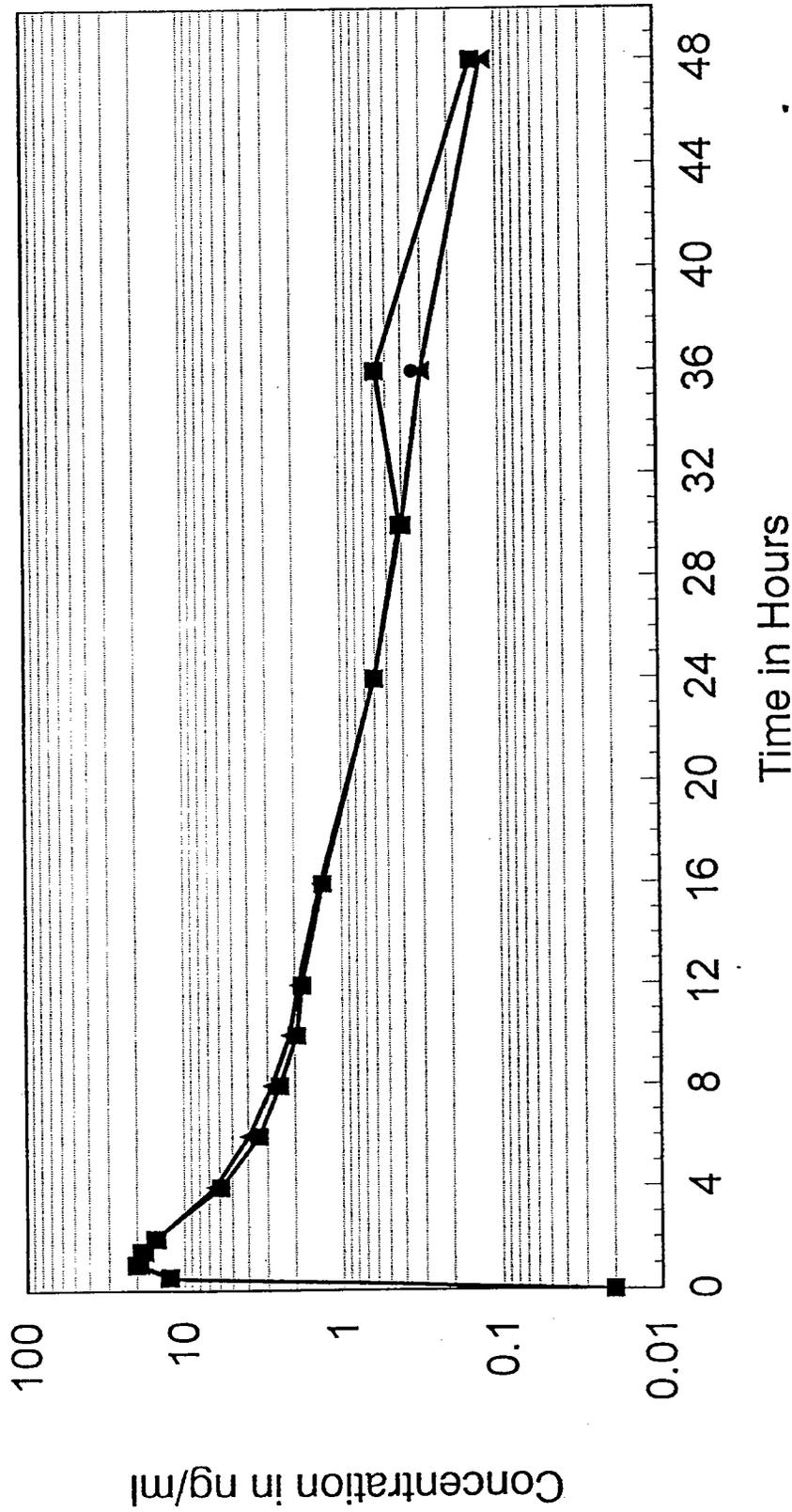Treatment B = No Thalidomide (Day 20)

Values for Treatments A and B are the least-square means (LSMEANS) from the ANOVA

Pct Difference = difference between treatments (A - B) expressed as a percentage of Treatment B

Mean Ratio = 100*A/B for all parameters

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Norethindrone Mean Concentrations

Thalidomide Drug Interaction Study PK-003

Table 17 Individual and Mean Serum Norethindrone Concentrations (ng/mL) Following Thalidomide 200 mg/day Given for 21 Days (Days 20 and 21)- Treatment A

Subject Number	Treatment Sequence	Study Period	441.9	442.5	443.0	443.5	444.0	446.0	448.0	450.0	452.0	454.0	458.0	466.0	472.0	478.0	490.0
2	AB	1															
3	BA	2															
4	AB	1															
5	BA	2															
6	AB	1															
8	BA	2															
9	AB	1															
10	AB	1															
11	BA	2															
12	BA	2															
Mean			0.0200	12.5	20.1	18.6	15.3	5.86	3.38	2.49	1.94	1.79	1.31	0.600	0.410	0.580	0.140
S.D.			0.0422	7.56	6.85	5.26	5.68	2.33	1.49	1.18	0.796	0.867	0.606	0.333	0.300	0.781	0.151
C.V.(%)			211	60.6	34.1	28.4	37.1	39.8	44.1	47.3	41.0	48.4	46.3	55.6	73.1	135	108
S.E.M.			0.0133	2.39	2.17	1.66	1.80	0.737	0.471	0.373	0.252	0.274	0.192	0.105	0.0948	0.247	0.0476
N			10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum																	
Maximum																	

. = sample value not reportable or missing.
Samples below the quantifiable limit of 0.05 are reported as 0.00.
Hours 432, 456 and 480 correspond to 19ᵗʰ - 21ˢᵗ dose of Thalidomide
Hour 442 corresponds to dose of Ortho-Novum

Table 18 Individual and Mean Serum Norethindrone Concentrations (ng/mL) in the Absence of Treatment with Thalidomide (Days 20 and 21) - Treatment B

Subject Number	Treatment Sequence	Study Period	441.9	442.5	443.0	443.5	444.0	446.0	448.0	450.0	452.0	454.0	458.0	466.0	472.0	478.0	490.0
1	B	1															
2	AB	2															
3	BA	1															
4	AB	2															
5	BA	1															
6	AB	2															
8	BA	1															
9	AB	2															
10	AB	2															
11	BA	1															
12	BA	1															
Mean			0.00	12.3	19.2	18.0	15.0	6.39	3.95	2.80	2.15	1.89	1.36	0.600	0.400	0.300	0.120
S.D.			0.00	6.54	6.93	6.12	5.09	2.09	1.36	1.09	0.911	0.929	0.534	0.302	0.254	0.163	0.103
C.V.(%)			.	53.1	36.1	34.1	33.9	32.7	34.4	38.9	42.4	49.2	39.2	50.3	63.5	54.4	86.1
S.E.M.			0.00	2.07	2.19	1.94	1.61	0.660	0.430	0.345	0.288	0.294	0.169	0.0955	0.0803	0.0516	0.0327
N			10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum																	
Maximum																	

. = sample value not reportable or missing.
Samples below the quantifiable limit of 0.05 are reported as 0.00.
* = Subject was not included in summary statistics.
Hour 442 corresponds to dose of Ortho-Novum

Individual and Mean Pharmacokinetic Parameter Values from Serum Norethindrone Concentrations following Thalidomide 200 mg/day Given for 20 days (Day 20) - Treatment A

Subject Number	Treatment Sequence	Study Period	Parameters								
			Cmax ng/mL	Tmax hr	AUC(0-inf) ng*hr/mL	AUC(0-t) ng*hr/mL	Kel 1/hr	T 1/2el hr	Cl/F L/hr	Varea/F L	MRT hr
2	AB	1									
3	BA	2									
4	AB	1									
5	BA	2									
6	AB	1									
8	BA	2									
9	AB	1									
10	AB	1									
11	BA	2									
12	BA	2									
Mean			21.2	1.2	97.5	94.8	0.0821	9.05	12.6	156	8.55
S.D.			6.60	0.35	37.1	35.5	0.0201	2.84	7.91	85.9	2.98
C.V.(%)			31.1	29	38.0	37.5	24.5	31.4	62.6	55.0	34.9
S.E.M.			2.09	0.11	11.7	11.2	0.00637	0.899	2.50	27.2	0.943
N			10.0	10	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum											
Maximum											

Individual and Mean Pharmacokinetic Parameter Values from Serum Norethindrone Concentrations in the Absence of Treatment with Thalidomide (Day 20) - Treatment B

Subject Number	Treatment Sequence	Study Period	Parameters								
			Cmax ng/mL	Tmax hr	AUC(0-inf) ng*hr/mL	AUC(0-t) ng*hr/mL	Kel 1/hr	T 1/2el hr	Cl/F L/hr	Varea/F L	MRT hr
1	B	1									
2	AB	2									
3	BA	1									
4	AB	2									
5	BA	1									
6	AB	2									
8	BA	1									
9	AB	2									
10	AB	2									
11	BA	1									
12	BA	1									
Mean			19.8	1.3	99.6	97.5	0.0845	8.84	11.7	147	8.63
S.D.			6.63	0.35	32.7	32.5	0.0247	2.57	6.38	79.9	2.57
C.V.(%)			33.4	27	32.8	33.4	29.2	29.1	54.6	54.3	29.8
S.E.M.			2.10	0.11	10.3	10.3	0.00780	0.814	2.02	25.3	0.812
N			10.0	10	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum											
Maximum											

* = Subject was not included in summary statistics.

Table 22 Statistical Comparisons of Serum Norethindrone Pharmacokinetic Parameters

Treatment A versus Treatment B

| | Treatment LSMEANS | | Pct | Mean | One Sided T-test P_values | |
Parameter	A	B	Difference	Ratio	A - .65B < 0	A - 1.35B > 0
Cmax	21.210	19.840	6.91	1.069	0.9999	0.9940
Tmax	1.203	1.308	-7.98	0.920	0.9809	0.9884
AUC(0-t)	94.856	97.499	-2.71	0.973	1.0000	1.0000
AUC(0-inf)	97.469	99.651	-2.19	0.978	1.0000	1.0000
T 1/2el	9.046	8.835	2.39	1.024	1.0000	0.9994
Kel	0.082	0.085	-2.85	0.971	0.9998	0.9995
Cl/F	12.615	11.699	7.83	1.078	1.0000	0.9991
Varea/F	156.140	147.282	6.01	1.060	1.0000	0.9996
MRT	8.552	8.625	-0.85	0.992	0.9999	0.9996
LN[AUC(0-t)]	4.467	4.515	-1.05	0.989	1.0000	1.0000
LN[AUC(0-inf)]	4.494	4.530	-0.98	0.990	1.0000	1.0000

Treatment A = Thalidomide 200 mg/day (Day 20)
Treatment B = No Thalidomide (Day 20)

Values for Treatments A and B are the least-square means (LSMEANS) from the ANOVA

Pct Difference = difference between treatments (A - B) expressed as a percentage of Treatment B

Mean Ratio = 100*A/B for all parameters

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Thalidomide Mean Data
Day 1 vs. Day 18

Study PK-003

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Thalidomide Mean Data
Day 1

Study PK-003

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Table 2 Individual and Mean Plasma Thalidomide Concentrations (ug/mL) for Thalidomide 200 mg (Day 1)

Subject Number	Treatment Sequence	Study Period	-0.1	0.5	1.0	2.0	4.0	6.0	8.0	12.0	16.0	23.9
						Sample Times (hr)						
2	AB	1										
3	BA	2										
4	AB	1										
5	BA	2										
6	AB	1										
•7	A	1										
8	BA	2										
9	AB	1										
10	AB	1										
11	BA	2										
12	BA	2										
Mean			0.0	0.07	0.510	1.30	1.88	1.97	1.73	1.00	0.460	0.0700
S.D.			0.0	0.157	0.509	0.826	0.627	0.432	0.617	0.440	0.227	0.116
C.V.(%)			.	224	99.7	63.5	33.3	21.9	35.6	44.0	49.4	166
S.E.M.			0.00	0.0496	0.161	0.261	0.198	0.137	0.195	0.139	0.0718	0.0367
N			10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum												
Maximum												

. = sample value not reportable or missing.
Samples below the quantifiable limit of 0.1 are reported as 0.0.
* = Subject was not included in summary statistics.

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Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations for Thalidomide 200 mg (Day 1)

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-inf) ug*hr/mL	AUC(0-t) ug*hr/mL	Kel 1/hr	T1/2el hr	Cl/F L/hr	Varea/F L	MRT hr
2	AB	1									
3	BA	2									
4	AB	1									
5	BA	2									
6	AB	1									
*7	A	1									
8	BA	2									
9	AB	1									
10	AB	1									
11	BA	2									
12	BA	2									
Mean			2.31	5.8	23.3	21.4	0.174	4.12	9.09	53.0	8.98
S.D.			0.507	2.0	5.79	5.51	0.0318	0.796	2.26	13.9	1.54
C.V.(%)			21.9	35	24.9	25.8	18.3	19.3	24.9	26.2	17.1
S.E.M.			0.160	0.64	1.83	1.74	0.0100	0.252	0.715	4.40	0.486
N			10.0	10	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum											
Maximum											

* = Subject was not included in summary statistics.

Compartmental Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations for Thalidomide 200 mg (Day 1)

Subject Number	Treatment Sequence	Study Period	Kel 1/hr	T1/2el hr	Ka 1/hr	T1/2abs hr	T lag hr	V/F L	Cl/F L/hr	AUC(0-inf) ug*hr/mL	r
2	AB	1									
3	BA	2									
4	AB	1									
5	BA	2									
6	AB	1									
*7	A	1									
8	BA	2									
9	BA	1									
10	AB	1									
11	BA	2									
12	BA	2									
Mean			0.241	3.03	0.351	2.45	1.15	39.5	9.16	23.0	0.970
S.D.			0.0613	0.676	0.205	0.939	0.993	11.7	2.26	5.56	0.0263
C.V.(%)			25.4	22.3	58.6	30.4	86.5	29.5	24.7	24.2	2.71
S.E.M.			0.0194	0.214	0.0650	0.297	0.314	3.69	0.715	1.76	0.0083
N			10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum											
Maximum											

* = Subject was not included in summary statistics.

Thalidomide Mean Data
Day 18-All Subjects
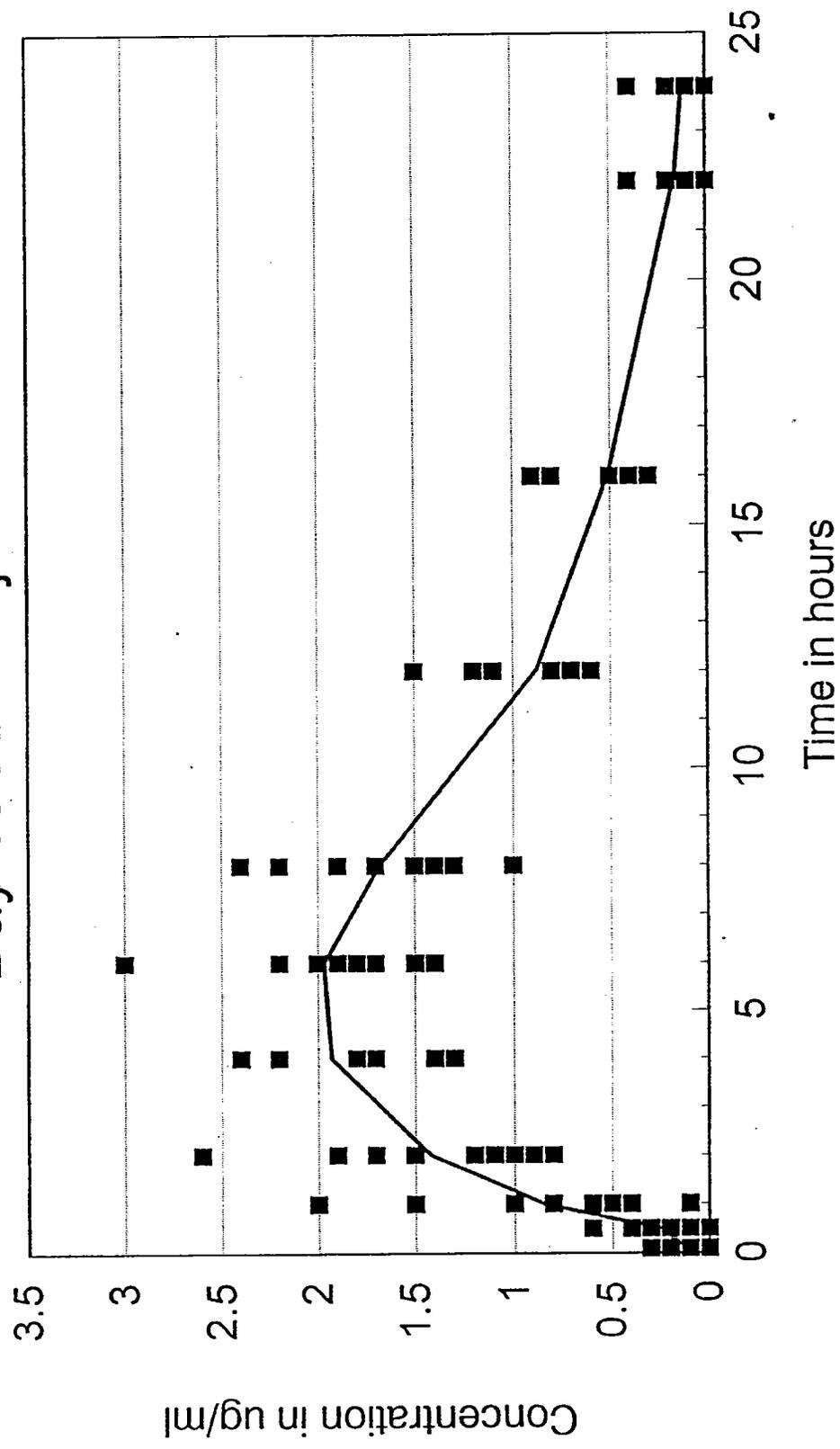
Study PK-003

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Table 3 Individual and Mean Plasma Thalidomide Concentrations (ug/mL) for Thalidomide 200 mg daily (Days 18 through 20)

Subject Number	Treatment Sequence	Study Period	407.9	408.5	409.0	410.0	412.0	414.0	416.0	420.0	424.0	430.0	431.9	454.0	478.0
									Sample Times (hr)						
2	AB	1													
3	BA	2													
4	AB	1													
5	BA	2													
6	AB	1													
8	BA	2													
9	AB	1													
10	AB	1													
11	BA	2													
12	BA	2													
Mean			0.120	0.250	0.850	1.42	1.93	1.97	1.68	0.880	0.510	0.160	0.120	0.170	0.180
S.D.			0.103	0.184	0.558	0.547	0.483	0.450	0.416	0.294	0.191	0.117	0.123	0.116	0.0837
C.V.(%)			86.1	73.6	65.7	38.5	25.0	22.8	24.7	33.4	37.5	73.4	102	68.2	46.5
S.E.M.			0.0327	0.0582	0.177	0.173	0.153	0.142	0.131	0.0929	0.0605	0.0371	0.0389	0.0367	0.0374
N			10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	5.00
Minimum															
Maximum															

. = sample value not reportable or missing.
Samples below the quantifiable limit of 0.1 are reported as 0.0.
Hours 400, 432, 456, and 400 correspond to 18th - 21st dose of Thalidomide

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Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations for Thalidomide 200 mg daily (Day 18)

								Parameters						
Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-24) ug*hr/mL	Cavg ug/mL	Cmin ug/mL	(Cmax-Cmin) /Cavg	(Cmax-Cmin) /Cmin	Kel 1/hr	T 1/2el hr	Cl/F L/hr	Varea/F L
2	AB	1											
3	BA	2											
4	AB	1											
5	BA	2											
6	AB	1											
8	BA	2											
9	AB	1											
10	AB	1											
11	BA	2											
12	BA	2											
Mean			2.3	5.0	22.6	0.943	0.1	2.33	16.6	0.164	4.45	9.15	58.2
S.D.			0.33	1.7	4.48	0.108	0.1	0.331	8.56	0.0353	1.15	1.67	15.7
C.V.(%)			14	34	19.8	19.9	100	14.2	51.7	21.6	25.8	18.3	26.9
S.E.M.			0.10	0.54	1.42	0.0594	0.04	0.105	3.24	0.0112	0.363	0.529	4.96
N			10	10	10.0	10.0	10	10.0	7.00	10.0	10.0	10.0	10.0
Minimum													
Maximum													

Compartmental Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations for Thalidomide 200 mg daily (Day 18)

						Parameters					
Subject Number	Treatment Sequence	Study Period	Kel 1/hr	T1/2el hr	Ka 1/hr	T1/2abs hr	T lag hr	V/F L	Cl/F L/hr	AUC(0-inf) ug*hr/mL	r
2	AB	1									
3	BA	2									
4	AB	1									
5	BA	2									
6	AB	1									
8	BA	2									
9	AB	1									
10	AB	1									
11	BA	2									
12	BA	2									
Mean			0.220	3.35	0.446	2.56	0.590	44.4	9.04	22.8	0.975
S.D.			0.0498	1.01	0.592	0.966	0.355	19.5	1.56	4.35	0.0167
C.V.(%)			22.6	30.3	133	37.7	60.2	44.0	17.3	19.1	1.71
S.E.M.			0.0158	0.321	0.187	0.305	0.112	6.18	0.494	1.37	0.0052
N			10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Minimum											
Maximum											

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NDA/IND# 20-785 Suppl/Amend.# 32 Submission Date: 12/23/97 Volume: n.a.

Study Type: Food/Fasting & BE   Study #   PK-006

Study Title: A Single-Dose, Three-Way Crossover Study of Two Formulations of Thalidomide and Relative Bioequivalence of Thalidomide With & Without Food When Administered Orally to Healthy Volunteers

Clinical Investigator ⌈   Analytical Investigator ⌈

Site   Site

                    ⌋ ̄   ⌋ ̄

Single Dose: Y   Multiple Dose: N   Washout Period: 1 week

Cross-Over Y   Parallel   Other Design: fasted BE leg included

Fasted   Y   Food Study Y   FDA High Fat Breakfast Y

If fasted, how long (hrs.)? 10hr

Subject Breakdown

Normal Y   Patients N   Young Y   Elderly N   Renal N   Hepatic N

Subject Type		All		Group	All	N=	13	M=	5	F=	8
Weight	Mean	74	Range	62.7-95.9kg	Group		N=		M=		F=	
Age	Mean	35.8	Range	20-46	Group		N=		M=		F=	

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
Fed & Fasted	200mg	capsules	4x50mg	UNK	UNK
Serral, S.A.	200mg	tablets	2x100mg	UNK	UNK

Sampling Times	
Plasma	Pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48hrs
Urine	n.a.
Feces	n.a.

Assay Method:	HPLC w/UV detection
Assay Sensitivity	see text
Assay Accuracy	see text

Labeling Claims From Study   Analysis of the fed vs. fasting portion of this study revealed that food caused a slight increase in thalidomide plasma levels even though peak plasma levels were delayed by almost two hours. In addition, small but statisically significant decreases in AUC were also noted when thalidomide was given with food. The clinical significance of these changes is unknown. In terms of the bioequivalency assessment the Serral, S.A. product produced plasma levels that were markedly lower (~50%) than levels produced by the Celgene product. The Serral, S.A. tablet is bioinequivalent to the Celgene capsule.

Celgene's Thalidomide
Fed vs. Fasted

Plasma Thalidomide Concentrations (ug/mL) Following 4 x Celgene Thalidomide 50 mg Capsules, Fasted (Treatment A)

Subject Number	Treatment Sequence	Study Period	0	0.5	1	1.5	2	2.5	3	4	5	6	8	10	12	24	36	48
1	CAB	2																
2	BCA	3																
3	ABC	1																
4	CAB	2																
5	ABC	1																
6	BCA	3																
7	BCA	3																
9	ABC	1																
10	BCA	3																
11	ABC	1																
12	CAB	2																
13	CAB	2																
14	BCA	3																
Mean			0.000	0.553	0.956	1.110	1.275	1.448	1.648	1.786	1.858	1.645	1.362	1.023	0.911	0.237	0.010	0.000
S.D.			0.000	0.379	0.459	0.479	0.486	0.519	0.513	0.464	0.473	0.392	0.284	0.217	0.331	0.180	0.036	0.000
C.V.(%)			.	68.55	48.01	43.23	38.14	35.83	31.17	26.03	25.49	23.83	20.91	21.26	36.39	75.96	360.6	.
S.E.M.			0.000	0.105	0.127	0.133	0.134	0.143	0.142	0.129	0.131	0.108	0.079	0.060	0.091	0.050	0.010	0.000
N			13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00
Minimum																		
Maximum																		

Samples below the quantifiable limit of 0.1 are reported as 0.000.

Table 6   Plasma Thalidomide Pharmacokinetic Parameters Following 4 x Celgene Thalidomide 50 mg Capsules, Fasted (Treatment A)

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-t) ug*hr/mL	AUC(0-inf) ug*hr/mL	T 1/2el hr	Kel 1/hr	AUMC ug*hr²/mL	MRT hr	LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	CAB	2											
2	BCA	3											
3	ABC	1											
4	CAB	2											
5	ABC	1											
6	BCA	3											
7	BCA	3											
9 *	ABC	1											
10	BCA	3											
11	ABC	1											
12	CAB	2											
13	CAB	2											
14	BCA	3											
Mean			1.986	4.00	23.03	24.71	5.803	0.1256	261.9	10.40	0.6664	3.113	3.186
S.D.			0.4103	1.13	5.105	5.131	1.716	0.0235	103.0	2.341	0.2080	0.2296	0.2237
C.V.(%)			20.66	28.2	22.17	20.76	29.56	18.77	39.34	22.51	31.22	7.377	7.022
S.E.M.			0.1138	0.326	1.416	1.423	0.4758	0.0065	28.58	0.6492	0.0577	0.0636	0.0620
N			13.00	12.0	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00
Minimum													
Maximum													

* = Tmax for subject 9 was statistically tested as an outlier
and was excluded from summary statistics. With subject 9 in Tmax, mean(s.d) = 4.62(2.47).

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Plasma Thalidomide Concentrations (ug/mL) Following 4 x Celgene Thalidomide 50 mg Capsules, Fed (Treatment B)

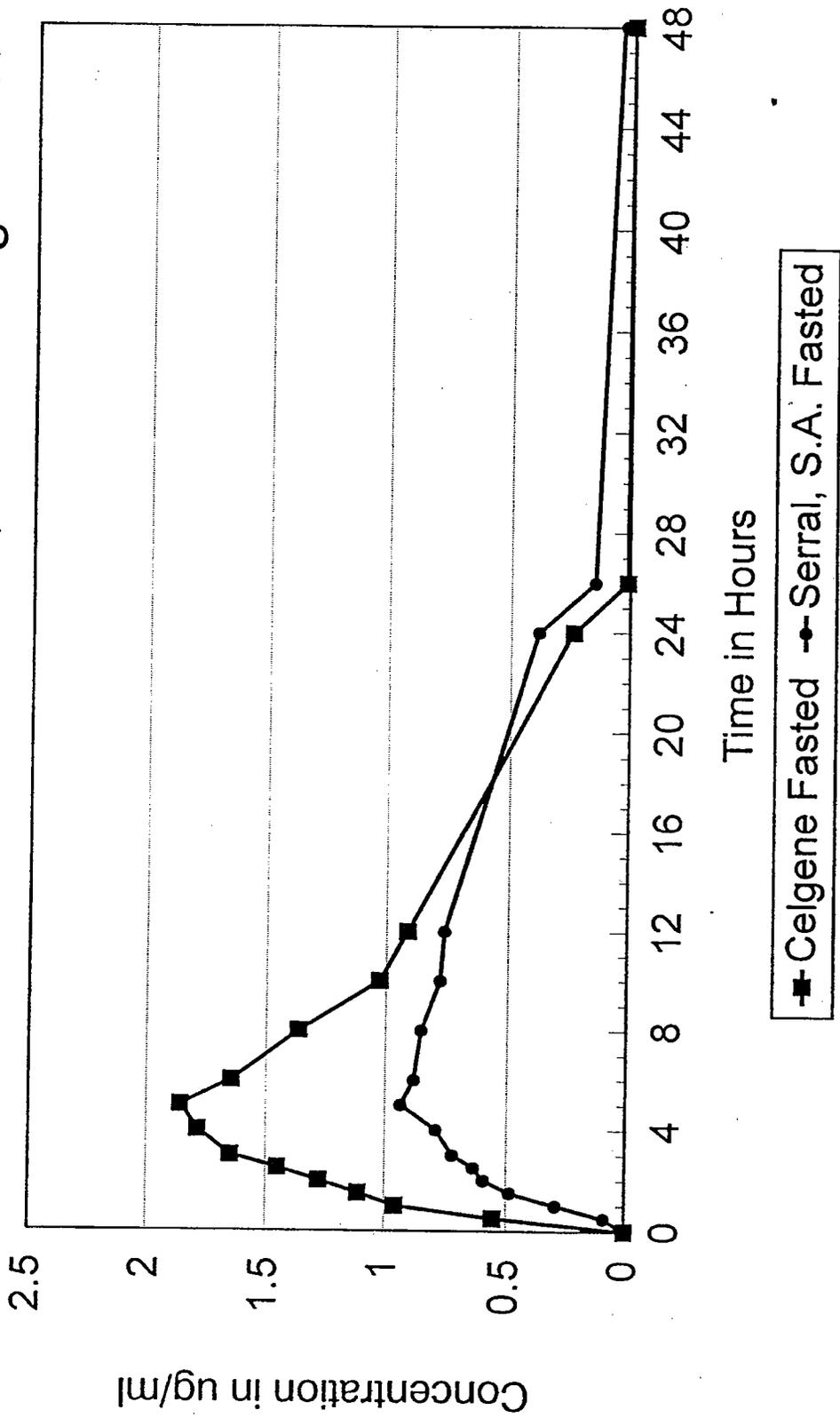| Subject Number	Treatment Sequence	Study Period	0	0.5	1	1.5	2	2.5	3	4	5	6	8	10	12	24	36	48
1	CAB	3																
2	BCA	1																
3	ABC	2																
4	CAB	3																
5	ABC	2																
6	BCA	1																
7	BCA	1																
9	ABC	2																
10	BCA	1																
11	ABC	2																
12	CAB	3																
13	CAB	3																
14	BCA	1																
Mean			0.000	0.000	0.103	0.243	0.436	0.656	0.979	1.425	2.018	1.782	1.625	1.353	1.042	0.243	0.000	0.000
S.D.			0.000	0.000	0.188	0.366	0.401	0.478	0.517	0.520	0.669	0.448	0.377	0.277	0.334	0.204	0.000	0.000
C.V.(%)			.	.	181.2	150.3	91.91	72.76	52.81	36.52	33.19	25.15	23.26	20.49	32.05	84.23	.	.
S.E.M.			0.000	0.000	0.052	0.101	0.111	0.132	0.143	0.144	0.185	0.124	0.104	0.076	0.092	0.056	0.000	0.000
N			13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00
Minimum																		
Maximum																		

Samples below the quantifiable limit of 0.1 are reported as 0.000.

Table 7 Plasma Thalidomide Pharmacokinetic Parameters Following 4 x Celgene Thalidomide 50 mg Capsules, ~~Fasted~~ (Treatment B)
Fed

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-t) ug*hr/mL	AUC(0-inf) ug*hr/mL	T 1/2el hr	Kel 1/hr	AUMC ug*hr²/mL	MRT hr	LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	CAB	3											
2	BCA	1											
3	ABC	2											
4	CAB	3											
5	ABC	2											
6	BCA	1											
7	BCA	1											
9	ABC	2											
10	BCA	1											
11	ABC	2											
12	CAB	3											
13	CAB	3											
14	BCA	1											
Mean			2.170	6.08	22.06	23.53	5.092	0.1407	259.0	10.90	0.7490	3.070	3.145
S.D.			0.5088	2.33	4.293	3.726	1.026	0.0254	74.52	1.963	0.2377	0.2493	0.1813
C.V.(%)			23.45	38.3	19.46	15.84	20.14	18.08	28.77	18.00	31.74	8.122	5.765
S.E.M.			0.1411	0.645	1.191	1.076	0.2960	0.0073	21.51	0.5667	0.0659	0.0691	0.0523
N			13.00	13.0	13.00	12.00	12.00	12.00	12.00	12.00	13.00	13.00	12.00
Minimum													
Maximum													

Bioequivalency Study

Celgene 50mg Capsule vs. Serral, S.A. 100mg Tablet

Legend: ■ Celgene Fasted ● Serral, S.A. Fasted

X-axis: Time in Hours

Y-axis: Concentration in ug/ml

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Plasma Thalidomide Concentrations (ug/mL) Following 2 x Serral Thalidomide 100 mg Tablets, Fasted (Treatment C)

Subject Number	Treatment Sequence	Study Period	0	0.5	1	1.5	2	2.5	3	4	5	6	8	10	12	24	36	48
1	CAB	1																
2	BCA	2																
3	ABC	3																
4	CAB	1																
5	ABC	3																
6	BCA	2																
7	BCA	2																
9	ABC	3																
10	BCA	2																
11	ABC	3																
12	CAB	1																
13	CAB	1																
14	BCA	2																
Mean			0.000	0.089	0.293	0.486	0.593	0.635	0.720	0.789	0.935	0.881	0.853	0.776	0.760	0.383	0.148	0.039
S.D.			0.000	0.101	0.180	0.208	0.238	0.237	0.296	0.310	0.334	0.189	0.175	0.283	0.249	0.096	0.101	0.064
C.V.(%)				113.7	61.60	42.85	40.20	37.33	41.20	39.29	35.81	21.45	20.52	36.44	32.82	25.16	68.02	163.4
S.E.M.			0.000	0.028	0.050	0.057	0.066	0.065	0.082	0.086	0.092	0.052	0.048	0.078	0.069	0.026	0.028	0.017
N			13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00
Minimum																		
Maximum																		

Samples below the quantifiable limit of 0.1 are reported as 0.000.

Table 8   Plasma Thalidomide Pharmacokinetic Parameters Following 4 x Celgene Thalidomide 50 mg Capsules, Fasted (Treatment C)

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-t) ug*hr/mL	AUC(0-inf) ug*hr/mL	T 1/2el hr	Kel 1/hr	AUUC ug*hr²/mL	MRT hr	LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	CAB	1											
2	BCA	2											
3	ABC	3											
4	CAB	1											
5	ABC	3											
6	BCA	2											
7	BCA	2											
9	ABC	3											
10	BCA	2											
11	ABC	3											
12	CAB	1											
13	CAB	1											
14	BCA	2											
Mean			048	6.23	19.05	22.66	13.50	0.0594	501.8	21.37	0.0098	2.921	3.102
S.D.			0.3068	1.88	4.257	4.447	6.769	0.0182	282.3	8,166	0.2829	0.2456	0.2042
C.V.(%)			29.26	30.1	22.35	19.63	50.13	30.76	56.27	38.21	2883	8.407	6.583
S.E.M.			0.0850	0.521	1.181	1.233	1.878	0.0050	78.31	2.265	0.0784	0.0681	0.0566
N			13.00	13.0	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00	13.00
Minimum													
Maximum													

Table 12 Statistical Comparisons of Plasma Thalidomide Pharmacokinetic Parameters: Treatment B versus Treatment A

Parameter	Treatment Means		Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	Mean Ratio
	B	A					
Cmax	2.179	2.007	8.54	0.1753	87.96	98.1 - 119.0	108.5
Tmax	6.179	3.820	61.75	0.0010*	20.45	133.9 - 189.6	161.7
AUC(0-t)	22.252	23.382	-4.83	0.2872	98.84	87.6 - 102.8	95.2
AUC(0-inf)	23.743	25.116	-5.47	0.2029	99.37	87.4 - 101.7	94.5
T 1/2el	4.707	5.900	-20.23	0.5072	8.62	28.2 - 131.4	79.8
Kel	0.142	0.126	12.86	0.1590	57.53	97.7 - 128.0	112.9
LN(Cmax)	0.754	0.678	11.19	0.2866	78.53	95.7 - 121.6	107.9
LN[AUC(0-t)]	3.080	3.130	-1.60	0.3003	97.94	87.7 - 103.1	95.1
LN[AUC(0-inf)]	3.155	3.203	-1.49	0.2598	99.43	88.8 - 102.3	95.3
AUMC	245.105	271.889	-9.85	0.7031	10.47	46.3 - 134.0	90.1
MRT	10.343	10.571	-2.15	0.9156	14.53	63.3 - 132.4	97.8

Treatment B = 4 x Celgene Thalidomide 50 mg Capsules, Fed: test
Treatment A = 4 x Celgene Thalidomide 50 mg Capsules, Fasted: reference

Values for Treatments B and A are the least-squares means (LSMEANS) from the ANOVA
Parameters with the 'LN' prefix are log-transformed parameters

Pct Difference = difference between treatments (B - A) expressed as a percentage of Treatment A

PR>|T| = ANOVA test for significant differences between treatments
(* difference is statistically significant, p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*test/reference for untransformed parameters
Mean Ratio = 100*exp(test-reference) for log-transformed parameters

Tmax value of subject 9 for treatment A was excluded from the analysis

Table 13 Statistical Comparisons of Plasma Thalidomide Pharmacokinetic Parameters: Treatment A versus Treatment C

Parameter	Treatment Means		Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	Mean Ratio
	A	C					
Cmax	2.007	1.056	90.17	0.0001*	36.50	170.3 - 210.1	190.2
Tmax	3.820	6.210	-38.49	0.0008*	47.72	44.5 - 78.5	61.5
AUC(0-t)	23.382	19.218	21.66	0.0006*	94.19	112.4 - 130.9	121.7
AUC(0-inf)	25.116	22.839	9.97	0.0342*	98.88	102.4 - 117.5	110.0
T 1/2el	5.900	13.601	-56.62	0.0002*	31.76	21.8 - 64.9	43.4
Kel	0.126	0.060	111.18	0.0001*	17.36	180.4 - 242.0	211.2
LN(Cmax)	0.678	0.017	3784.1	0.0001*	78.53	171.9 - 218.2	193.6
LN[AUC(0-t)]	3.130	2.930	6.83	0.0003*	97.94	112.7 - 132.5	122.2
LN[AUC(0-inf)]	3.203	3.110	3.00	0.0286*	99.63	102.5 - 117.5	109.8
AUMC	271.889	508.613	-46.54	0.0019*	29.25	30.9 - 76.0	53.5
MRT	10.571	21.492	-50.82	0.0001*	50.93	32.8 - 65.5	49.2

Treatment A = 4 x Celgene Thalidomide 50 mg Capsules, Fasted: test
Treatment C = 2 x Serral Thalidomide 100 mg Tablets, Fasted: reference

Values for Treatments A and C are the least-squares means (LSMEANS) from the ANOVA
Parameters with the 'LN' prefix are log-transformed parameters

Pct Difference = difference between treatments (A - C) expressed as a percentage of Treatment C

PR>|T| = ANOVA test for significant differences between treatments
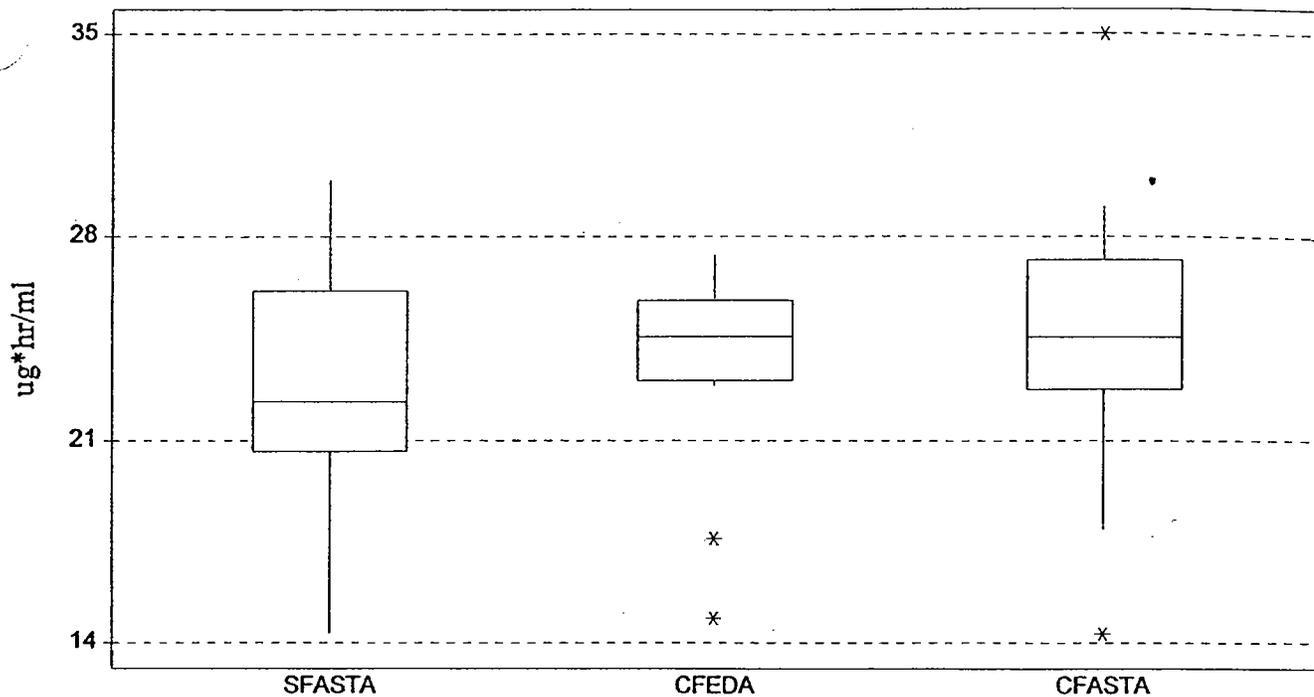(* difference is statistically significant, p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*test/reference for untransformed parameters
Mean Ratio = 100*exp(test-reference) for log-transformed parameters

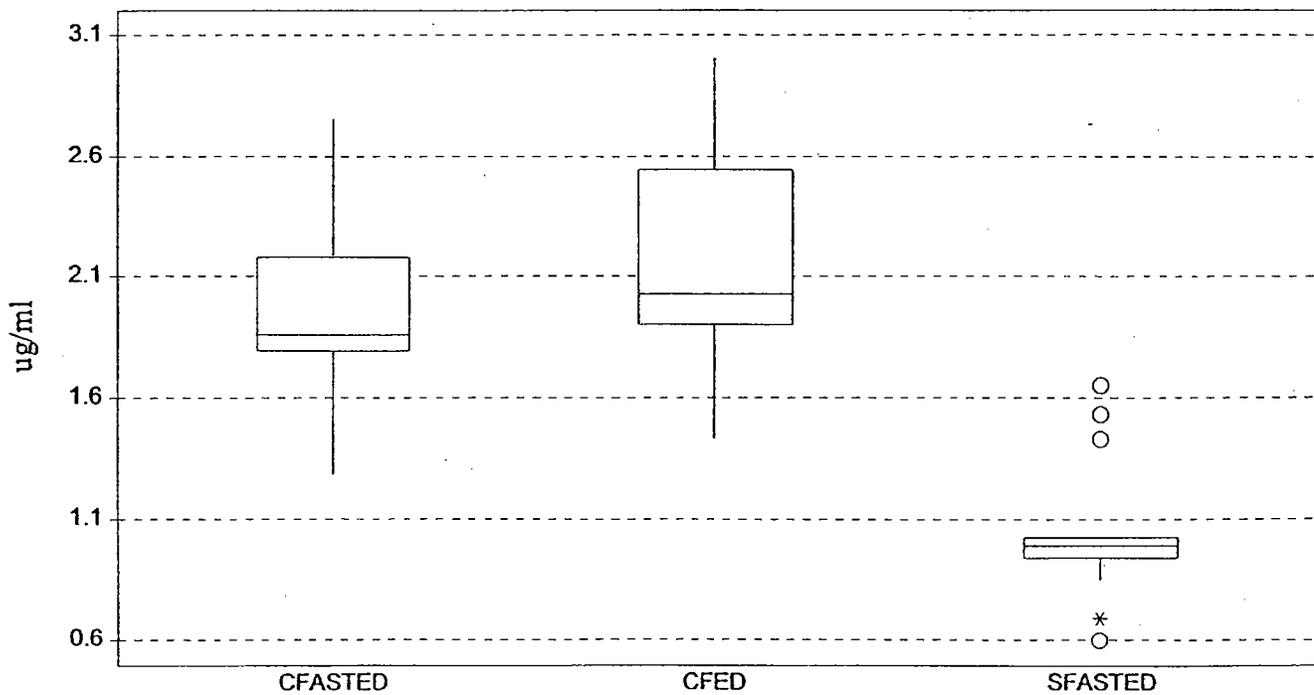Tmax value of subject 9 for treatment A was excluded from the analysis

Box and Whisker Plot of AUC0-inf

SFASTA=Serral, CFEDA/CFASTA=Celgene

38 cases   1 missing cases

Box and Whisker Plot of Cmax

CFASTED/CFED=Clegene, SFASTED=Serral

39 cases

25

NDA/IND# [   ] Suppl/Amend.# N136 Submission Date: 1/14/98   Volume: n.a.

Study Type: Dose Proportionality   Study #   PK-UK001

Study Title: A Single-Dose, Two-Way, Crossover Study of Thalidomide 100mg and 200mg (as 50mg capsules) Administered Orally to Fasting Male Volunteers Who are HIV-Seropositive.

Clinical Investigator   [Analytical Investigator   Unknown

Site   Site   [

Single Dose: Y   Multiple Dose: N   Washout Period: 1 week

Cross-Over   Y   Parallel   Other Design:

Fasted   Y   Food Study   N   FDA High Fat Breakfast

If fasted, how long (hrs.)? 10hr

Subject Breakdown

Normal   Patients Y   Young Y   Elderly   N   Renal N   Hepatic N

	Subject Type		Males		Group	Males	N=	16	M=	16	F=	0
Weight	Mean	77.1	Range	60-96kg		Group		N=		M=		F=	
Age	Mean	31.5	Range	16-41 yrs		Group		N=		M=		F=	

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size	
Trt. A	100mg	Capsules	2x50mg	DEV2400	[	]
Trt. B	200mg	Capsules	4x50mg	DEV2400	[	]

Sampling Times	
Plasma	Pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20 and 24hrs. post-dose
Urine	n.a.
Feces	n.a.

Assay Method:	HPLC
Assay Sensitivity	see text
Assay Accuracy	see text

Labeling Claims Although a slight decrease in peak plasma level was noted with the 200mg treatment arm
From Study   (when compared to the scaled 100mg arm), this difference although statistically significant
                (lower 90% CI=74.7%) is most likely due to the poor solubility of thalidomide in gastric
                fluid and does not represent an alteration in pharmacokinetics due to HIV-Seropositivity.

Table 1

Summary of Demographic Information

Variable	Summary statistic		All subjects
Age (years)	Mean		31.5
	S.D.		5.1
	Minimum		24.0
	Maximum		41.0
	Number		16.0
Height (centimeters)	Mean		179.9
	S.D.		5.9
	Minimum		168.0
	Maximum		191.0
	Number		16.0
Weight (kilograms)	Mean		77.1
	S.D.		8.4
	Minimum		60.0
	Maximum		96.0
	Number		16.0
Ethnicity	Number	BLACK	1.0
	Number	CAUCASIAN	14.0
	Number	OTHER	1.0

Medications Received at Baseline

Medications by Category	N (%)
Antiretroviral Agents	5 (31)
Indinivir	1 (6)
Lamivudine (3TC)	2 (13)
Stavudine (D4T)	3 (19)
Didanosine (DDI)	2 (13)
Zidovudine (AZT)[1]	3 (19)
Other Antiretroviral Agents	5 (31)
Acyclovir as HSV Prophulaxis	4 (25)
Valaciclovir	1 (16)
Anti-infectives	3 (19)
Copimoxazole for PCP Prophylaxis	2 (13)
Chlorhexidine	1 (6)
Other Medications	5 (31)
Antidepressants (fluoxetine, paroxetine)	2 (13)
Alprazon	1 (6)
Cetirizine HCl	1 (6)
E45 Cream	1 (6)
Ollatum B	1 (6)
Pulmicort	1 (6)
Vitamin C	1 (6)

[1] Discontinued prior to Period 2 in1 subject.

4.3   Protocol Deviations

Any protocol deviations can be determined from the subject data listings
(Appendix 4).

Thalidomide Dose Proporitionality 100 vs. 200mg in HIV Seropositive Patients
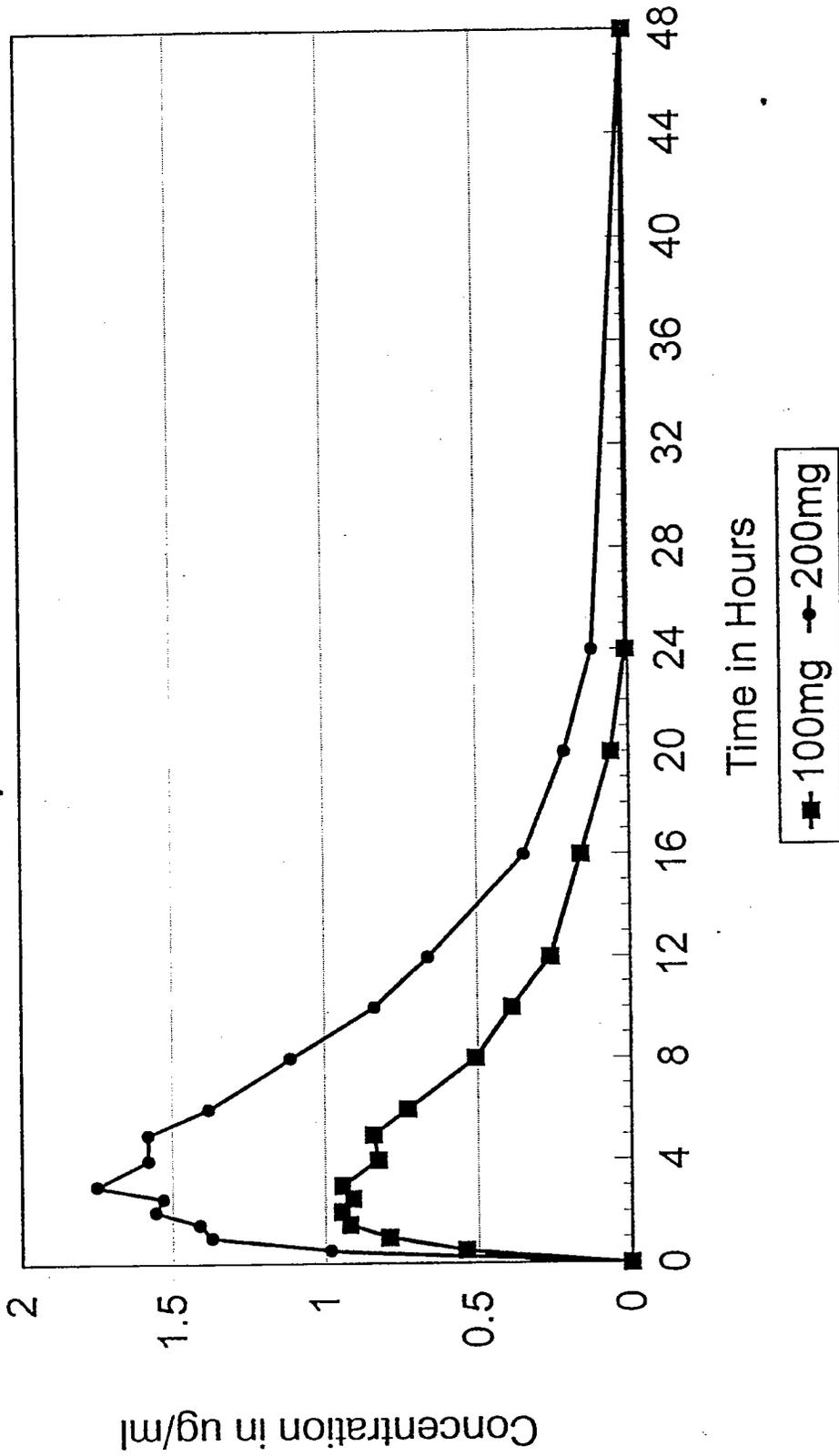
Individual and Mean Plasma Thalidomide Concentrations (ug/mL)
for Thalidomide 100 mg (2 x 50 mg capsules)

Subject Number	Treatment Sequence	Study Period	-0.5	0.5	1	1.5	2	2.5	3	4	5	6	8	10	12	16	20	24	48
								Sample Times (hr)											
1	AB	1																	
2	BA	2																	
3	AB	1																	
4	BA	2																	
5	AB	1																	
6	AB	2																	
7	BA	2																	
*8	AB	1																	
9	BA	2																	
10	AB	1																	
11	BA	2																	
12	BA	2																	
13	BA	1																	
14	AB	2																	
*15	AB	1																	
16	AB	2																	
Mean			0.00	0.539	0.786	0.916	0.943	0.906	0.941	0.821	0.836	0.724	0.506	0.387	0.260	0.159	0.0571	0.0071	0.00
S.D.			0.00	0.445	0.364	0.419	0.300	0.235	0.236	0.191	0.248	0.212	0.0985	0.111	0.113	0.0745	0.0751	0.0267	0.00
C.V.(%)				82.6	46.3	45.7	31.8	25.9	25.1	23.2	29.7	29.3	19.5	28.6	43.4	47.0	111	374	
S.E.M.			0.00	0.119	0.0974	0.112	0.0802	0.0628	0.0631	0.0509	0.0664	0.0567	0.0263	0.0296	0.0302	0.0199	0.0201	0.0071	0.00
N			14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0
Minimum																			
Maximum																			

. = sample value not reported
Samples below the quantifiable limit of 0.10 are reported as 0.00.
* = Subject was not included in summary statistics.

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Individual and Mean Pharmacokinetic Parameter Values (from Plasma Thalidomide Concentrations)
for Thalidomide 100 mg (2 x 50 mg capsules) - No Dose Adjustment

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-t) ug·hr/mL	AUC(0-inf) ug·hr/mL	T 1/2el hr	Kel 1/hr	LN (Cmax)	LN [AUC(0-t)]	LN [AUC(0-inf)]
					Parameters					Log-Parameters	
1	AB	2									
2	BA	2									
3	AB	1									
4	BA	2									
5	AB	1									
6	AB	2									
7	BA	2									
*8	BA	1									
9	AB	2									
10	AB	1									
11	BA	2									
12	BA	2									
13	BA	2									
14	AB	1									
*15	AB	1									
16	AB	2									
Mean			1.15	2.5	8.76	9.76	4.85	0.148	0.121	2.15	2.27
S.D.			0.243	1.5	1.67	1.62	1.07	0.0253	0.217	0.177	0.155
C.V.(%)			21.0	60	19.0	16.6	22.1	17.1	179	8.24	6.85
S.E.M.			0.0648	0.40	0.445	0.434	0.286	0.0067	0.0580	0.0474	0.0415
N											
Minimum											
Maximum											
Lower 90% C.I.			1.04	1.8	7.97	8.99	4.35	0.136	0.0186	2.07	2.19
Upper 90% C.I.			1.27	3.22	9.54	10.5	5.36	0.160	0.224	2.24	2.34

* = Subject was not included in summary statistics.

Individual and Mean Modeled Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for Thalidomide 100 mg (2 x 50 mg capsules)
Compartmental Analysis

| | | | | | | | ---------- Parameters ---------- | | | | |
Subject Number	Treatment Sequence	Study Period	Kel 1/hr	T 1/2el hr	Ka 1/hr	T 1/2abs hr	T lag hr	V/F L	Cl/F L/hr	AUC(0-inf) ug·hr/mL	r
1	AB	1									
2	BA	2									
3	AB	1									
4	BA	2									
5	AB	1									
6	AB	1									
7	BA	2									
*8	BA	2									
9	AB	1									
10	AB	1									
11	BA	2									
12	BA	2									
13	BA	2									
14	AB	1									
*15	BA	2									
16	AB	1									
Mean			0.161	4.59	1.85	0.945	0.168	69.9	10.4	10.1	0.949
S.D.			0.0454	1.18	1.41	0.963	0.195	15.6	2.06	2.75	0.0515
C.V.(%)			28.2	25.6	76.2	102	116.2	22.3	19.9	27.1	5.42
S.E.M.			0.0121	0.314	0.376	0.257	0.052	4.17	0.550	0.735	0.0138
N			14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0
Minimum											
Maximum											

. = data could not be modeled
* = Subject was not included in summary statistics.

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for Thalidomide 100 mg (2 x 50 mg capsules)
Noncompartmental Analysis

| | | | | | | ---------- Parameters ---------- | | | | |
Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-inf) ug·hr/mL	Kel 1/hr	T 1/2el hr	Cl/F L/hr	Varea/F L	HRT hr
1	AB	1								
2	BA	2								
3	AB	1								
4	BA	2								
5	AB	1								
6	AB	1								
7	BA	2								
*8	BA	2								
9	AB	1								
10	AB	1								
11	BA	2								
12	BA	2								
13	BA	2								
14	AB	1								
*15	BA	2								
16	AB	1								
Mean			1.15	2.5	9.76	0.148	4.85	10.5	72.8	8.23
S.D.			0.243	1.5	1.62	0.0253	1.07	1.54	15.5	2.08
C.V.(%)			21.0	60	16.6	17.1	22.1	14.7	21.3	25.2
S.E.M.			0.0648	0.40	0.434	0.0067	0.286	0.411	4.14	0.555
N			14.0	14	14.0	14.0	14.0	14.0	14.0	14.0
Minimum										
Maximum										
Lower 90% C.I.			1.04	1.79	8.99	4.35	0.136	9.76	65.5	7.25
Upper 90% C.I.			1.27	3.22	10.5	5.36	0.160	11.2	80.1	9.21

* = Subject was not included in summary statistics.

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Individual and Mean Plasma Thalidomide Concentrations (ug/mL)
for Thalidomide 200 mg (4 x 50 mg capsules)

Subject Number	Treatment Sequence	Study Period	Sample Times (hr)																
			-0.5	0.5	1	1.5	2	2.5	3	4	5	6	8	10	12	16	20	24	48
1	AB	2																	
2	BA	1																	
3	AB	1																	
4	AB	2																	
5	AB	1																	
6	AB	2																	
7	AB	1																	
8	AB	2																	
9	AB	1																	
10	AB	2																	
11	BA	1																	
12	BA	1																	
13	BA	1																	
14	BA	1																	
15	BA	2																	
16	AB	2																	
Mean			0.00	0.981	1.37	1.41	1.56	1.53	1.75	1.58	1.58	1.38	1.11	0.832	0.657	0.345	0.211	0.119	0.00
S.D.			0.00	0.456	0.533	0.640	0.552	0.372	0.556	0.479	0.507	0.421	0.309	0.228	0.157	0.0957	0.0750	0.0759	0.00
C.V.(%)				46.5	38.9	45.3	35.4	24.4	31.8	30.3	32.1	30.5	28.0	27.5	23.9	27.7	35.5	64.0	0.00
S.E.M.			0.00	0.122	0.143	0.171	0.148	0.0995	0.149	0.128	0.136	0.113	0.0826	0.0613	0.0420	0.0256	0.0201	0.0203	0.00
N			14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0
Minimum																			0.00
Maximum																			14.0

* = Sample value not reported ...
. Samples below the quantifiable limit of 0.10 are reported as 0.00.
* = Subject was not included in summary statistics.

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for Thalidomide 200 mg (4 x 50 mg capsules) - No Dose Adjustment

Subject Number	Treatment Sequence	Study Period	Parameters						Log-Parameters		
			Cmax ug/mL	Tmax hr	AUC(0-t) ug*hr/mL	AUC(0-inf) ug*hr/mL	T 1/2el hr	Kel 1/hr	LN (cmax)	LN [AUC(0-t)]	LN [AUC(0-inf)]
1	AB	2									
2	BA	1									
3	AB	1									
4	AB	2									
5	AB	1									
6	AB	2									
7	AB	1									
*8	AB	2									
*9	AB	1									
10	AB	2									
11	BA	1									
12	BA	1									
13	BA	1									
14	BA	1									
*15	BA	2									
16	AB	2									
Mean			1.92	1.3	18.2	19.4	5.23	0.138	0.627	2.89	2.95
S.D.			0.467	1.4	3.56	3.56	1.22	0.0273	0.245	0.157	0.164
C.V.(%)			24.2	44	19.55	18.4	23.4	19.7	39.1	5.97	5.56
S.E.M.			0.125	0.38	0.951	0.953	0.327	0.0073	0.0655	0.0461	0.0438
N			14.0	14	14.0	14.0	14.0	14.0	14.0	14.0	14.0
Minimum											
Maximum											

* = Subject was not included in summary statistics.

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for Thalidomide 200 mg (4 x 50 mg capsules)
Noncompartmental Analysis

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-inf) ug*hr/mL	Kel 1/hr	T 1/2el hr	Cl/F L/hr	Varea/F L	MRT hr
1	AB	2								
2	BA	1								
3	AB	2								
4	BA	1								
5	AB	2								
6	AB	2								
7	BA	1								
*8	BA	1								
9	AB	2								
·10	AB	2								
11	BA	1								
12	BA	1								
13	BA	1								
14	AB	2								
*15	BA	1								
16	AB	2								
Mean			1.92	3.3	19.4	0.138	5.23	10.6	79.8	8.99
S.D.			0.467	1.4	3.56	0.0273	1.22	1.57	21.7	1.84
C.V.(%)			24.2	44	18.4	19.7	23.4	14.8	27.2	20.5
S.E.M.			0.125	0.38	0.953	0.0073	0.327	0.419	5.80	0.492
N			14.0	14	14.0	14.0	14.0	14.0	14.0	14.0
Minimum										
Maximum										
Lower 90% C.I.			1.7	2.57	17.7	4.65	0.125	9.84	69.5	8.12
Upper 90% C.I.			2.15	3.93	21.1	5.80	0.151	11.3	90.1	9.86

* = Subject was not included in summary statistics.

Individual and Mean Modeled Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for Thalidomide 200 mg (4 x 50 mg capsules)
Compartmental Analysis

Subject Number	Treatment Sequence	Study Period	Kel 1/hr	T 1/2el hr	Ka 1/hr	T 1/2abs hr	T lag hr	V/F L	Cl/F L/hr	AUC(0-inf) ug*hr/mL	r
1	AB	2									
2	BA	1									
3	AB	2									
4	BA	1									
5	AB	2									
6	AB	2									
7	BA	1									
*8	BA	1									
9	AB	2									
10	AB	2									
11	BA	1									
12	BA	1									
13	BA	1									
14	AB	2									
*15	BA	2									
16	AB	2									
Mean			0.148	5.32	1.82	1.19	0.126	82.7	10.8	19.0	0.937
S.D.			0.0507	2.15	3.00	1.17	0.224	34.9	1.67	3.60	0.076
C.V.(%)			34.2	40.5	165	98.2	178	42.2	15.4	19.0	8.2
S.E.M.			0.0135	0.576	0.803	0.313	0.0598	9.34	0.447	0.961	0.0204
N			14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0
Minimum											
Maximum											

. = data could not be modeled.
* = Subject was not included in summary statistics.

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Statistical Comparisons of Plasma Thalidomide Pharmacokinetic Parameters

Treatment B versus Treatment A
For Dose Adjusted Parameters

Parameter	Treatment Means B	A	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	Mean Ratio
Cmax	0.963	1.157	-16.77	0.0042*	96.67	74.7 - 91.7	83.2
Tmax	3.147	2.420	30.05	0.1296	14.74	97.1 - 163.0	130.0
AUC(0-t)	9.067	8.682	4.44	0.0305*	99.99	101.2 - 107.7	104.4
AUC(0-inf)	9.621	9.671	-0.51	0.7257	99.99	96.9 - 102.0	99.5
T 1/2el	5.183	4.808	7.81	0.3438	63.16	93.7 - 121.9	107.8
Kel	0.139	0.149	-6.56	0.2162	95.14	84.5 - 102.4	93.4
LN(Cmax)	-0.066	0.125	-152.9	0.0053*	90.34	74.7 - 91.3	82.6
LN[AUC(0-t)]	2.191	2.147	2.06	0.0249*	99.99	101.4 - 107.8	104.5
LN[AUC(0-inf)]	2.252	2.258	-0.28	0.6373	99.99	97.0 - 101.7	99.4

Treatment B = Thalidomide 200 mg (4 x 50 mg capsules): test
Treatment A = Thalidomide 100 mg (2 x 50 mg capsules): reference

Values of Cmax, AUC(0-t), AUC(0-inf), LN[Cmax], LN[AUC(0-t)], and LN[AUC(0-inf)] are dose adjusted.

Values for Treatments B and A are the least-square means (LSMEANS) from the ANOVA
Parameters with the 'LN' prefix are log-transformed parameters

Pct Difference = difference between treatments (B - A) expressed as a percentage of Treatment A

PR>|T| = ANOVA test for significant differences between treatments
(* difference is statistically significant: p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*test/reference for untransformed parameters
Mean Ratio = 100*exp(test-reference) for log transformed parameters
Calculations exclude subjects 8 and 15.

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Clinical Pharmacology/Biopharmaceutics Review

Thalidomide Capsules 50mg
Synovir™
NDA 20-785
Reviewer:E.D. Bashaw, Pharm.D.

Celgene, Inc.
Warren, NJ

Addendum to Review of an NDA

Introduction

This addendum clarifies the Division of Pharmaceutical Evauation-III's position regarding the approvabilitiy of Celgene's thalidomide product. From a strict regulatory point of view, the sponsor has demonstrated the in vivo pharmacokinetics of thalidomide from their dosage form as required under 21CFR320. For most NDA's, this is all that is required as it is assumed that their NDA stands on its own clinical data. In the case of thalidomide this is not the case. In the original biopharmaceutics review, emphasis was placed on the bioequivalency of the Celgene "clinically studied" product to the Celgene "to-be-marketed" product. This addendum presents a more detailed summary of the Celgene-Tortuga bioequivalency comparison.

Database

The clinical portion of the thalidomide NDA contains data from less than 20 subjects who have been given Celgene's product in uncontrolled or partially controlled studies. In the United States the distribution of thalidomide for ENL has been done either by the Public Health Service directly or through an associated clinical program. Over the years thalidomide has been obtained from a variety of suppliers for use in this program. Originally representations were made to the FDA that Celgene was a major supplier to this program. Investigation and examination of the records at the PHS Hansen's Disease Clinic and elsewhere indicates that they have not been an active supplier to the program. Recently, in the light of the sparse clinical data with their own product, it has developed that for approval Celgene is attempting to utilize the database of other suppliers of thalidomide to the PHS program to demonstrate the efficacy of their product. A case in point is the Tortuga brand of thalidomide.

Tortuga

Tortuga brand thalidomide has been used in the PHS Hansen's Disease program on and off since the 1980's. While there is not a large "clinical study" database of patients, there has accumulated over the years a large database of patient-physician experience with this drug along with the associated medical records. Celgene has made an attempt to tap into this experience by using a biopharmaceutic comparison between their product and the Tortuga product. This comparison was reviewed in the primary review on pages 5-7. The results of this study indicate that both the Celgene clinically studied and to-be-marketed dosage forms of the product are bioinequivalent to the Tortuga product. The Celgene products are themselves bioequivalent to

each other. The Celgene products produce markedly higher plasma levels and have a much shorter plasma half-life than the Tortuga product. (see Fig. 1, below):

Mean Plasma Concentrations
Study PK-001
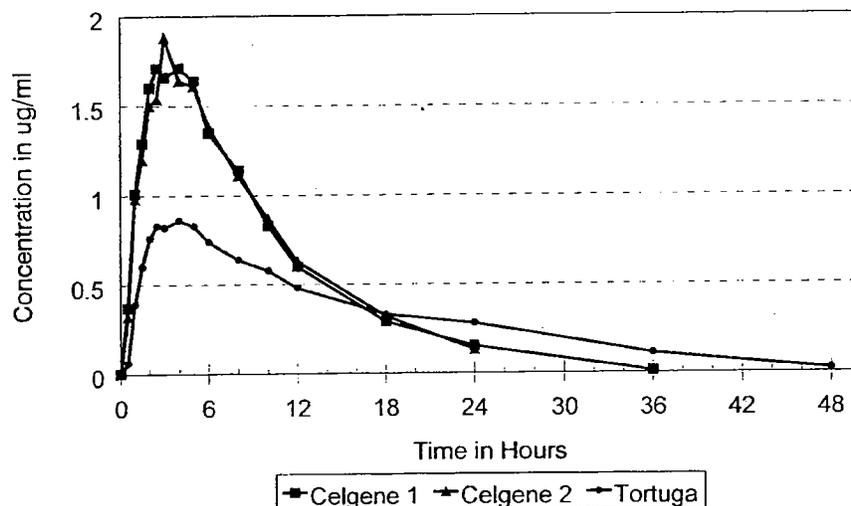
Clearly the products represented here are markedly different and cannot be considered bioequivalent by any relevant measure. While it may be true by analogy that the Celgene product must be effective if the Tortuga product is effective (based on the attainment of higher plasma levels). It is also true that any information regarding the safety of the Tortuga dosage form would be equally inapplicable here as there is no way to extrapolate safety to reflect the attainment of these higher plasma levels. The doubling of peak plasma concentrations (1.05 vs. 2.1ug/ml) and the prolonged half-life (15.3 vs. 5.4hrs) for thalidomide from Tortuga and Celgene commercial capsules, respectively, clearly highlight the altered absorption characteristics between the products. Any attempt to include information from the Tortuga database in the approval/ non-approval decision for Celgene's product is inappropriate and not supported by the data.

Conclusion

Based on the information provided by the applicant it is clear that Celgene's thalidomide product is markedly different and bioinequivalent to the Tortuga product. Any attempt to "bridge" the Tortuga clinical experience to the Celgene experience is unsupportable based on this finding of bioinequivalency. This leads to a two-fold biopharmaceutic recommendation:

1.)   Provided that the Celgene NDA can stand on its own clinical data and that they honor the commitments they have made to the Agency, then the application would be acceptable to the Division of Pharmaceutical Evaluation-III under the provisions of 21CFR320.21.

2).   Should approval of the Celgene NDA require use of the Tortuga database, the applicant would have to demonstrate bioequivalency between the products. Bioequivalency is the only way in which the Agency has accepted cross-product/cross-formulation data to be used. As they have already demonstrated the bioinequivalency of their product to Tortuga's the use of this data to support either clinical efficacy or safety would not be possible due to the observed statistically significant differences in the plasma level profiles. The net result of this would be to render the clinical data portion of the NDA unacceptable.
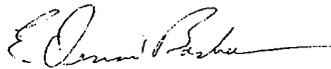
E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

Secondary Review, John Lazor, Pharm.D.

CC: NDA 20-785   (ORIG),
HFD-540/DIV File
HFD-540/CSO/White
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy
HFD-344(Viswanathan)

Clinical Pharmacology/Biopharmaceutics Review

Thalidomide Capsules 50mg
Synovir™
NDA 20-785
Reviewer:E.D. Bashaw, Pharm.D.
AWH

Celgene, Inc.
Warren, NJ

Submission Date:
Dec. 20, 1996-Orig
Jan. 23, 1997-BZ
June 2, 1997-BB

Review of an NDA

I. Background

Thalidomide is a sedative-hypnotic that was originally developed in the early 1960's as a non-addictive alternative to barbituates. Unfortunately, thalidomide was also a very potent teratogen that was species selective, i.e., rats and mice were unusually resistant to the teratogenic effects. The teratogenic potential of thalidomide was not appreciated until an unusual pattern of severe limb malformations (phocomelia-"seal extremeties") was detected in Europe in the children of women who had recieved thalidomide during pregnancy. Although an NDA for thalidomide was submitted by the Richardson Merrill Co. (NDA ℃   7), thalidomide was never marketed in the United States, and was removed from the world-wide market in 1961. Chemically it is N-phthalimidoglutarimide and has the following structure:

Figure 2.1
Chemical Structure of Thalidomide
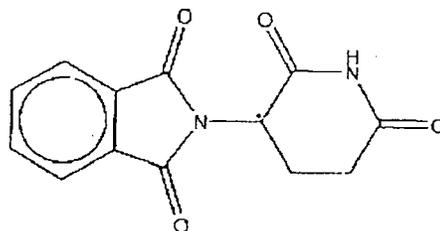
Since its' abandoment in the 1960's, research interest in thalidomide has centered primarily on its mechanism of teratogenicity Recent work has suggested that it is potent inhibitor of TNFα (tumor necrosis factor), which is responsible for, among other things, regulation of the growth of new blood vessels. This finding has led to an understanding of the devastating nature of the teratogenic effects of thalidomide and potential for new clinical uses. Currently there are published articles calling for the use of thalidomide in the treatment of solid tumors, eye disorders, HIV wasting, and Erythema Nodosum Leprosum (ENL). Of these indications ENL is the most widely accepted use for thalidomide with the World Health Organization (WHO) endorsing thalidomide for this use in the late 1970's. It should be noted that thalidomide is not a cure for

Hansen's Disease. It only mitigates the cutaneous manifestations of the disease known as ENL. This NDA was submitted by Celgene, Inc. for use in the treatment of ENL.

II. Recommendation

At the present time the information submitted in support of this NDA is adequate for approval, provided that the applicant honors their commitments to finish study PK-007 as soon as possible. There are significant pieces of information missing from the pharmacokinetic database and significant shortcomings in the analysis presented in the reports provided by the applicant. During a meeting with the applicant on Feb. 11, 1997 they were apprised of some, but not all of the problems with the application at that time. The Agency's concerns were subsequently transmitted to the applicant via a letter from HFD-540 which listed missing and/or incomplete information needed to complete the review (see also the list of noted comments and deficiencies, page 16. At the present time some of the pharmacokinetic issues raised in this letter and in this review are still outstanding. The applicant has committed both to a timeline to provide the information from ongoing studies within the next few months and to the performance of an additional pk trial. From a pharmacokinetic standpoint the information submitted in support of this NDA combined with the commitments made by the applicant, are sufficient to meet the provisions of 21CFR320 as they relate to the pharmacokinetic requirements of a New Drug Application.

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PK-006	Food/Fasting	(Completed-Draft Report In Process)
PK-007	Relative Bioavailability	(Protocol Reviewed-To Be Initiated)

Supportive Trials-INCOMPLETE

PKUK-001	Dose Proportionality-HIV Seropositive	(ONGOING) *
E-003/P	Steady-State Pharmacokinetics in ENL	(ONGOING) *
PK-003	Drug Interaction-Oral Contraceptives	(Completed-Draft Report In Process)

==

III. NDA Overview

As noted above in the recommendations section, the information presented, while incomplete, is adequate from a pharmacokinetic standpoint. In this NDA the applicant has submitted the results of three in vivo pharmacokinetic trials. Two of these trials were done in healthy volunteers and one study was done in subjects with Hansen's disease. At present there are three studies still in progress and two studies completed with the reports in process, and one study in the planning stages. Of these studies the food/fasting, relative bioavailability, and steady-state pharmacokinetic trials can be considered pivotal. Food/fasting studies are not normally in this category but current plans call for the inclusion of a solution treatment in the trial. This will allow for an assessment of the relative bioavailability of the to-be-marketed dosage form. Earlier attempts at this type of a study were hampered by the extremely poor solubility of thalidomide in a non-toxic solvent at volumes which were realistic. Subsequent research by the FDA Biopharmceutics laboratory has revealed a number of non-toxic solvents which are suitable for such a study.

While it is unlikely that these studies will be completed prior to the meeting of the Dermatololty Advisory Committee approval it is necessary that the applicant commit to performing these studies and that they provide an acceptable timeline of when the results from these studies will be available for review. As it is hoped that the applicant will move swiftly to resolve these issues, the information that has been submitted to date will be reveiwed here and any missing or incomplete items will be forwarded to the applicant for resolution.

IV. Analytical Methods

Throughout the current Celgene sponsored studies on thalidomide, two different analytical methods were used to analyze the in vivo plasma samples. The first method, developed by Celgene and used for the single dose pk studies (PK-001 and PK-004), was a high performance liquid chromatography (HPLC) method. The second method, developed by [   ] was a liquid chromatography/mass spectrometry (LC/MS) method that was developed from the Celgene HPLC method. The LC/MS method was used in PK-005 in Hansen's patients to look for both parent and the N-OH, 3-OH, and 4-OH metabolites of thalidomide in both plasma and urine. An overview of each method is presented below along with representative data on accuracy and linearity. A summary of the analytical validation for each individual trial is attached as part of the Study Summary Sheets found in the appendicies.

HPLC Method

The HPLC method used in PK-001 and -004 was originally developed by Celgene with the assistance of [   ] who was the analytical laboratory of record. Briefly, thalidomide was extracted from plasma using a series of acid/base rinses. The resulting material was further extracted from the aqueous media using an unlisted organic solvent. The organic solvent was then evaporated away and the resulting material was solubilized using [

] [

] Detection of thalidomide was done via UV detection at 218nm. The internal standard was phenacetin.

While the applicant has presented only a brief sketch of the analytical procedures used during the trial, they have included all of the results from the analytical portion of the NDA as they relate to accuracy, linearity, and lower detectable limit. This material is located in volume 1.18 of the NDA and is adequate for demonstration of the accuracy and linearity of the methods used in these trials.

LC/MS Method

The LC/MS method was developed by [   ] from the original HPLC methodolgy. It was done so as to quantify both parent and the three most likely metabolites (identified in the literature) in the plasma and the urine. Briefly, [

] were analyzed by

LC/MS using [

                                                                    ]

Throughout the assay daily standard curves for both urine and plasma were constructed for thalidomide and its three likely metabolites (3-OH, 4-OH, and N-OH). In addition daily quality control samples for all three species in both fluids were also prepared. Throughout the analysis phase of the study the validation of the assay for thalidomide was acceptable in terms of linearity, accuracy, specificity, and precision. The same was true for most of the other species of interest except the N-OH metabolite. It repeatedly failed the acceptance criteria for both accuracy and precision in both fluids. For the 3-OH and 4-OH metabolites there were occasional failures of the assay in regards to the residual standard error at one concentration or another, but no systematic pattern of assay failure was noted for these species.

Unlike the validation provided for the HPLC assay reported above, the applicant has provided a detailed sketch of the analytical procedures used during the trial. The study report contained detailed information on the accuracy, linearity, specificity and lower detectable limit for thalidomide and its theoretical metabolites. While the N-OH metabolite data did show significant variability at all concentrations, the assay was acceptable as a qualitative tool to detect the presence or absence of N-OH-thalidomide. This material is located in volume 1.18 of the NDA and is adequate for demonstration of the accuracy and linearity of the methods used in these trials.

V. General Pharmacokinetics

Up until the present series of studies, the pharmacokinetic profile of thalidomide has not been systematically studied. This was primarily due to the discontinuation of active large scale research on thalidomide prior to the recognition of pharmacokinetics as a science. The studies reported below were done as part of an agreement with the applicant as to the number and types of studies to be performed to meet the regulatory burden of both identifying the pharmacokinetics of thalidomide itself and the applicant's capsule dosage form.

Study PK-001:Bioavailability/Bioequivalence of Thalidomide

During the development of thalidomide for this indication, two different suppliers of thalidomide capsules have been used by Celgene. The primary clinical manufacturer and the manufacturer of the to-be-marketed product and the lots used in the biostudies was [

          ] Some of the earlier clinical studies were done using lots of drug supplied by the [   ] Because of the need to link thesr data, the applicant undertook a standard evaluation of the bioequivalency assessment between the two suppliers. In addition the applicant also elected to include in this study a third arm consisting of an alternative manufacturer of thalidomide that is referred to as the "Tortuga" formulation. The Tortuga formulation has no relationship to either of the two Celgene lots. It is included in this study as it was commonly used from time to time in the Hansen's program and there were questions as to the validity of extrapolating the results from subjects treated with the Tortuga formulation to the Celgene material.

In addition to the obvious bioequivalency aspects of clinically studied vs. to-be-marketed formulations, there is an issue of polymorphism that has to be dealt with. Thalidomide exits as at

least two polymorphs α and β. Polymorphs, as a function of their altered crystalline structure demonstrate different physio-chemical properties. As these properties may play a role in the bioavailability of an insoluble compound, the effect of polymorphism on bioavailability must also be determined. In this study the [   ] formulation referred to as Formulation 1 is primarily composed of the β polymorph, while [   ] Formulation 2 is primarily the α polymorph. A comparative formulation table is presented below:

Componets (in mg)	[ ] Formulation 1	[ ] Formulation 2
Thalidomide	50	50
Lactose	[ ]	
Magnesium Stearate	[ ]	
[ ]		[ ]
[ ]		
Stearic Acid NF		
[ ]		
[ ]		
Anhydrous Lactose NF		
Fill Weight (mg)	[ ]	[ ]

The study itself was designed as a three-way crossover trial in 17 healthy male subjects. Healthy subjects were chosen in this trial as the recruitment of adequate numbers of subjects for an in vivo bioequivalency trial in ENL patients would entail a prohibitively long enrollment period, as ENL is an orphan indication. Attached in Appendix I is the study summary sheet for this trial detailing the location, demographics, analytical validation, and study procedure outline. In addition the supportive data tables for the summary tables and figures presented below are also included in the appendix as pages 2-6. Reproduced below are the summary results extracted from these tables:

Mean PK Parameters (%CV)

	[ ] Formulation 1 (4x50mg caps.)	[ ] Formulation 2 (4x50mg caps.)	Tortuga Formulation (2x100mg caps.)
AUC_{0-t} (ug*hr/ml)	18.1(17.1%)	18.1(17.3%)	14(31.9%)
AUC_{0-inf} (ug*hr/ml)	19.8(18.2%)	20.3(14.1%)	18.7(25.1%)
Cmax (ug/ml)	2.0(27.6%)	2.1(25.9%)	1.05(24.8%)
Tmax (hr)	3.2(43.8%)	3.5(45.7%)	3.4(41.2%)
T1/2 (hr)	6.17(41.5%)	5.42(24.5%)	15.3(39.2%)
Cl/F (L/hr)	10.5(19.1%)	10(14%)	11.4(26.8%)
MRT (hr)	8.8	9.27	14.88

A visual examination of the dataset clearly suggests that the two Celgene formulations are very similar if not bioequivalent. The Tortuga formulation is, however, markedly different as evidenced by both AUC, Cmax, and half-life. It appears to be very poorly absorbed relative to either of the other two formulations. Further evidence of this is presented below as a mean plot

of the individual plasma concentraions (see pages 3-5, Appendix I).

Mean Plasma Concentrations
Study PK-001
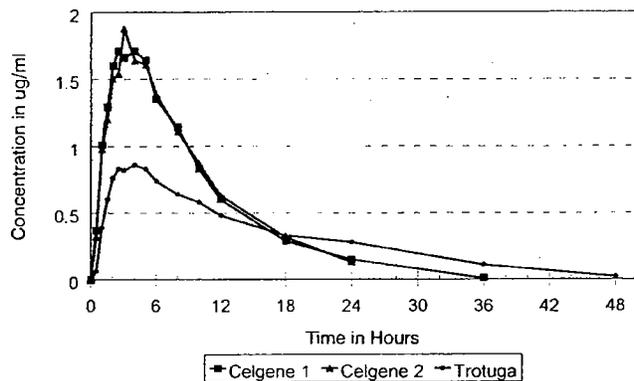
Clearly the relative bioavailability of thalidomide from the Tortuga formulation is much less than that of either Celgene formulation. As part of the comparison across treatments this reviewer calculated a mean residence time (MRT) for each of the formulations. MRT is a measure of the time required for 63.2% of the amount of drug absorbed to be eliminated. As such it provides for a relative rate comparison between the products. The MRT for the Tortuga formulation is almost 60% higher (14hrs vs. ~9hrs) than that for either of the Celgene formulations. This suggests a delayed pattern of absorption for the Tortuga product. It is apparent from this data that the Tortuga product is not bioequivalent to either of the Celgene dosage forms. As for a direct comparison of Celgene 1 to Celgene 2, the following table summarizes these results:

	Celgene 1 vs. 2 (90% Confidence Intervals)	Pr>[T] (ANOVA)	Power% (ANOVA)
AUC_{0-t} (ug*hr/ml)*	91.6-109.6	0.9735	95.3
AUC_{0-inf} (ug*hr/ml)*	89.3-107.4	0.7002	94.3
Cmax (ug/ml)*	84.9-105.7	0.41	84.8
Tmax (hr)	66.4-116.6	0.5712	24.8
T1/2 (hr)	74.4-172.9	0.4188	9.12
Cl/F (L/hr)	91.6-113	0.7162	86.4

*Calculation based on ln transformed data

Using the standard bioequivalency test (90% confidence intervals based on a two 1-sided t-test) it appears that the two Celgene formulations arc bioequivalent to each other. As for the issue of polymorphism, as each formulation represents a different polymorphic form, the study also addresses this issue completely. According to input from the HFD-540 Chemistry Team Leader, Dr. Tony DeCamp, t'⸤

⸥ While this study does demonstrate bioequivalency at extremes of polymorphism, whether or not polymorphism may play a role in shelf-life stability is not known at this time.

Study PK-004: Dose Proportionality

This study was done to assess the degree of dose proportionality present in the final formulation across a range of single doses from 50 to 400mg. A total of 15 healthy subjects (14 males/1female) were enrolled in the trial and 14 subjects completed all phases of the trial (one subject was dropped from the trial after developing a *sore throat*.) Each dose was accompanied with 240ml of water and the subjects were instructed to fast for 10hrs before each dose and for 4 hours after each dose. A two-week washout period was used between each dosing period. Attached as pages 7-11, Appendix I is the Study Summary Sheet which describes the condition and methods used in summary form. Throughout each dosing phase blood samples were obtained to determine the in vivo profile of thalidomide following each dosing period. Reproduced below are the summary results from this trial:

	1x50mg	4x50mg	8x50mg
AUC_{0-t} (ug*hr/ml)	3.44(19%)	15.6(25%)	31.4(31%)
AUC_{0-inf} (ug*hr/ml)	4.90(16%)	18.9(17%)	36.4(26%)
Cmax (ug/ml)	0.622(52%)	1.76(30%)	2.82(28%)
Tmax (hr)	2.9(66%)	3.5(57%)	4.3(37%)
T1/2 (hr)	5.52(37%)	5.53(25%)	7.29(36%)
Cl/F (L/hr)	10.4(17%)	10.9(17%)	11.7(24%)
MRT (hr)	9.08(34%)	9.83(21%)	11.7(25%)

One of the easisest ways of assessing relative dose proportionality is to compare the ratio of a pharmacokinetic parameter, such as AUC or Cmax, to dose as a function of dose. Presented below is a figure that demonstrates the effect of increases in dose on AUC0-t, AUC0-inf, and Cmax.

Thalidomide Dose Proportionality-PK004
AUC vs AUC/dose and Cmax vs Cmax/dose
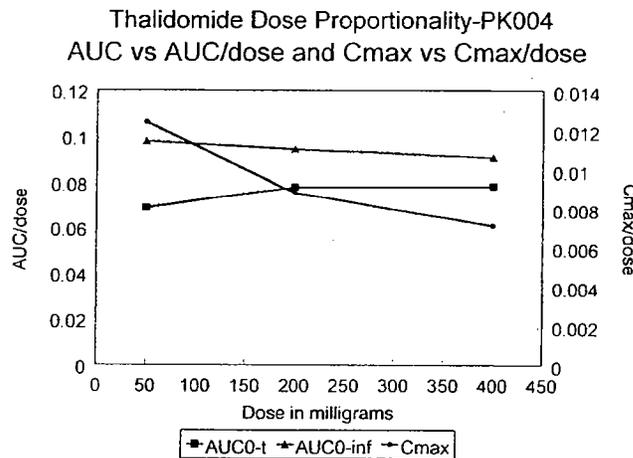
Ideally, in the case of dose proportionality, the resulting slopes of the lines would be zero representing a proportional increase in the parameter with dose. Examination of the figure from this study indicates that while there is indeed a rough dose proportionality for either AUC parameter, there is a significant drop off in Cmax. This less than proportional increase in Cmax is possibly due to the combined effects of the poor solubility of thalidomide in aqueous media,

along with the number of dosage units given. While the Tmax values also show a shifting to the right with increasing doses (from 2.9 to 4.3 hours), the strongest evidence for an alteration in absorption pattern comes from the mean residence time (MRT) values which increase from 9.08hrs for a 50mg dose to 11.7hrs for a 400mg dose. This represents a mean 15% increase across the subjects. (MRT is a measure of the time required to eliminate 63.2% of the absorbed dose and is indicative of a delay in absorption.) A mean plot of the raw data from this trial is presented below:

Thalidomide Dose Proportionality-PK004
Mean Data
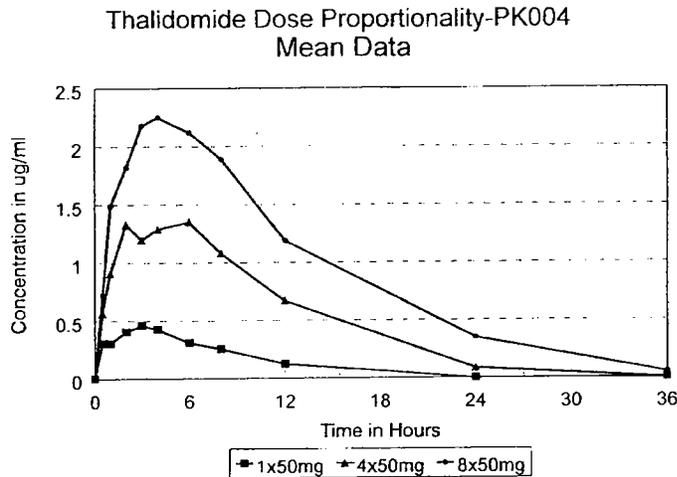
This figure, along with the data from the trial indicates that oral administration of Synovir® capsules demonstrates dose-proprotionality across for AUC but not Cmax across the range of doses used. Reasons for the delay in thalidomide absorption have not been adequately determined by the applicant but are most likely a consequence of the poor aqueous solubility of thalidomide. For doses larger than 200mg it appears that divided doses would be the best approach.

Study PK-005: Effect of Disease State (Hansen's Disease) on Thalidomide Pharmacokinetics

The majority of the submitted pharmacokinetic work has been done in healthy adults. This was due primarily to the difficulty in recruiting patients(i.e., both ENL and Hansen's Disease are considered orphan diseases) and the need to collect relatively large volumes of blood from patients who have circulatory problems as a consequence of their disease raises recruitment and ethical issues. In a pre-NDA meeting with the applicant it was decided that for approval the applicant would submit a single-dose study in a limited number of Hansen's Disease patients. In addition the applicant agreed to collect pk samples at steay-state (trough levels) in an ongoing clinical trial of patiets with ENL(E-001). At the present time the steady-state data are not available for review.

Trial PK-005 was originally intened to be a definitive metabolism study of thalidomide using radio-labelled drug. Unfortunately, due to concerns over the ethics of exposing patients with an orphan disease to radioactive tracers it was decided that the study would be done with cold techniques. The analytical method chosen for this trial was the previously summarized LC/MS method that was validated for detection of both parent and the N-OH, 3-OH, and 4-OH

metabolites of thalidomide in both plasma and urine. These metabolites were chosen as being those most likely to be detected given what is known about the hydrolysis of thalidomide in blood.

A total of six Hansen's patients (4males and 2females) were enrolled in the trial and received a single 400mg dose of thalidomide. Attached as pages 12-24 in Appendix I is the study summary data sheet for this trial along with the supportive data. A summary of the data collected from this trial is presented below:

| | Mean Plasma Data (%CV) | | | |
	Thalidomide	N-OH-thalidomide	3-OH-thalidomide	4-OH-thalidomide
AUC0-t(ug*hr/ml)	45.1(47)	()	()	()
AUC0-inf(ug*hr/ml)	46.4(44.1)	()	()	()
Cmax(ug/mL)	3.44(52.6)	()	()	()
Tmax(hr.)	5.7(27)	()	()	()
MRT(hr.)	12.4(12)	()	()	()
Cl/F(L/hr)	10.1(41.6)	()	()	()
T1/2(hr.)	6.86(17.1)	()	()	()
	Mean Urine Data (%CV)			
	Thalidomide	N-OH-thalidomide	3-OH-thalidomide	4-OH-thalidomide
Total in Urine(ug)	2750(84.7)	()	()	70.3(96.2)
% of Dose in Urine	0.687(0.02)	()	()	0.0176(96)
Clr(ml/min)	1.15(0.2)	()	()	()

As the table above amply demonstrates, the results of this trial were quite disappointing. While it was intended that this trial would provide some idea of the metabolic routes and relative contribution of the metabolites to plasma thalidomide levels, none of the expected metabolites were seen in the plasma. As the limit of quantification of the assay was 50ng/ml, it appears that if these metabolites are formed, they must only be intermediate metabolites with an extremely short residence time (if any) in the blood.

One of the other objectives of this trial was to assess the effect of disease state on the pharmacokinetics of thalidomide, relative to normal volunteers in other trials. This issue is an important one as the commonly used agents to treat Hansen's Disease and ENL are known metabolic inhibitors/inducers (rifampin, dapsone, etc.) For the six subjects in this trial there were a total of 43 concomitant medications listed in the patient record (see pages 22-24, Appendix I). Examples of the drugs used included dapsone 6/6 pts. and acetaminophen 2/6 pts. Reproduced below is representative figure of the mean plasma concentrations produced by thalidomide in these patients (a plot of the individual subject data is attached as page 19, Appendix I) combined with mean plasma concentration data from the 400mg dose leg from PK-004.

**Comparative Mean Plasma Concentration 400mg Dose
Study PK-005 and PK-004**
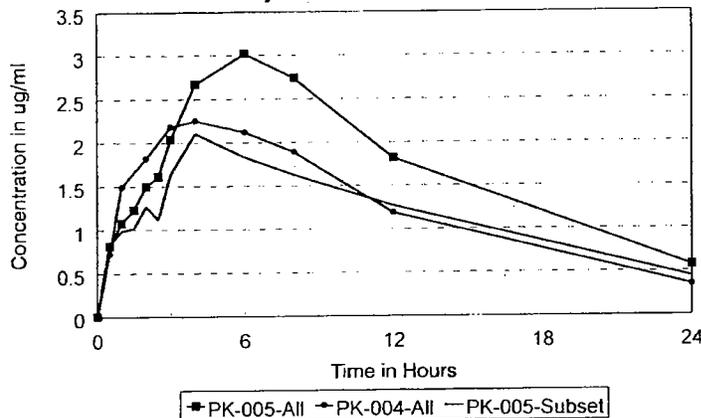
Examination of the data suggests that there is a prolonged absorption phase present which causes an increase in the total area under the curve of almost 44%. Most of this increase was traced to two individuals who had peak levels of 4.7 and 6.2 ug/ml. When they were removed from the study analysis most of the differences were attenuated. However, there is no obvious justification for removing these subjects from the analysis. Examination of the individual plasma curve fitting done by the applicant shows no apparent reason for this increased absorption. Whether these results indicate a true representation of the variability present in absorption or are artifactual in nature is unclear due to the small number of subjects (n=6) in the trial.

The elimination rate of thalidomide does not appear to be changed across the treatments, this suggests that the increase in plasma levels is due not to alterations in disposition, but due to changes in absorption. Possible explanations for this increase include inhibition of first pass metabolism, increased absorption due to a drug-drug mediated interaction, or some recycling phenomena.

One part of this study remains undocumented. In this trial the applicant also collected fecal samples throughout the sampling interval. These samples were frozen after collection with the intention that they would be analyzed for parent and metabolites as part of the analytical program. So far the applicant has refused to complete the analysis on this material. The applicant has cited the cost of the analysis as the primary reason for not completing this part of the study analysis. It is this reviewers opinion that the analysis of this material should be a priority.

VI. Supportive Literature Reports

The use of literature reports to support this NDA is primarily limited to describing the physio-chemistry of thalidomide itself. Over the years there have been many formulations and many manufacturers with little or no standardization. This has tended to make the published clinical data difficult to interpret as the bioavailability of thalidomide can vary widely, due to its poor solubility in aqueous media. From the articles submitted by the applicant, two areas of interest were identified and are abstracted below. These areas deal with the hydrolysis of thalidomide and its interconversion between isomers.

Hydrolysis of Thalidomide

Throughout the 1960's investigation of the mechanism of teratogenicity was the only area of active research on thalidomide. While the metabolic break-down products of thalidomide were unknown, initially, much work was done on the spontaneous hydrolysis of thalidomide into a number of chemical species. While there is some dispute regarding the relative importance of the different pathways and the exact number of products formed it is clear from the proposed hydrolysis scheme proposed below by Czejka and Koch (1987) that it is extensive:
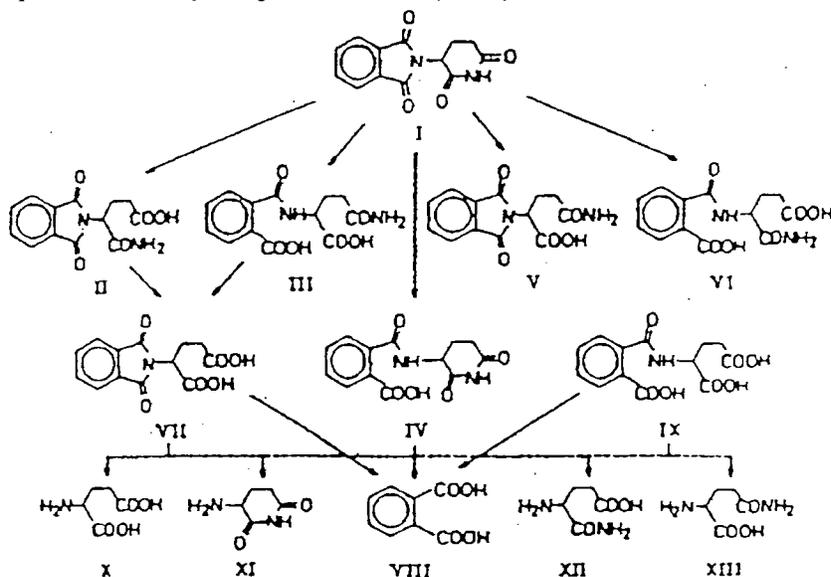
Czejka, M.J., and Koch, H.P.. "Determination of Thalidomide and Its Major Metabolites by High Performance Liquid Chromoatography", Journal of Chromatography, 413 (1987)181-187.

A number of metabolic/hydrolysis schemes for thalidomide have been published since the 1960's. Unfortunately there is not a commonality across the studies in either the naming convention for the breakdown prouducts or the stepwise scheme followed. What can be said for the breakdown products of thalidomide is that with its four carbonyl's present in two nitrogen containing rings, there is ample opportunity for ring opening hydrolysis reactions forming either the corresponding carboxcyclic acids or amides.

Attempts to quantify the precise breakdown of thalidomide in vivo in humans have not been successful to date as there has been a reluctance to administer radio-labelled thalidomide to even healthy adult males due to concerns over the residence time of some of the metabolites in vivo. Examination of the proposed and in vitro hydrolysis products suggests that definitive evaluation of the metabolic products of thalidomide will require the administration of two doses of radiolabelled thalidomide. The first dose containing the label in the benzene ring, the second dose containing the label at the chiral center. In doing so, both the stereochemistry and the metabolic fate of the two sides of the molecule, connected through a nitrogen, can be determined. Due to the nature of the reaction, i.e., hydrolysis, it is apparent that a tritium label would be readily lost to the environment. Only a C_{14} study would provide sufficient specificity.

Interconversion of Thalidomide Isomers

As to the issue of stereochemistry, thalidomide has one chiral center and as such exists as both R and S enantiomers. In the mid-70's when analytical techniques were developed for the separation of isomers, a number of reseachers postulated that the toxicity of thalidomide was related to one isomer (the S) while the clinical efficacy (as a sedative-hypnotic) was related to the R isomer. This was supported by some in vivo animal studies in rats that indicated, with intraperitoneal injection, that there was no interconversion between isomers.

Eriksson, T., Bjorkman, S., Roth, B., Fyge, A. and Hoglund, P., "Stereospecific Determination, Chiral Inversion In Vitro and Pharmackinetics in Humans of the Enantiomers of Thlaidomide", Chirality, 7, (1995) 44-52.

This article, published in 1995 presents the results following a single dose administration of thalidomide to six healthy male volunteers as either pure (+)-R- or pure (-)-S- or racemate. Pharmacokinetic samples were drawn frequently over the first 24 hours following each dose. A chiral specific HPLC assay was used to detect and quantify the individual isomers. The results of the study indicated that the half-life of interconversion was approximately 2.5hrs for the transition from R to S or S to R(k_{rs}= 0.30+/-0.017, k_{sr}=0.31+/-0.019). Contrasted with a plasma half-life of 4 hours for the elimination of thalidomide the article strongly suggests that administration of either isomer in an attempt to avoid or attenuate thalidomide induced birth defects would not be successful. It also demonstrates that there is not a preferential uptake or metabolism for thalidomide, following oral adminstration.

VII. Supportive In Vitro Studies

In Vitro Metabolism

Because of the concern over both the metabolic fate of thalidomide and the problem of concomitant drug administration, the applicant, at the direction of the FDA, undertook an investigation of the in vitro metabolism of thalidomide by both cloned human and harvested rat microsomes. These experiments were carried out by [ ] under contract from Celgene. The reseach protocol used by [ ] included evaluation of the potential for thalidomide metabolism under the following conditions:

1. Aroclor-induced rat hepatic microsomes and S9
2. Phenobarbital-induced rat hepatic microsomes and S9
3. Pooled human hepatic microsomes
4. Microsomes containing specific cloned human P-450 isozymes (CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4).

In addition, the assay conditions of incubation time (0.5 and 4hrs), pH (6.0-8.0), and thalidomide concentrations (1-200ug/ml) were varied to see if they had any effect on the metabolism of thalidomide. The results of these studies demonstrated that while small amounts of the 3-OH and 4-OH-thalidomide are present at the limit of detection, thalidomide is not metabolised to any significant extent by any of the enzyme systems tested. The concentrations of thalidomide used were equivalent to 40x the peak plasma concentrations seen in vivo following a 400mg dose.

In addition to the effect of enzymes upon thalidomide, a follow-up study was also done to see if the presence of thalidomide caused either an induction or inhibition of enzymatic activity. This study revealed that thalidomide does not affect the metabolic activity of any of the enzyme systems tested (see page 41, Appendix II).

The cumulative results of this trial strongly suggest that the common pathways of metabolic inactivation do not apply to the initial metabolism of thalidomide. Whether or not these enzyme systems are involved to a significant extent to the downstream metabolism of thalidomide hydrolysis products is unknown. One potential problem noted in the report by the applicant was the poor activity of some of the cloned microsomes. As part of the validation process of the assay, parallel control samples were run against thalidomide using the specific metabolic substate for the cloned microsome. All of the tested systems demonstrated lower in vitro activity than was claimed by the supplier (see page 42, Appendix II). For the CYP 2B6 microsome the demonstrated activity of the cloned system was 17x lower than that claimed by the supplier. No specific reason for the loss of metabolic activity was identified by the laboratory, although age, poor handling, and differences in laboratory procedures were introduced as possible reasons.

While the results of this study are useful in a qualitative sense, the lack of consistency between the labeled and demonstrated potency of the claimed microsomes is a point of some concern. Clearly mis-handled enzyme systems are not overly reliable. In this case, the laboratory has attempted to overcome this shortcoming by increasing the molar concentration of both enzyme and substrate to maximize the conditions of the test. The net result of this was the lack of any additional thalidomide metabolizing activity. Given the limitations of the assay potency, the results of this study suggests that thalidomide itself is not a preferred substrate for any of the common P-450 metabolizing enzymes.

In Vitro Dissolution

The in vitro dissolution method proposed by Celgene is a modification of the proposed FDA dissolution mongraph for thalidomide tablets and capsules prepared by the Division of Drug Analysis (1989). The proposed method is as follows:

Apparatus:	USP Paddle (apparatus 2)
Medium:	4000ml of 0.225M HCl and 1ml of Brij-35[1]
Speed:	75rpm
Temperature:	37C
Sampling Times:	0, 15, 30, 45, and 60 min.
Specification:	Q=70% at 60min.

The only modification between this method and the proposed FDA monograph method is that the applicant has raised the Q value from the FDA proposed C $\mathfrak{J}$ to 70% at 60min. This increase in Q value is in keeping with the performance of the Celgene produced capsules to date, see below:

---

[1]   polyoxyethylene (23) lauryl ether solution

Thalidomide Capsule Mean Dissolution
FDA Monograph Method

At S1 level Q=Q + 5%
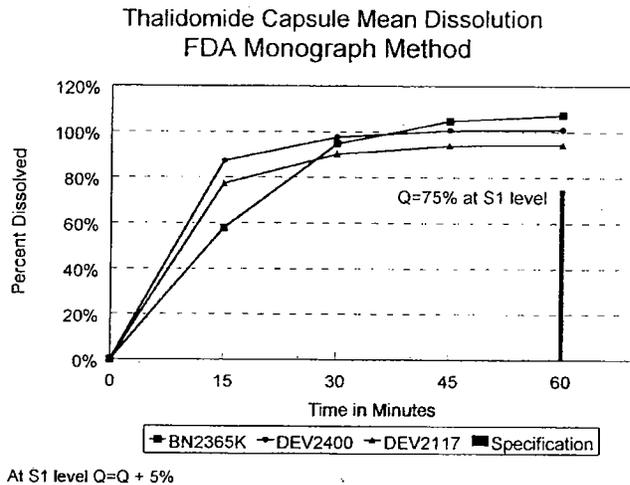
As demonstrated by the mean data above, the performance of the Celgene produced has relatively good dissolution performance, under the conditions of the test. The FDA proposed spec. of Q= [ ] is clearly inadequate. The applicant's proposed spec. of Q=70% is a marked improvement and could possibly be tighted further still to Q=75% without too much difficulty (see individual capsule data as pages 43-45, Appendix II, attached). While it could most likely be done, it must also be realized that unlike most manufacturers, Celgene has not really scaled up this product like most applicants to the million dosage unit range. It is quite possible that once the product is scaled-up (if ever) that the dissolution performance may drop somewhat to reflect the true nature of manufacturing variability. The proposed specification is an improvement over the FDA monograph specification and is not unreasonable. The applicant's proposed modification of the FDA monograph method is acceptable.

VIII. Conclusions

From the studies undertaken by the applicant in this NDA the following conclusions can be made:

1. The extent of thalidomide bioavailability is unknown. This lack of information is due to the lack of a soluble form of thalidomide at the start of the development program. As a suitable solvent has now been found, and the applicant will be required to do such a study as a condition of approval.

2. Thalidomide is slowly absorbed orally with peak plasma levels not occuring until 4-5hrs. after dosing. The mean residence time of thalidomide ranges from 7-11hrs which also suggests a slow absorption phase.

3. Thalidomide demonstrates dose proportionality in normal subjects across a range of single doses from 50 to 400mg for AUC. Peak plasma levels are less than proportional across the same dosage range, suggesting a further reduction in absorption rate, possibly due to the large volume of capsules (8) used to administer the 400mg dose.

4. In Hansen's disease patients the rate, but not the extent of absorption appears to be increased. Whether or not this is due to the effects of disease state or

concomitant drug administration is unknown. The terminal elmination rate is similar between the two groups.

5. While the specific pattern of metabolism is still unknown, it is thought to be primarily due to hydrolysis. In vitro studies using isolated rat hepatocytes and cloned human microsomes have indicated that the primary metabolism of thalidomide is not mediated by CYP-450.

6. Investigations into the stereochemistry and interconversion of thalidomide isomers have revealed that the rate of interconversion between R and S enantiomers is sufficiently rapid, relative to terminal elimination rate, to make administration of either isomer impractible.

7. Celgene's investigational formulation of thalidomide is bioequivalent to the to-be-marketed formulation. There is no pharmacokinetic difference between the α and β polymorphs of thalidomide. Neither version of Celgene's thalidomide is bioequivalent to the "Tortuga"formulation.

8. The proposed in vitro dissolution methodology is acceptable with the revised Q specification of Q= $\sqsubset$ $\sqsupset$ at 60min.

9. Adequate labeling has not been submitted.

As noted in the recommendation section on page 2 of this review, there is still a significant amount of information outstanding for this NDA. From a biopharmaceutic standpoint, some of this information is critical (i.e., relative bioavailability) from a regulatory point of view. Clearly additional data are needed. The applicant, Celgene, has a number of studies underway and has committed to perform other studies in this area. Given that this drug is being approved for an orphan indication and given that the applicant has done pharmacokinetic studies with their clinical and to-be-marketed dosage forms, the amount of information submitted in support of this NDA is sufficient for approval provided that the applicant makes a firm commitment to supply the other information outlined in this review in a timely manner.

IX. Comments

1. The labeling proposed by the applicant is inadequate as it neither follows the current recommended format of the Office of Clinical Pharmacology and Biopharmaceutics nor is it factually correct in regards to metabolic fate, differences between Hansens subjects and normal volunteers or the adequacy of the assessment of gender effects.

X. Deficiencies

1. At the present time significant amounts of information are yet to be submitted to the NDA. These include timelines for the completion of the food effect study and the submission of the steady-state pk data from E-001.

2. The sponsor has yet to fulfill their commitment made in the protocol to the analysis of fecal samples collected during study PK-005.

(signature)

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

Secondary Review, John Lazor, Pharm.D. _for_ _(signature)_ Janice Barnett Jenkins 8/13/97

CC: NDA 20-785 (ORIG),
HFD-540/DIV File
HFD-540/CSO/White
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy
HFD-344(Viswanathan)

Appendix-I

Appears This Way
On Original

DA/IND# 20-785   Suppl/Amend.# Orig.   Submission Date: 12/20/96   Volume: 2.14

Study Type: Comparative Bioavailability   Study # PK-001

Study Title: Comparative Bioavailability of Two Different Celgene Polymorphic Formulations vs. Tortuga Thalidomide

Clinical Investigator [_____   Analytical Investigator [_____

Site _____   Site _____

_____]   _____]

Single Dose: Y   Multiple Dose: N   Washout Period: 1 week

Cross-Over Y   Parallel ___   Other Design: _____

Fasted Y   Food Study ___   FDA High Fat Breakfast _____

If fasted, how long (hrs.)? 12

Subject Breakdown

Normal XX Patients ___   Young XX   Elderly ___   Renal ___   Hepatic ___

	Subject Type	Males		Group	Males	N=	17	M=	17	F=	0
Weight	Mean 174 Range	211-140lbs		Group		N=		M=		F=	
Age	Mean 32.5 Range	43-20yrs		Group		N=		M=		F=	
	Subject Type			Group		N=		M=		F=	
Weight	Mean Range			Group		N=		M=		F=	
Age	Mean Range			Group		N=		M=		F=	

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
A. Commercial	200mg	capsule	50mg	DEV2117	[ ]
B. Clinical Celgene	200mg	capsule	50mg	BN2365K	[ ]
C. Tortuga	200mg	capsule	100mg	001	UNK

Sampling Times

Plasma   5ml, at time 0 and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, and 48hrs post dosing

Urine   N/A

Feces   N/A

Assay Method: HPLC (orig)

Assay Sensitivity 0.1 μg/ml thalidomide

Assay Accuracy   Target|Observed|%RSD;0.1|0.07|7.9%;1|.89|1.3%;5|4.1|0.77

Labeling Claims   Based on the results of this study the clinically studied Celgene material is
From Study   bioequivalent to the to-be-marketed product, while the Tortuga formulation
demonstrates a reduced bioavailability. The presence of product produced
exclusively of polylmorph α or β has no effect on bioequivalency.

2

Commercial – Celgene
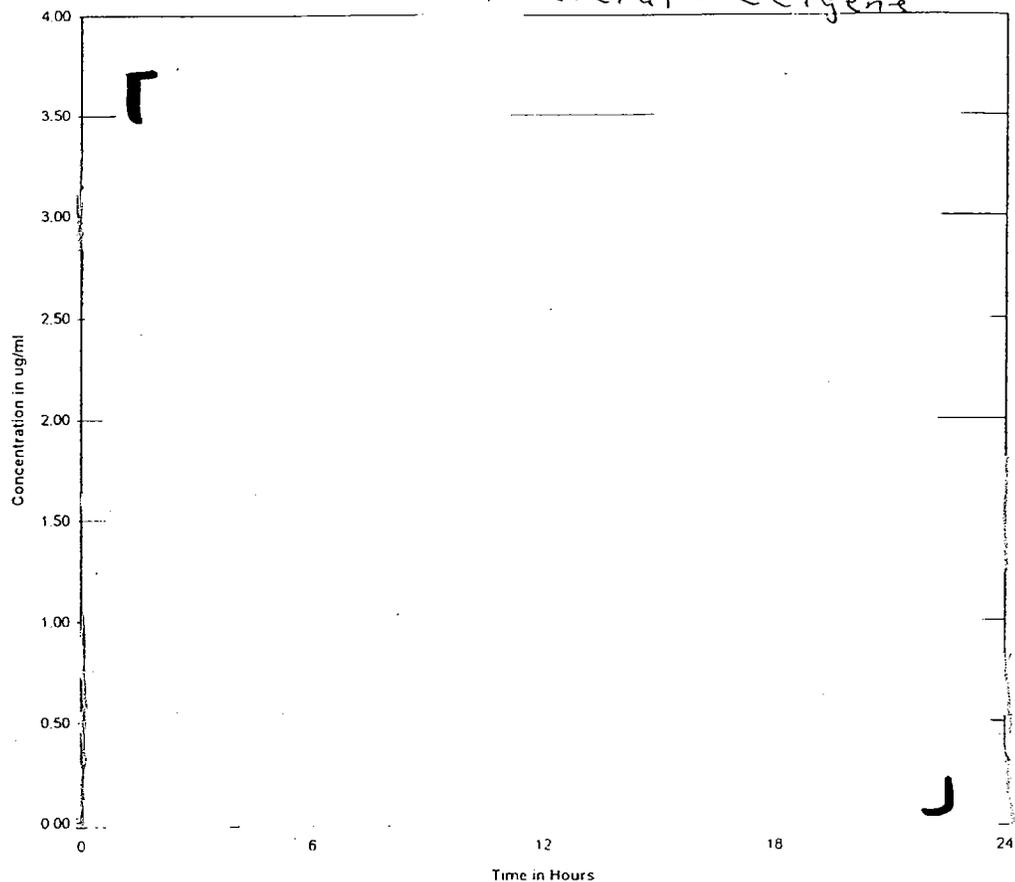
Concentration in ug/ml

4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

0   6   12   18   24

Time in Hours

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for 4x50 mg capsules, Celgene Commercial Formulation
(Trt A)

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-t) ug*hr/mL	AUC(0-inf) ug*hr/mL	T 1/2el hr	Kel 1/hr	CL/F L/hr	LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	ABC	1										
2	BCA	3										
3	CAB	2										
4	ABC	1										
5	CAB	2										
6	BCA	3										
7	CAB	2										
8	BCA	3										
9	ABC	1										
10	ABC	1										
11	BCA	3										
13	BCA	3										
14	CAB	2										
15	ABC	1										
16	ABC	1										
17	BCA	3										
18	CAB	2										
Mean			2.00	3.2	18.1	19.8	6.17	0.125	10.5	0.661	2.88	2.97
S.D.			0.553	1.4	3.09	3.61	2.56	0.0361	2.01	0.246	0.176	0.185
C.V.(%)			27.7	42	17.0	18.2	41.5	28.9	19.2	37.7	6.10	6.25
S.E.M.			0.134	0.33	0.750	0.902	0.640	0.00902	0.503	0.0596	0.0426	0.0463
N			17.0	17	17.0	16.0	16.0	16.0	16.0	17.0	17.0	16.0
Minimum												
Maximum												

3

Clinical - Celgene

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for 4x50 mg capsules, Celgene Clinical Trials Formulation
(Trt B)

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-t) ug•hr/mL	AUC(0-inf) ug•hr/mL	T 1/2el hr	Kel 1/hr	CL/F L/hr	LN(Cmax)	Log-Parameters LN[AUC(0-t)]	LN[AUC(0-inf)]
1	ABC	2										
2	BCA	1										
3	CAB	3										
4	ABC	2										
5	CAB	3										
6	BCA	1										
7	CAB	3										
8	BCA	1										
9	ABC	2										
10	ABC	2										
11	BCA	1										
13	BCA	1										
14	CAB	3										
15	ABC	2										
16	ABC	2										
17	BCA	1										
18	CAB	3										
Mean			2.10	3.5	18.1	20.3	5.42	0.133	10.0	0.709	2.88	3.00
S.D.			0.543	1.6	3.14	2.87	1.33	0.0224	1.40	0.273	0.191	0.140
C.V.(%)			25.8	44	17.3	14.1	24.6	16.9	14.0	38.5	6.65	4.65
S.E.M.			0.132	0.38	0.761	0.740	0.344	0.00578	0.361	0.0662	0.0464	0.0361
N			17.0	17	17.0	15.0	15.0	15.0	15.0	17.0	17.0	15.0
Minimum												
Maximum												
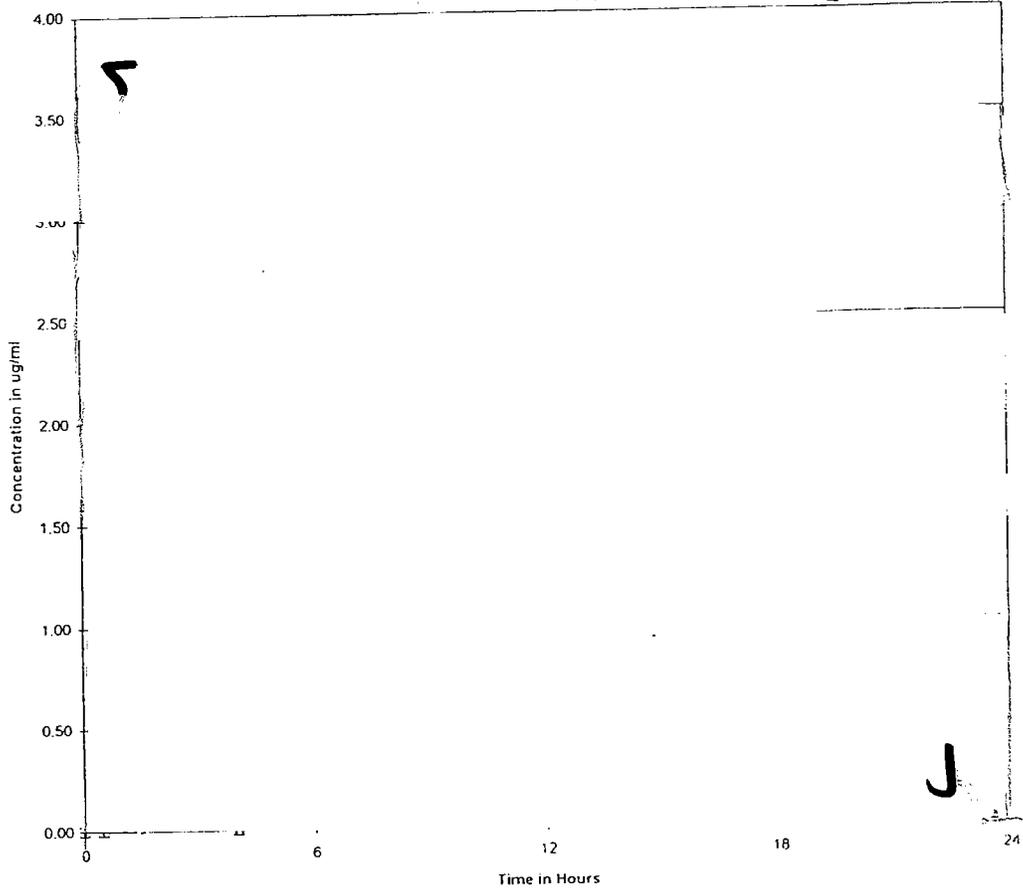
4

Clinical - Tortuga

Concentration in ug/ml vs Time in Hours

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for 2x100 mg capsules. Tortuga Formulation
(Trt C)

Subject Number	Treatment Sequence	Study Period	Parameters								Log-Parameters		
			Cmax ug/mL	Tmax hr	AUC(0-t) ug·hr/mL	AUC(0-inf) ug·hr/mL	T 1/2el hr	Kel 1/hr	CL/F L/hr		LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	ABC	3											
2	BCA	2											
3	CAB	1											
4	ABC	3											
5	CAB	1											
6	BCA	2											
7	CAB	1											
8	BCA	2											
9	ABC	3											
10	ABC	3											
11	BCA	2											
13	BCA	2											
14	CAB	1											
15	ABC	3											
16	ABC	3											
17	BCA	2											
18	CAB	1											
Mean			1.05	3.4	14.0	18.7	15.3	0.0503	11.4	0.0211	2.59		2.90
S.D.			0.260	1.4	4.46	4.70	5.99	0.0148	3.05	0.252	0.311		0.260
C.V.(%)			24.7	40	31.9	25.2	39.2	29.5	26.8	1200	12.0		8.97
S.E.M.			0.0631	0.33	1.08	1.36	1.73	0.00428	0.881	0.0611	0.0754		0.0751
N			17.0	17	17.0	12.0	12.0	12.0	12.0	17.0	17.0		12.0
Minimum													
Maximum													

5

| | Treatment Means | | | | | Confidence Intervals | Mean |
Parameter	A	B	Pct Difference	PR>|T|	Power (%)	(90% Confidence)	Ratio
Cmax	2.008	2.119	-5.24	0.3898	89.66	84.6 - 104.9	94.8
Tmax	3.206	3.503	-8.47	0.5712	24.75	66.4 - 116.6	91.5
AUC(0-t)	18.130	18.111	0.11	0.9800	99.34	92.9 - 107.4	100.1
AUC(0-inf)	19.683	20.046	-1.81	0.7055	97.90	90.1 - 106.3	98.2
T 1/2el	6.186	5.003	23.65	0.4188	9.12	74.4 - 172.9	123.7
Kel	0.125	0.135	-7.57	0.2895	78.20	80.5 - 104.4	92.4
CL/F	10.461	10.226	2.30	0.7162	86.38	91.6 - 113.0	102.3
LN(Cmax)	0.665	0.719	-7.53	0.4100	84.78	84.9 - 105.7	94.7
LN[AUC(0-t)]	2.883	2.882	0.06	0.9735	95.32	91.6 - 109.6	100.2
LN[AUC(0-inf)]	2.965	2.986	-0.70	0.7002	94.28	89.3 - 107.4	97.9

Treatment A = 4x50 mg capsules, Celgene Commercial Formulation: test
Treatment B = 4x50 mg capsules, Celgene Clinical Trials Formulation: reference

| | Treatment Means | | | | | Confidence Intervals | Mean |
Parameter	A	C	Pct Difference	PR>|T|	Power (%)	(90% Confidence)	Ratio
Cmax	2.008	1.066	88.34	0.0001*	35.87	168.1 - 208.6	188.3
Tmax	3.206	3.435	-6.67	0.6616	23.94	67.7 - 118.9	93.3
AUC(0-t)	18.130	14.073	28.83	0.0001*	93.91	119.5 - 138.2	128.8
AUC(0-inf)	19.683	18.491	6.45	0.2452	94.12	97.2 - 115.7	106.4
T 1/2el	6.186	15.335	-59.66	0.0001*	48.07	23.4 - 57.3	40.3
Kel	0.125	0.047	168.60	0.0001*	13.36	231.9 - 305.3	268.6
CL/F	10.461	11.415	-8.35	0.1712	89.85	81.5 - 101.8	91.6
LN(Cmax)	0.665	0.030	2117.4	0.0001*	84.78	169.0 - 210.5	188.6
LN[AUC(0-t)]	2.883	2.598	10.97	0.0001*	95.32	121.5 - 145.5	133.0
LN[AUC(0-inf)]	2.965	2.891	2.58	0.2020	91.95	97.7 - 118.8	107.7

Treatment A = 4x50 mg capsules, Celgene Commercial Formulation: test
Treatment C = 2x100 mg capsules, Tortuga Formulation: reference

| | Treatment Means | | | | | Confidence Intervals | Mean |
Parameter	B	C	Pct Difference	PR>|T|	Power (%)	(90% Confidence)	Ratio
Cmax	2.119	1.066	98.75	0.0001*	35.87	178.5 - 219.0	198.8
Tmax	3.503	3.435	1.97	0.8970	23.94	76.4 - 127.6	102.0
AUC(0-t)	18.111	14.073	28.69	0.0001*	93.91	119.4 - 138.0	128.7
AUC(0-inf)	20.046	18.491	8.41	0.1618	90.76	98.4 - 118.4	108.4
T 1/2el	5.003	15.335	-67.38	0.0001*	42.52	14.4 - 50.9	32.6
Kel	0.135	0.047	190.60	0.0001*	12.07	251.1 - 330.1	290.6
CL/F	10.226	11.415	-10.42	0.1152	85.30	78.7 - 100.5	89.6
LN(Cmax)	0.719	0.030	2298.0	0.0001*	84.78	178.4 - 222.3	199.1
LN[AUC(0-t)]	2.882	2.598	10.90	0.0001*	95.32	121.3 - 145.2	132.7
LN[AUC(0-inf)]	2.986	2.891	3.31	0.1314	87.92	99.1 - 122.2	110.0

Treatment B = 4x50 mg capsules, Celgene Clinical Trials Formulation: test
Treatment C = 2x100 mg capsules, Tortuga Formulation: reference

Values for Treatments B and C are the least-square means (LSMEANS) from the ANOVA
Parameters with the 'LN' prefix are log-transformed parameters

Pct Difference = difference between treatments (B - C) expressed as a percentage of Treatment C

PR>\|T\| = ANOVA test for significant differences between treatments
(* difference is statistically significant; p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*test/reference for untransformed parameters
Mean Ratio = 100*exp(test-reference) for log transformed parameters

NDA/IND# 20-785   Suppl/Amend.# Orig   Submission Date: 12/20/96   Volume: _____

Study Type: Dose Proportionality   Study #   PK-004

Study Title: Dose Proportionality in Healthy Volunteers

Clinical Investigator ⌈   Analytical Investigator ⌈
Site   Site

Single Dose: Y   Multiple Dose: _____   Washout Period: 1 week

Cross-Over y   Parallel _____   Other Design: _____

Fasted   Y   Food Study _____   FDA High Fat Breakfast _____

If fasted, how long (hrs.)?   12

Subject Breakdown

Normal XX   Patients _____   Young XX   Elderly _____   Renal _____   Hepatic _____

	Subject Type	Males	Group	Normal	N= 15	M= 14	F= 1
Weight	Mean 178 Range	216-147lbs	Group		N=	M=	F=
e	Mean 36.1 Range	54-20yrs	Group		N=	M=	F=
	Subject Type	Females	Group		N=	M=	F=
Weight	Mean 33 Range	33yrs	Group		N=	M=	F=
Age	Mean 182 Range	182lbs	Group		N=	M=	F=

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
A	50	Capsule	50mg	DEV2400	⌈ ⌉
B	200	Capsule	50mg	DEV2400	⌈ ⌉
C	400	Capsule	50mg	DEV2400	⌈ ⌉

Sampling Times

Plasma   9.5ml at time 0 and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48hrs post-dosing

Urine   pooled over the entire plasma collection interval

Feces   N/A

Assay Method: HPLC (orig)

Assay Sensitivity   0.1 μg/ml thalidomide

say Accuracy   Target|Observed|%RSD;0.1|0.085|4.9%;1|.91|1.1%;5|4.5|0.63%

Labeling Claims   The results of this study indicate that the Celgene thalidomide capsules are dose
From Study   proportional for AUC but not for Cmax. This lack of dose proportionality for Cmax
    may be due to a prolonged absorption phase for the 400mg dose due to the relative
    insolubility of thalidomide. A increase in MRT also supports this theory.

7

Individual Subject Data-PK004
1x50mg Thalidomide
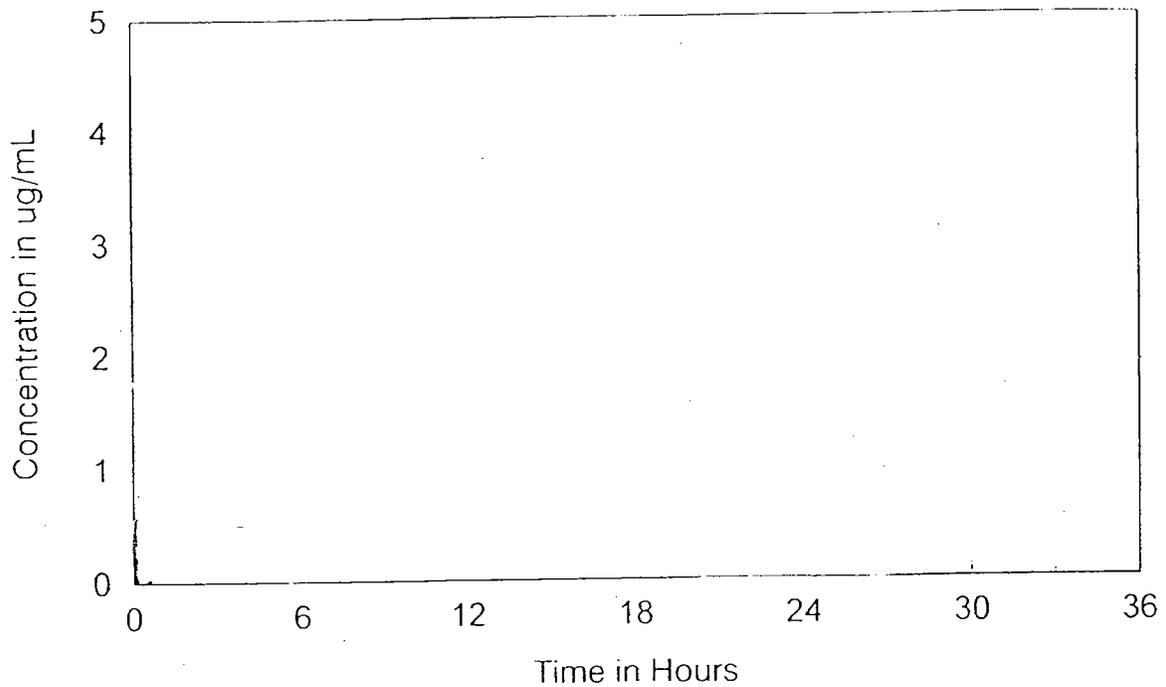
Concentration in ug/mL

5 —

4 —

3 —

2 —

1 —

0 —

Time in Hours: 0   6   12   18   24   30   36

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for Thalidomide 1 x 50 mg capsules
(Trt A)

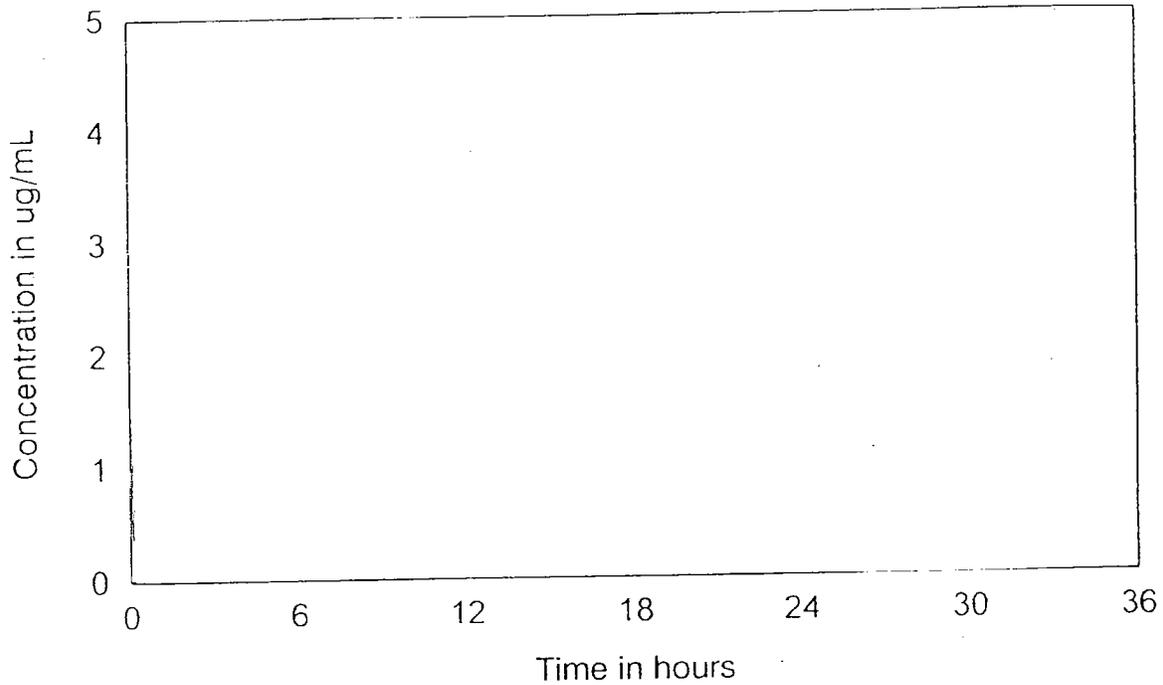| Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-t) ug*hr/mL	AUC(0-inf) ug*hr/mL	T 1/2el hr	Kel 1/hr	CL/F L/hr	MRT hr
1	CAB	2								
2	ABC	1								
3	BCA	3								
5	CAB	2								
6	ABC	1								
7	BCA	3								
8	CAB	2								
9	ABC	1								
10	ABC	1								
11	BCA	3								
12	CAB	2								
13	CAB	2								
14	BCA	3								
15	ABC	1								
Mean			0.622	2.9	3.44	4.90	5.52	0.138	10.4	9.08
S.D.			0.320	1.9	0.655	0.770	2.04	0.0403	1.75	3.06
C.V.(%)			51.4	65	19.0	15.7	36.9	29.2	16.7	33.7
S.E.M.			0.0855	0.51	0.175	0.257	0.679	0.0134	0.583	1.02
N			14.0	14	14.0	9.00	9.00	9.00	9.00	9.00
Minimum										
Maximum										

8

Individual Subject Data-PK004
4x50mg Thalidomide

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for Thalidomide 4 x 50 mg capsules
(Trt B)

Subject Number	Treatment Sequence	Study Period	Parameters Cmax ug/mL	Tmax hr	AUC(0-t) ug*hr/mL	AUC(0-inf) ug*hr/mL	T 1/2el hr	Kel 1/hr	CL/F L/hr	MRT hr
1	CAB	3								
2	ABC	2								
3	BCA	1								
4 *	B	1								
5	CAB	3								
6	ABC	2								
7	BCA	1								
8	CAB	3								
9	ABC	2								
10	ABC	2								
11	BCA	1								
12	CAB	3								
13	CAB	3								
14	BCA	1								
15	ABC	2								
Mean			1.76	3.5	15.6	18.9	5.53	0.132	10.9	9.83
S.D.			0.524	2.0	3.82	3.28	1.40	0.0320	1.86	2.08
C.V.(%)			29.8	58	24.5	17.4	25.2	24.2	17.1	21.1
S.E.M.			0.140	0.54	1.02	0.911	0.387	0.00887	0.516	0.576
N			14.0	14	14.0	13.0	13.0	13.0	13.0	13.0
Minimum										
Maximum										

* = Subject was not included in summary statistics.

9

Individual Subject Data-PK004
8x50mg Thalidomide
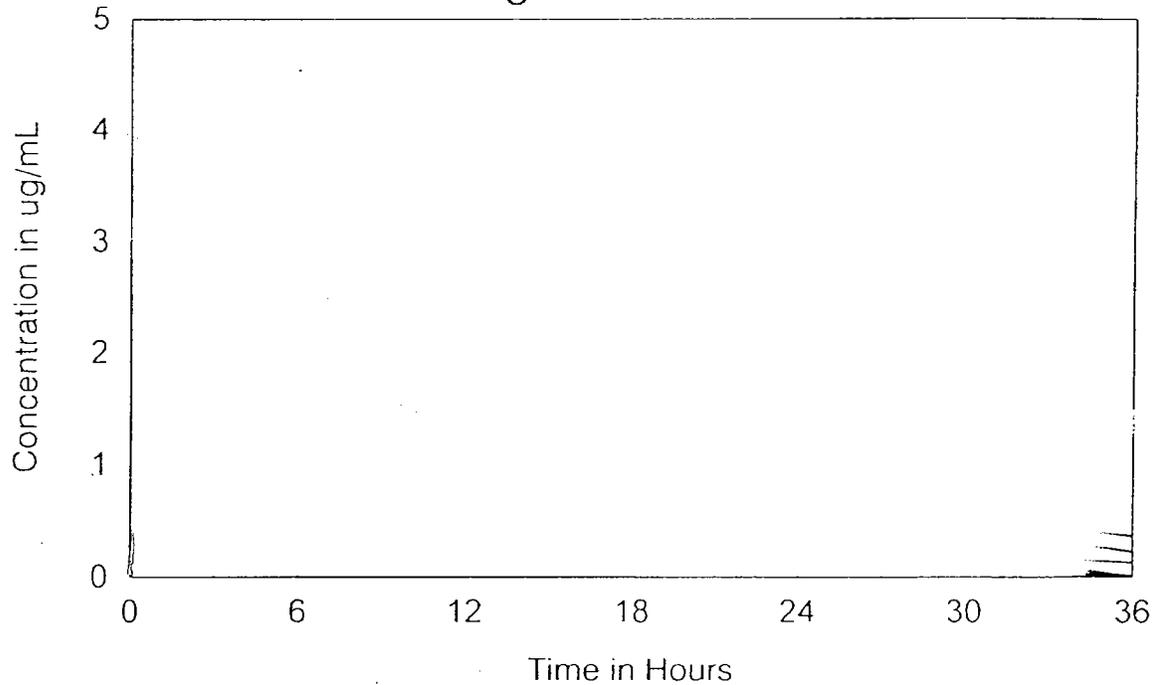

Concentration in ug/mL vs Time in Hours

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for Thalidomide 8 x 50 mg capsules
(Trt C)

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-t) ug*hr/mL	AUC(0-inf) ug*hr/mL	T 1/2el hr	Kel 1/hr	CL/F L/hr	MRT hr
1	CAB	1								
2	ABC	3								
3	BCA	2								
5	CAB	1								
6	ABC	3								
7	BCA	2								
8	CAB	1								
9	ABC	3								
10	ABC	3								
11	BCA	2								
12	CAB	1								
13	CAB	1								
14	BCA	2								
15	ABC	3								
Mean			2.82	4.3	31.4	36.4	7.29	0.104	11.7	11.7
S.D.			0.801	1.6	9.65	9.55	2.62	0.0302	2.82	2.98
C.V.(%)			28.4	38	30.7	26.3	35.9	29.0	24.2	25.4
S.E.M.			0.214	0.44	2.58	2.76	0.755	0.00871	0.814	0.860
N			14.0	14	14.0	12.0	12.0	12.0	12.0	12.0
Minimum										
Maximum										

Box and Whisker Plot

Treatments
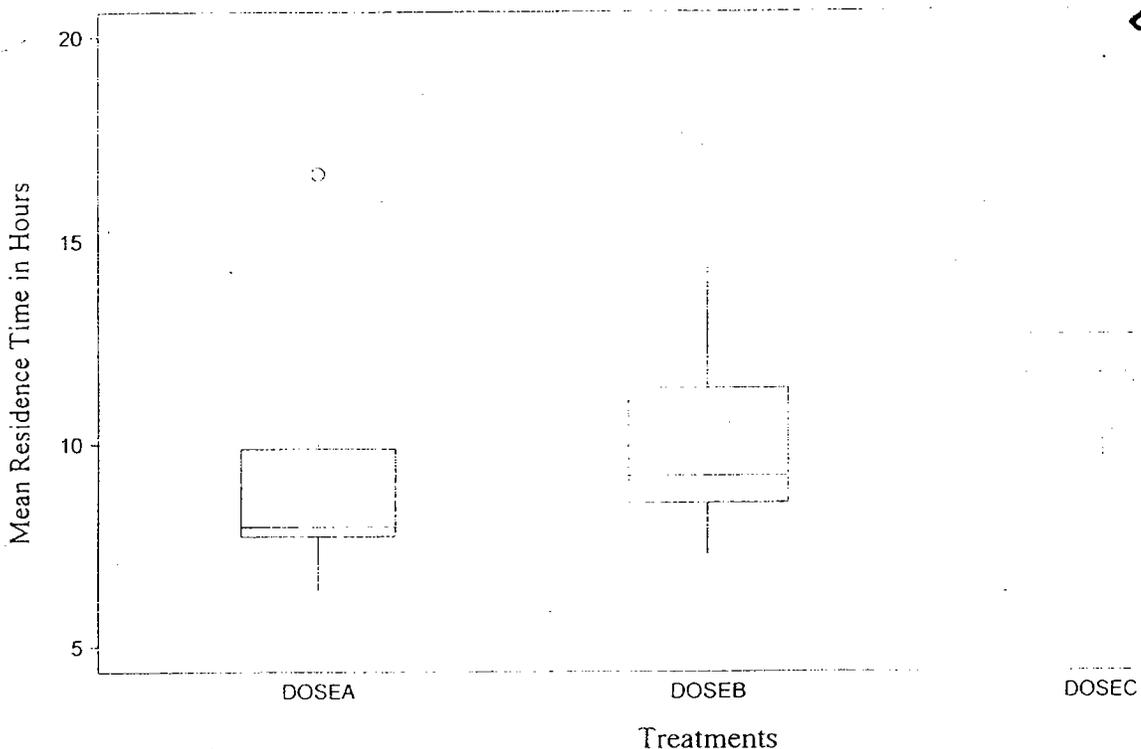
Dose A=50mg, Dose B=200mg, Dose C=400mg

DESCRIPTIVE STATISTICS

	DOSEA	DOSEB	DOSEC
N	9	12	12
LO 95% CI	6.7319	8.5110	9.8349
MEAN	9.0822	9.8350	11.728
UP 95% CI	11.433	11.159	13.620
SD	3.0576	2.0839	2.9787
VARIANCE	9.3492	4.3426	8.8726
SE MEAN	1.0192	0.6016	0.8599
C.V.	33.666	21.188	25.399
MINIMUM	6.3400	7.2500	7.9400
1ST QUARTI	7.5250	8.5125	9.8450
MEDIAN	7.9400	9.1900	11.700
3RD QUARTI	10.005	11.550	12.800
MAXIMUM	16.600	14.400	19.400
BIASED VAR	8.3104	3.9807	8.1333
SKEW	1.8234	0.8684	1.2269

DA/IND# 20-785 Suppl/Amend.# Orig Submission Date: 6/2/97 Volume: 9.2
Study Type: Pharmacokinetics in Pts. Study # PK-005
Study Title: Pharmacokinetics of Thalidomide in Patients with Hansen's Disease

Clinical Investigator ⌐ Analytical Investigator ⌐
Site Site

⌐⌐ ⌐

Single Dose: Y Multiple Dose: N Washout Period: N
Cross-Over N Parallel N Other Design:
Fasted Y Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 10

Subject Breakdown

Normal ___ Patients Y Young ___ Elderly Y Renal ___ Hepatic ___

Subject Type	Males	Group Hansen N=	6	M=	2	F=	4
Weight	Mean 221 Range 242-201lbs	Group	N=	M=	F=		
;e	Mean 57 Range 67-48yrs	Group	N=	M=	F=		
Subject Type	Females	Group	N=	M=	F=		
Weight	Mean 171 Range 247-142lbs	Group	N=	M=	F=		
Age	Mean 62 Range 69-54yrs	Group	N=	M=	F=		

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
Hansen's Disease	400mg	Capsule	50mg	DEV2400	⌐ ⌐

Sampling Times

Plasma 15ml at time 0 and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72hours post-dosing

Urine All urine to be collected pre-dose and 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72hrs post-dosing

Feces All feces to be timed and collected for analysis

Assay Method: ⌐ ⌐ LC/MS method validated for Thalidomide and N-OH, 4-OH, and 3-OH

Assay Sensitivity See Attached

ssay Accuracy See Attached

Labeling Claims This study was designed to detect and identify the primary metabolites of thalidomide.
From Study Unfortunately none of the validated metabolites were detected in man. Less than 1% of the
dose was excreted in the urine as thalidomide and less than 0.1% was excreted as the 4-OH
metabolite. The pharmacokinetics of thalidomide are similar to those in normal subjects. 12

Table 4. Plasma QC Precision and Accuracy

THALIDOMIDE							
Standard Level	Set 1 %RSD	Set 1 %RE	Set 2 %RSD	Set 2 %RE	Set 3 %RSD	Set 3 %RE	Set 4 %RSD	Set 4 %RE
80								
800								
4000								
Mean	7.81	-1.52	4.79	0.81	3.19	-10.8	5.67	-4.17

N-OH THALIDOMIDE							
Standard Level	Set 1 %RSD	Set 1 %RE	Set 2 %RSD	Set 2 %RE	Set 3 %RSD	Set 3 %RE	Set 4 %RSD	Set 4 %RE
80								
800								
4000								
Mean	49.9	-35.7	12.2	83.2	24.2	-54.1	6.15	-15.8

3-OH THALIDOMIDE							
Standard Level	Set 1 %RSD	Set 1 %RE	Set 2 %RSD	Set 2 %RE	Set 3 %RSD	Set 3 %RE	Set 4 %RSD	Set 4 %RE
80								
800								
4000								
Mean	18.2	-3.71	10.0	110	12.4	-12.1	10.0	-4.00

4-OH THALIDOMIDE							
Standard Level	Set 1 %RSD	Set 1 %RE	Set 2 %RSD	Set 2 %RE	Set 3 %RSD	Set 3 %RE	Set 4 %RSD	Set 4 %RE
80								
800								
4000								
Mean	21.2	-8.72	4.84	5.32	15.4	-20.7	16.3	2.59

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2 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Table 5. Urine Calibration and QC Standards Precision and Accuracy

THALIDOMIDE						
Calibration Level	Set 5 %RSD	Set 5 %RE		QC Level	Set 5 %RSD	Set 5 %RE
50						
100						
400						
1000						
2000						
5000						
Mean	7.99	-0.004			9.25	3.83

N-OH THALIDOMIDE						
Calibration Level	Set 5 %RSD	Set 5 %RE		QC Level	Set 5 %RSD	Set 5 %RE
50						
100						
400						
1000						
2000						
5000						
Mean	11.2	-0.072			22.5	16.0

3-OH THALIDOMIDE						
Calibration Level	Set 5 %RSD	Set 5 %RE		QC Level	Set 5 %RSD	Set 5 %RE
50						
100						
400						
1000						
2000						
5000						
Mean	14.2	-0.019			11.5	15.1

4-OH THALIDOMIDE						
Calibration Level	Set 5 %RSD	Set 5 %RE		QC Level	Set 5 %RSD	Set 5 %RE
50						
100						
400						
1000						
2000						
5000						
Mean	12.1	-0.123			9.69	10.3

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2 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Thalidomide Study PK-005
Mean and Individual Subject Data

Concentration in ug/mL

Time in Hours
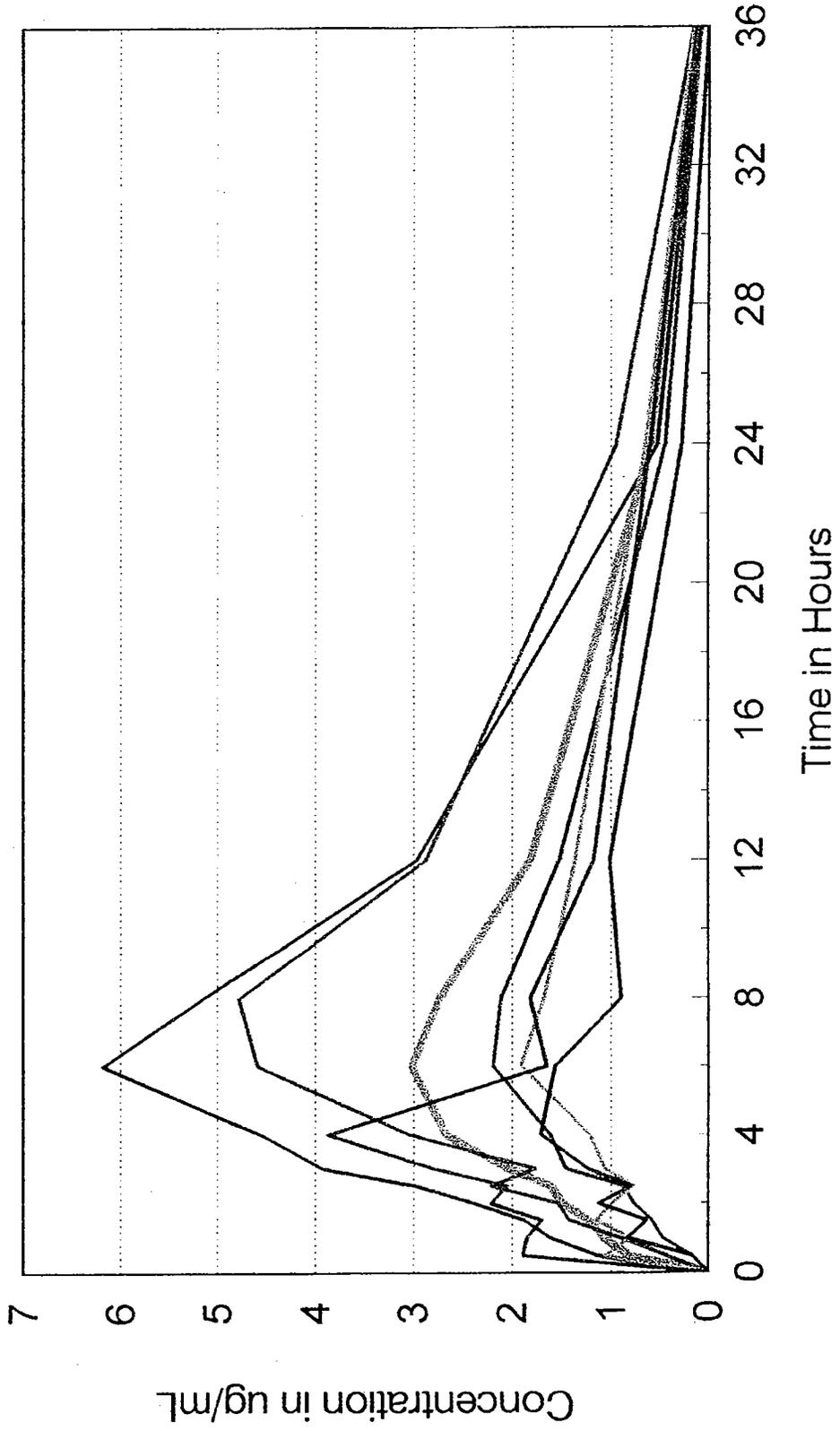
Pts. w/Hansen's Disease

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Table 11

Individual and Mean Pharmacokinetic Parameter Values from Plasma Thalidomide Concentrations
for Thalidomide

------------------------------------ Parameters ------------------------------------

Subject Number	Treatment Sequence	Study Period	Cmax ug/mL	Tmax hr	AUC(0-t) ug*hr/mL	AUC(0-inf) ug*hr/mL	MRT hr	CL/F L/hr	Kel 1/hr	Rel T 1/2el hr	Total Amount Excreted in Urine ug	% of Dose Excreted in Urine	CLr mL/min
1	A	1											
2	A	1											
3	A	1											
4	A	1											
5	A	1											
6	A	1											
Mean			3.44	5.7	45.1	46.4	12.4	10.1	0.104	6.86	2750	0.687	1.15
S.D.			1.81	1.5	21.2	20.4	1.48	4.19	0.0211	1.17	207	0.0515	0.489
C.V.(%)			52.6	27	47.0	44.1	12.0	41.6	20.3	17.1	7.54	7.50	42.4
S.E.M.			0.739	0.61	8.64	8.34	0.605	1.71	0.0086	0.479	84.7	0.0210	0.200
N			6.00	6.0	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
Minimum													
Maximum													

Table 12

Individual and Mean Pharmacokinetic Parameter Values from Plasma 4-OH-Thalidomide Concentrations
for Thalidomide

			----- Parameters -----	
			Total Amount % of Dose	
			Excreted	Excreted
Subject	Treatment	Study	in Urine	in Urine
Number	Sequence	Period	ug	
1	A	1		
2	A	1		
3	A	1		
4	A	1		
5	A	1		
6	A	1		
Mean			70.3	0.0176
S.D.			67.6	0.0169
C.V. (%)			96.2	96.0
S.E.M.			27.6	0.00688
N			6.00	6.00
Minimum				
Maximum				

Appendix 4.24.1

Concomitant Medications

Subject Number	Period	Any Concomitant Medication?	Drug Name	Dose	Units	Route	Indication	Start Date	Start Time	Stop Date	Stop Time
1	Screen	Yes	DAPSONE	100	MG	PO	HANSEN'S DISEASE				
			MULTIPLE VITAMIN	1	TAB	PO	HEALTH SUPPLEMENT				
			VOLTAREN	225	MG	PO	ARTHRITIS				
			QUININE SULFATE	300	MG	PO	LEG CRAMPS				
	1	Yes	CORRECTOL	1	TAB	PO	CONSTIPATION	09/25/96	6:00	09/25/96	6:00
2	Screen	Yes	DAPSONE	50	MG	PO	HANSEN'S DISEASE				
	1	Yes	AFRIN NASAL SPRAY	2	PUFF	INH	STUFFY NOSE	09/24/96	14:25	09/24/96	14:25
3	Screen	Yes	DAPSONE	100	MG	PO	HANSEN'S DISEASE				
			ASPIRIN EC	300	MG	PO	BLOOD THINNER				
			CALCIUM CARBONATE	2500	MG	PO	HEALTH SUPPLEMENT				
			VITAMIN-MINERAL /VIT.	1	TAB	PO	HEALTH SUPPLEMENT				
			CONJUGATED ESTROGENS	625	MG	PO	ESTROGEN REPLACEMENT				
	1	Yes	PRUNE JUICE	1	CAN	PO	CONSTIPATION PREVENTION	09/25/96	6:00	09/25/96	6:00

Route: PO = Per Oral, INH = Inhalation, TOP = Topical, OU = Eyes

Appendix 4.24.1

Concomitant Medications

Subject Number	Period	Any Concomitant Medication?	Drug Name	Dose	Units	Route	Indication	Start Date	Start Time	Stop Date	Stop Time
4	Screen	Yes	AKWA TEARS	4	GTTS	OU	LUBRICATE EYES				
			CARDIZEM CD	300	MG	PO	HIGH BLOOD PRESSURE				
			MEVACOR	40	MG	PO	HIGH CHOLESTEROL				
			DIAZEPAM	5	MG	PO	ANXIETY				
			DAPSONE	50	MG	PO	HANSEN'S DISEASE				
			HYDROCHLOROTHIA ZIDE	25	MG	PO	HIGH BLOOD PRESSURE				
			AK-PRED	2	GTTS	OU	LUBRICATING EYES				
			FLUOCINOLONE ACETONIDE		UNK	TOP	DRY SKIN				
			CATAPRESS-TTS-2	0.2	MG		HIGH BLOOD PRESSURE				
			NITRO PATCH	0.4	MG		ANGINA	09/24/96	3:00	09/24/96	3:00
			TYLENOL	650	MG	PO	HEADACHE				
	1	Yes	TYLENOL	650	MG	PO	HEADACHE	09/24/96	13:00	09/24/96	13:00
			MAALOX EXTRA STRENGTH	30	CC	PO	INDIGESTION	09/25/96	13:15	09/25/96	13:15
			TYLENOL	650	MG	PO	LEG CRAMPS	09/26/96	14:30	09/26/96	14:30
5	Screen	Yes	DAPSONE	100	MG	PO	HANSEN'S DISEASE				
			LEVOTHYROXINE	150	MCG	PO	THYROID REPLACEMENT				
			CYCLOBENZAPRINE	10	MG	PO	LEG CRAMPS				
			METOCLOPRAMIDE	30	MG	PO	ESOPHAGEAL REFLUX				
			RANITIDINE	150	MG	PO	STOMACH				
			LISINOPRIL	10	MG	PO	HIGH BLOOD PRESSURE				
			INDAPAMIDE	2.5	MG	PO	BLOOD PRESSURE				
	1	Yes	CORRECTOL	2	TAB	PO	CONSTIPATION	09/25/96	6:00	09/25/96	6:00

Route: PO = Per Oral, INH = Inhalation, TOP = Topical, OU = Eyes

Celgene Corporation
Thalidomide Protocol PK-005
1 Project 18772

Appendix 4.24.1

Concomitant Medications

Subject Number	Period	Any Concomitant Medication?	Drug Name	Dose	Units	Route	Indication	Start Date	Start Time	Stop Date	Stop Time
6	Screen	Yes	DAPSONE	100	MG	PO	HANSEN'S DISEASE				
			HYDROCHLOROTHIAZIDE	100	MG	PO	BLOOD PRESSURE				
			MULTIPLE VITAMIN	1	TAB	PO	HEALTH SUPPLEMENT				
			CLOTRIMAZOLE		UNK	TOP	FUNGUS ON TOES				
			MYCELEX		UNK	TOP	RASH ON RIGHT UPPER LEG				
	1	Yes	TYLENOL	1000	MG	PO	HEADACHE	09/24/96	14:30	09/24/96	14:30

Route: PO = Per Oral, INH = Inhalation, TOP = Topical, OU = Eyes

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Appendix-II

Table 11. Effect of Thalidomide on Metabolism of P450 Substrates

Microsomal Preparation	% of Activity	
	HHM 216	Cloned P450
Sustrate/P450 Isozyme		
7-ERR / CYP 1A2	NA	93
COU / CYP 2A6	106	90
ETC / CYP 2B6	101	118
DICLO / CYP 2C9	94	100
ME / CYP 2C19	120	106
BF / CYP 2D6	110	111
PNP / CYP 2E1	100	97
TES / CYP 3A4	106	118

NA = no activity was detected in presence or absence of thalidomide.
HHM 216 = Pooled-human microsomal preparation.
Cloned P450s represent a different batch of microsomes containing the
specific P450 for each isozyme of P450 indicated in column 1.

Appears This Way
On Original

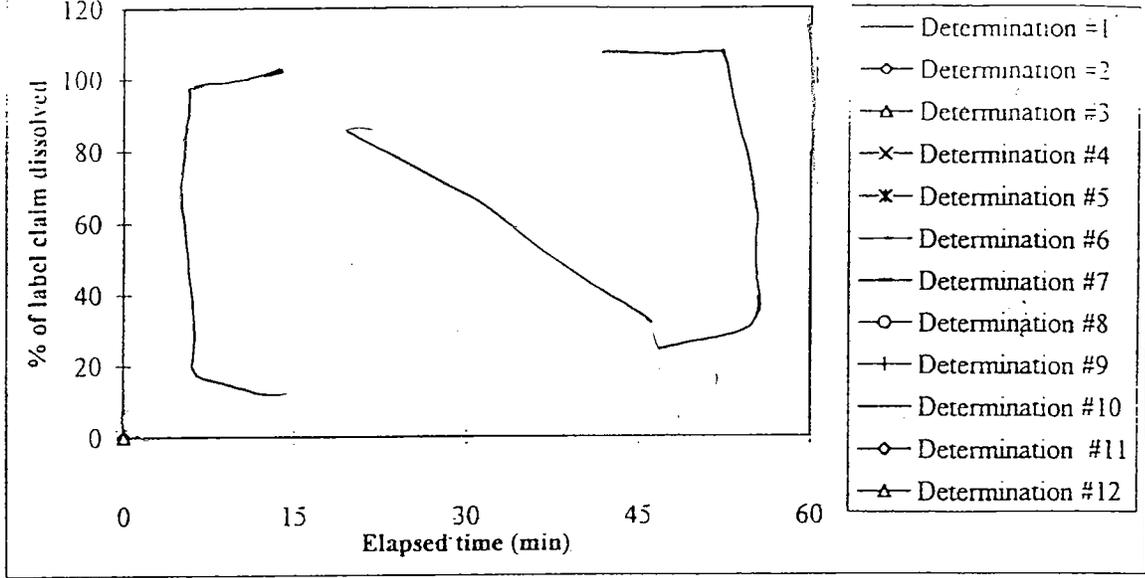# 7 PAGE(S) COPYRIGHT MATERIAL - REMOVED FROM THIS SECTION

Table 10. P450-Dependent Monooxygenase Activities of Microsomes Used In This Study

Microsomal Preparation	7-ERR CYP 1A2	COU CYP 2A6	ETC CYP 2B6	Diclo CYP 2C9	ME CYP 2C19	BF CYP 2D6	PNP CYP 2E1	TES CYP 3A4
HHM 215 - Measured in this study[a,e]	ND[b]	693	194	3911[c]	13.9	222	636	2748
HHM 215 - Suppliers Quoted Activity	NS[d]	800	NS	NS	71	NS	NS	3000
HHM 216 - Measured in this study[a,e]	ND	482	155	2460[c]	8.6	120	500	1925
HHM 216 - Suppliers Quoted Activity	NS	1380	NS	NS	47	NS	NS	2100
Cloned P450 - Measured in this study[a,f]	27.4	299	17	921	12.8	325	675	308
Cloned P450 - Suppliers Quoted Activity	120	1860	290	3360	63	780	1820	1950

[a] Values are mean of 2 determinations minus activity seen in the absence of the NADPH-regenerating system expressed as pmole/min/mg microsomal protein. Microsomal protein concentrations used for calculations were those supplied by the microsomal preparation supplier.

Abbreviations are 7-ERR, 7-ethoxyresorufin O-deethylase; COU, coumarin hydroxylase; ETC, 7-ethoxy-4-trifluoromethylcoumarin deethylase; Diclo, diclofenac hydroxylase; ME, mephenytoin hydroxylase; BF, bufuralol hydroxylase; PNP, p-nitrophenol hydroxylase; TES, testosterone 6β-hydroxylase.

[b] ND = no detectable activity (i.e. less than or equal to background response).

[c] Instrument response exceeded highest response for standard curve. Values therefore are minimums.

[d] NS = value not supplied by manufacturer.

[e] HHM 215 and 216 = Pooled-human microsomal preparations.

[f] Cloned P450s represent a different batch of microsomes containing the specific P450 for each isozyme of P450 indicated in row 1.

Dissolution Profiles of BN2365K ℓ C   ) (caps.)

Legend:
- Determination #1
- Determination #2
- Determination #3
- Determination #4
- Determination #5
- Determination #6
- Determination #7
- Determination #8
- Determination #9
- Determination #10
- Determination #11
- Determination #12

Axis: % of label claim dissolved (0–120) vs Elapsed time (min) (0, 15, 30, 45, 60)

Elapsed time (min)	0	15	30	45	60
% of label claim dissolved					
Determination #1					
Determination #2					
Determination #3					
Determination #4					
Determination #5					
Determination #6					
Determination #7					
Determination #8					
Determination #9					
Determination #10					
Determination #11					
Determination #12					
Average of #1 - #6	0	54.7	96.3	105.8	109.0
SD of #1 - #6	0	11.5	3.9	2.3	3.2
%RSD of #1 - #6		21.0	4.0	2.2	2.9
Average of #7 - #12	0	61.0	93.0	103.5	105.6
SD of #7 - #12	0	13.7	8.3	2.4	1.6
%RSD of #7 - #12		22.5	8.9	2.3	1.5
Average #1 - #12	0	57.8	94.7	104.7	107.3
SD of #1 - #12	0	12.5	6.4	2.5	3.0
%RSD of #1 - #12		21.6	6.7	2.4	2.8

Note: Determinations #1 - #6 were the QC sample tested on 8/19/94

Determinations #7 - #12 were the 3 month (25°C ambient RH) sample tested on 2/7/95

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Dissolution Profiles of DEV2400 ([ ] copa)

Legend:
- Determination #1
- Determination #2
- Determination #3
- Determination #4
- Determination #5
- Determination #6
- Determination #7
- Determination #8
- Determination #9
- Determination #10
- Determination #11
- Determination #12

X-axis: Elapsed time (min) — 0, 15, 30, 45, 60
Y-axis: % of label claim dissolved — 0 to 120

Elapsed time (min)	0	15	30	45	60
% of label claim dissolved					
Determination #1					
Determination #2					
Determination #3					
Determination #4					
Determination #5					
Determination #6					
Determination #7					
Determination #8					
Determination #9					
Determination #10					
Determination #11					
Determination #12					
Average of #1 - #6	0	87.2	97.5	100.6	100.7
SD of #1 - #6	0	3.8	2.0	3.0	2.7
%RSD of #1 - #6		4.3	2.1	3.0	2.7
Average of #7 - #12	0	87.3	97.8	100.9	101.2
SD of #7 - #12	0	1.3	2.0	1.7	1.5
%RSD of #7 - #12		1.5	2.0	1.6	1.5
Average #1 - #12	0	87.2	97.6	100.7	101.0
SD of #1 - #12	0	2.7	1.9	2.3	2.1
%RSD of #1 - #12		3.1	2.0	2.3	2.1

Note: Determinations #1 - #6 were the QC sample tested on 12/18/95

Determinations #7 - #12 were the 3 month (25'C,60%RH) sample tested on 11/7/96

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06 2085

Dissolution Profiles of DEV2117 ([ ] caps)

Legend:
- Determination #1
- Determination #2
- Determination #3
- Determination #4
- Determination #5
- Determination #6
- Determination #7
- Determination #8
- Determination #9
- Determination #10
- Determination #11
- Determination #12

Elapsed time (min)	0	15	30	45	60
% of label claim dissolved					
Determination #1					
Determination #2					
Determination #3					
Determination #4					
Determination #5					
Determination #6					
Determination #7					
Determination #8					
Determination #9					
Determination #10					
Determination #11					
Determination #12					
Average of #1 - #6	0	72.9	84.6	88.6	89.1
SD of #1 - #6	0	5.5	1.5	2.2	1.2
%RSD of #1 - #6		7.6	1.8	2.5	1.3
Average of #7 - #12	0	81.9	95.8	99.2	99.7
SD of #7 - #12	0	8.0	2.5	2.5	3.2
%RSD of #7 - #12		9.7	2.6	2.6	3.2
Average #1 - #12	0	77.4	90.2	93.9	94.4
SD of #1 - #12	0	8.1	6.2	6.0	6.0
%RSD of #1 - #12		10.4	6.8	6.4	6.3

Note: Determinations #1 - #6 were the QC sample tested on 5/31/95

Determinations #7 - #12 were the 3 month (25'C.60%RH) sample tested on 8/27/96

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MEMO

To: Jonathan Wilkin, MD, Div. Dir. HFD-540

Through: Nicholas Fleischer, Ph.D., Div. Dir. HFD-880   *[handwritten] Jacaya fin N Fleischer 2/26/97*

From: E. Dennis Bashaw, Pharm.D. *[handwritten initials]*

Date: Monday, February 24, 1997

Subject: Thalidomide Requirements

As an outgrowth of discussions held both internally between HFD-540 and HFD-880 and with Celgene a number of biopharmaceutic issues have arisen that need resolution and/or concurrence. This memo lists the current outstanding biopharmaceutic needs that should be conveyed to the sponsor.

1.) When discussions were originally held between the sponsor and the FDA it was not possible to produce a solution of thalidomide in a reasonable volume of liquid that would allow for the assessment of relative bioavailability for their oral capsule. Since that time the FDA's laboratory has completed a research project in which the solubility of thalidomide was assessed in various media (see attachment I). Examination of the results of this research now indicates that a safe solvent for thalidomide is available for oral use. In light of this new information the Agency would like the sponsor to initiate an in vivo bioavailability assessment of their product using a solution reference. Such a study is normally a requirement for all new drugs, but it was initially deferred due to the lack of a suitable oral solvent. Such a study could be done in a number of ways:

   a.) re-doing the comparative bioavailability study between the Celgene and Tortuga formulations and a solution reference.
   b.) adding a solution treatment to the already planned food/fasting study.
   c.) initiating an entirely new study comparing the solution to Celgene's to-be-marketed product.

In any event, the study needs to be initiated prior to NDA approval such that this information can be rapidly incorporated into the knowledge database for thalidomide.

2.) While the sponsor has provided the Agency with the copy of a journal article detailing the stereospecific disposition of thalidomide in man, there is still some concern, due primarily to the original ambiguity in the literature, regarding the accuracy of this non-primary data. The Agency would like Celgene to commit to determining the

stereospecific disposition of thalidomide in man. Initially, this could be done by taking peak/trough samples in an ongoing clinical trial of thalidomide and analyzing them via a stereospecific assay technique. The need for additional data would be based on the outcome of this study. Such stereospecific information could be obtained in phase IV.

3.) The Agency also notes that at the present time we have yet to receive the results of the fecal sample analysis from the study in Hansen's patients. Due to the extremely low urinary excretion of thalidomide it is the Agency's position that this information is critical to examining the fate of thalidomide in man.

CC: NDA 20-785 (ORIG),
HFD-540/DIV File
HFD-540/CSO/White
HFD-880(Bashaw)
HFD-880(Lazor)
HFD-850 (Mira Millison, Drug, Chron Files)
HFD-344(Viswanathan)

MEMO

To: Thalidomide NDA File

From: E. Dennis Bashaw, Pharm.D.

Date: Thursday, January 16, 1997

Subject: DPE-III Filing Issues

On Jan. 10, 1997 an internal biopharmaceutics filing meeting was held in the office of Dr. Nicholas Fleischer, Dir. DPE-III. In attendance was Drs. Lazor, Bashaw, and Kumi. The issue being discussed was the filing status of the thalidomide NDA being sponsored by Celgene (SYNOVIR®, NDA 20-785) for erythema nodosum leprosum (ENL). During this meeting Dr. Bashaw presented to the group a summary of the pharmacokinetic trials perfomed by applicant (see Attachment I) and a copy of the Agency memo (Attachment II) that was developed with input from the clinical division as to what pharmacokinetic studies would be required for this drug given that it has both Orphan Drug and Sub-part E status.

From this meeting two concerns were noted by division management that needed clarification/justification. They are:

1 - Acceptance of literature data for the issue of stereochemistry issues.

2 - The lack of a traditional in vivo bioavailability study against an acceptable reference product.

As to the issue of stereochemistry, thalidomide has one chiral center and as such exists as both R and S enantiomers. After the 1960's experience with thalidomide related birth defects most research with thalidomide, except for orphan indications, was stopped. In the mid-70's when newer analytical techniques were developed for the separation of isomers of optically active compounds, a number of reseachers postulated that the toxicity of thalidomide was related to one isomer (the S) while the clinical efficacy (as a sedative-hypnotic) was related to the R isomer. This was supported by some in vivo animal studies in rats that indicated, with intraperitoneal injection, that there was no interconversion between isomers. Subsequent to this finding another article appeared in the literature (Attachment III) which reported on the effect of giving the individual isomers to four healthy adult males in a two-way crossover study. From these subjects pharmacokinetic samples were drawn frequently over the first 24 hours. A chiral specific HPLC assay was used to detect and quantify the

individual isomers. The results of the study indicated that the half-life of interconversion was approximately 2.5hrs for either R to S or S to R. Contrasted with a plasma half-life of 4 hours for the elimination of thalidomide the article strongly suggests that administration of either isomer in an attempt to avoid or attenuate thalidomide induced birth defects would not be successful.

It was on the basis of this article that the applicant elected to use a non-specific assay for thalidomide in their trials. As to the acceptability of this article one must put it in proper perspective. First of all, interconversion or the lack of it is an inherient property of a drug that is not affected by formulation issues. Secondly, with bi-directional interconversion the hypothesis of single enantiomer administration as a method of toxicity avoidance is nullified. Thirdly, with the individual rates of interconversion being so similar between to two rate processes (k_{rs}= 0.30+/-0.017, k_{sr}=0.31+/-0.019) equilibrium will be reached relatively quickly after individual isomer administration. While the sponsor clearly could have used a chiral specific assay, the results of this trial suggest that the use of a non-specific assay would also be acceptable as a chiral specific assay is only merited where one suspects or has knowledge of an alteration in the disposition or ratio of enantiomers over time. The article itself is well written and thoroughly documented. It presents some of the indivdual data from the study and provides a good description of the methods used and what steps were taken to ensure assay quality control. As a pivotal biopharmceutic trial it would clearly be insufficient, but as a trial used to support the selection of a non-specific method over a chiral specific method, it is this reviewers opinion that the burden of proof has been reached.

As to the lack of an assessment of in vivo bioavailability, it is true that the applicant is not doing a classical in vivo study using either a solution or other solubilized dosage form. This is primarily related to both its poor aqueous solubility and the toxicity of other solvent systems. The aqueous solubility of thalidomide is approximately 0.06mg/ml. In order to administer a standard 200mg dose a subject would have to consume approximately 4.6L of water or a bit over 1 gallon, an amount that is not really feasible from a practical standpoint. As to organic solubility, thalidomide is somewhat more soluble in ethanol (0.2mg/ml). This works out to only 1L of alcohol for a 200mg dose, feasible in volume, but when one considers that this is 1 L of absolute alcohol it also becomes unreasonable due to the side effects of consuming even a 50/50 dilution of this much alcohol over a short interval. While thalidomide is soluble (50mg/ml) in other solvents such as dimethyl sulfoxide (DMSO) and N,N-dimethylformamide (DMF)[1], these solvents have their own toxicity and other problems that make their selection unacceptable. Unfortunately there is not a known solvent for thalidomide that is both safe and reasonable for oral administration.

At the present time the applicant has completed an in vivo biostudy in six subjects with ENL. These subjects received single doses of 400mg of thalidomide using the

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[1]   OSHA exposure limit 10ppm

to-be-marketed formulation. In these subjects plasma, urine and fecal samples were collected for 72 hrs after dosing. Given the 4 hour half-life of thalidomide and an assay that has been validated for the parent and three most likely metabolites an estimate of bioavailability can be calculated from this trial. While it is not the best method of obtaining oral bioavailability, it will provide an estimate that, owing to the circumstances, is probably the best that can be done at this time.

It was on the basis of this reviewers scientific judgement and evaluation of the options that the two approaches used by the applicant were selected.

CC: NDA 20-785 (ORIG),
HFD-540/DIV File
HFD-540/CSO/White
HFD-880(Bashaw)
HFD-880(Fleischer)
HFD-850 (Mira Millison)
HFD-344(Viswanathan)

Attachment I

5. Summary of Pharmacokinetic Clinical Studies

Table 2.23

Summary of Celgene-sponsored pharmacokinetic clinical studies

Study Number	Route of Admin.	Study Design Dosage Form	Dose	Batch No. Manufacturer Date of Manuf.	No. of Subjects	IND Sub. Date	Applicant Conclusion
PK-001	Oral	Open-label, single dose, three-way crossover bioequivalence study.			17	IND ∠ ⅃ 29 December 1995 (Serial No. 045)	The PK and statistical analyses showed that Celgene thalidomide formulations were bioequivalent. However, the Tortuga formulation was not bioequivalent with either of the Celgene formulations, and resulted in lower and more variable absorption.
		50 mg capsule	200 mg	DEV2117[1] ∠ ⅃ 5/11/95			
		50 mg capsule	200 mg.	BN2365K ∠ ⅃ 8/2/94			
		100 mg capsule	200 mg	001 Tortuga			

[1]Intended commercial formulation

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Table 2.23 - continued
Summary of Celgene-sponsored pharmacokinetics clinical studies

Study Number	Route of Admin.	Study Design Dosage Form	Dose	Batch No. Manufacturer Date of Manuf.	No. of Subjects	IND Sub. Date	Applicant Conclusion
PK-004	Oral	Open label, single dose, three-way crossover pharmacokinetics 50 mg capsule	50 mg 200 mg 400 mg	DEV2400[1] 11/2/95	15[2]	IND 48,177; 27 June 1996 (Serial No. 029)	The PK and statistical analyses demonstrate that thalidomide was dose-proportional in terms of AUC across clinically relevant dosing range studied. Therefore the extent of absorption as well as the clearance of thalidomide is independent of dose up to a total dose of 400 mg. Thalidomide was not dose proportional in terms of C_{max}; this may be due to the limited aqueous solubility of thalidomide. There is no apparent difference in clearance between smokers and non smokers.
PK-005	Oral	Open label single period, single dose metabolic study.	400 mg	DEV2400[1] 11/2/95	6	IND 48,177; 5 September 1996 (Serial No. 035)	There is no apparent difference in the pharmacokinetics of thalidomide between patients with Hansen's disease and healthy human volunteers, nor is there an apparent difference between males and females. The urinary excretion of thalidomide is low (<1% of dose). No metabolites were detectable in the plasma; small amounts (<0.01% of dose) of 4-OH-thalidomide were detected in the urine.

[1]Proposed commercial formulation
[2]One subject discontinued after first period and is not included in pharmacokinetic calculations

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Table 2.23 - continued
Summary of Celgene-sponsored pharmacokinetic clinical studies

Study Number	Route of Admin.	Study Design Dosage Form	Dose	Batch No. Manufacturer Date of Manuf.	No. of Subjects	IND Sub. Date	Applicant Conclusion
E-001 (amendment 1)	Oral	Steady state pharmacokinetics over a single dosing interval in patients receiving ongoing thalidomide treatment.	50-200 mg in patients receiving maintenance treatment, up to 400 mg/day in patients receiving acute treatment for flare-ups	DEV2117 5/11/95	Up to 90	IND 48,177; 12 September 1996 (Serial No. 036)	Study ongoing Data pending.
E-003/P (amendment 1)	Oral	Steady state pharmacokinetics over a single dosing interval in patients receiving ongoing thalidomide treatment.	Patients receive 200 or 300 mg for 7-days acute treatment	DEV2400 11/2/95	20-30	IND 48,177; 12 September 1996 (Serial No. 036)	Planned Data pending.

Memorandum

To: *Mary-Jane Walling*
From: *E. Dennis Bashaw, Pharm.D.*
Date: *May 15, 1996*
Subject: *Thalidomide-PK Requirements*

From our joint meeting on May 6th between the staff of the Division of Pharmaceutical Evaluation-III and the ODE-V medical staff involved in the review of thalidomide, the following pharmacokinetic trials were classified as those required for the filing of an NDA for ENL:

1. Single dose bioequivalency study (clinically studied vs. to-be-marketed).

2. A dose proportionality study over the clinically studied range (50-400mg as single doses).

3. A definitive metabolism/disposition study (c-14 or tritium or other accepted technique) in patients with leprosy. This data should also be used in conjunction with in vitro metabolism studies to provide preliminary information on the metabolic character of thalidomide and to provide preliminary information on drug-drug interactions.

4. In vitro dissolution method (in conjunction with FDA St. Louis lab).

Ideally these studies should be done with subjects with ENL, however, given the nature of the disease and the number of subjects involved, the use of normal volunteers is unavoidable. One may want to consider the possibility of using subjects with either ENL or leprosy in the definitive metabolism study as this type of study normally includes less than 5 subjects.

Those studies that are being either deferred or made as a phase IV requirement:

1. Multiple dose steady-state (may be added to an ongoing clinical study).

2. Food effect study (modify ongoing clinical protocols to indicate fasted dosing).

3. Special populations (hepatic & renal) will be labeled as not studied (metabolism study data may be useful here). In addition information on the effect of gender, race, and age will need to be developed.

4. Drug interaction studies (e.g., dapsone and rifampin). The results of the definitive in vivo metabolism study may be useful in selecting in vitro screening methods (using P-450 isoenzymes) for drug interactions. In vivo work may be required for confirmatory studies.

As an unstated issue on the table that the sponsor needs to address is a rationale for using a non-specific assay technique for a racemic drug product. Inter-conversion between the two forms may become an issue. Published data in the scientific literature may be useful here.

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