CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-430

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☒ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Graham H. Burton, FRCP, MBBS, FFPM	Sr. Vice President Regulatory Affairs, Worldwide Pharmacovigilance and Project Management
FIRM / ORGANIZATION	
Celgene Corporation	
SIGNATURE	DATE
Megan Parisi for	5/10/05

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

DEBARMENT CERTIFICATION

Celgene Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Megan Parisi for

Graham H. Burton, FRCP, MBBS, FFPM
Sr. Vice President
Regulatory Affairs, Worldwide Pharmacovigilance
And Project Management

May 13, 2005

DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Brian Gill
Senior Director PR/IR
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

RE: NDA # 20-785 & 21-430
Thalomid® (thalidomide) Capsules
MACMIS ID# 14290

Dear Mr. Gill:

This letter is to advise the Regulatory Affairs Department of Celgene Corporation (Celgene) of comments on a draft Press Release for Thalomid (thalidomide) Capsules submitted to the Division of Drug Marketing, Advertising, and Communications (DDMAC) on May 15, 2006, pursuant to subpart H regulation 21 CFR 314.550.

DDMAC has reviewed this press release and offers the following comments. These comments apply to this material, in addition to current and future materials that contain the same or similar claims or presentations. These comments are tentative pending finalization of the Thalomid product label. This press release should be updated to reflect the final Approved Product Labeling (PI) approved by the Division of Drug Oncology Products (DDOP).

- DDMAC reminds Celgene that in order to provide adequate context, when presenting the indication for Thalomid the full approved indication:

  > Thalomid (thalidomide) in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma.
  >
  > The effectiveness of Thalomid is based on response rates ... There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.

  should be communicated. In addition, DDMAC recommends that the indication be adequately communicated before or in conjunction with the initial claims of efficacy.

- The claim [redacted] is misleading and minimizes the risks associated with Thalomid therapy because this drug is associated with severe adverse events as outlined in a Boxed Warning. DDMAC recommends omitting this misleading claim.

- Claims regarding adverse drug events are misleading and minimize the risks associated with Thalomid therapy because they fail to communicate important contextual information regarding the incidence of the adverse events presented. Further, this piece fails to

communicate that the incidence of all-grade and grade 3/4 fatigue, constipation, peripheral neuropathy, thrombosis/embolism, and rash were higher in the Thal/Dex treatment arm than with dexamethasone alone. DDMAC recommends reporting this important contextual and risk information with a prominence and placement comparable to the presentation of efficacy information.

- [redacted]

- The claim "[redacted] patients and Celgene stakeholders" misleadingly implies a clinical benefit regarding Thalomid therapy that has not been demonstrated by substantial evidence. DDMAC recommends omitting these misleading claims.

- Claims regarding the risk of venous thromboembolic events [redacted] are misleading and minimize the risks associated with Thalomid therapy because they fail to communicate the important risk information that preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment. DDMAC recommends reporting this important risk information with a prominence and placement comparable to the presentation of efficacy information.

If you have any questions, please direct them to me by facsimile at (301) 796-9877 or by written communication at the **Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705.** In all future correspondence regarding this matter, please refer to MACMIS ID # 14290 in addition to the NDA number. DDMAC reminds Celgene that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Joseph Grillo
5/24/2006 09:37:09 AM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **DDMAC /HFD-42**
Attention: Joseph Grillo

FROM: HFD-150/Carl Huntley

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5-17-05		21-430	Draft Dear Doctor Letter	May 15, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Thalomid (Thalidomide)		IMID	

NAME OF FIRM: Celgene

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- X DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please see attached Dear Doctor Letter. This is another version with the addition of proper references to sections and subsections of the prescribing information. The MedWatch on-line and mailing address have been updated.

SIGNATURE OF REQUESTER Thanks, Carl Huntley	METHOD OF DELIVERY (Check one) e- MAIL
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

2 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Carl Huntley
5/17/2006 09:51:03 AM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Celgene Corporation
86 Morris Avenue
Summit NJ, 07901

2. TELEPHONE NUMBER *(Include Area Code)*
(908) 673-9000

3. PRODUCT NAME
Thalidomide; registered name THALOMID

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N021430

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
Not Required

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Megan Parisi /for	Graham Burton , FRCP, MBBS, FFPM Sr. Vice President, Regulatory Affairs	May 13, 2005

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ONCOLOGY DRUG PRODUCTS

DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road
Beltsville, Maryland 20705

PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

NOTE: resent - cf. 2-1-06 fax

FROM: Carl Huntley
Project Manager

Total number of pages, including cover sheet 2

Date: May 8, 2006

COMMENTS: Regarding sNDA 21-430 for Thalomid, we have reviewed the safety data regarding the thromboembolic events that occurred in EA100 and have the following safety questions that should be addressed as part of a required Phase 4 post-marketing commitment.

Safety Questions.

1. What is the failure rate for each of the different types of thromboembolic prophylaxis (e.g. antiplatelet or anticoagulant therapy) for MM patients treated with a thalidomide-containing regimen?

2. What is the failure rate for each type of DVT treatment (dose-adjusted heparin, low molecular weight heparin, coumadin) for those patients with MM and a DVT who continue to receive ongoing treatment with thalidomide?

3. What is the failure rate for each type of post-DVT thromoboembolic prophylaxis for those patients with MM and a DVT who continue to receive ongoing treatment with thalidomide?

Phase 4 post-marketing commitment requests (additional).

1. We request that an epidemiologic study entitled (insert protocol name) be conducted to address the above using the STEPS patient registry database. This commitment, along with completion dates agreed upon, is listed below.

   Protocol Submission: xx/xx
   Study Start: xx/xx
   Final Report Submission: xx/xx

2. You have agreed to submit the study report and data from the study, THAL-MM-003, a randomized, multicenter, parallel-group, double-blind, placebo-controlled study of the efficacy and safety of the combination of thalidomide plus a glucocorticoid versus a glucorticoid alone as induction therapy in patients with previously untreated multiple myeloma when completed.

   Protocol Submission: xx/xx
   Study Start: xx/xx
   Final Report Submission: xx/xx

Thanks.
Regards,
-carl

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/s/

Carl Huntley
5/8/2006 05:30:50 PM
CSO

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ONCOLOGY DRUG PRODUCTS

DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road
Beltsville, Maryland 20705

PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Megan Parsi,
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager

Total number of pages, including cover sheet 2
Date: 5-10-06

COMMENTS: Regarding sNDA 21-430 for Thalomid, please see the response to your e-mail of May 5, 2005 regarding the label.

1) Regarding ———: We were unable to use standardized criteria to document the efficacy of Thal given the lack of a complete picture of response in patients (e.g., bone marrow infiltration and bone survey data was not uniformly assessed in all patients) and the large amount of missing data in the application. For those reasons, we felt that the inclusion of ——— in the label would be misleading.

2) Regarding ——— : If you wish to propose an alternative sentence in place of the ———, you are welcome to do so.

3) Please let us know when you plan to get the Dear Health Care letter out (as part of the phase 4 commitment).

Thanks.

Regards,
-carl

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/s/

Carl Huntley
5/10/2006 10:37:52 AM
CSO

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 27, 2006

FROM: Rita Ouellet-Hellstrom, Ph.D., M.P.H.
Epidemiologist
Division of Drug Risk Evaluation

THROUGH: Rosemary Johann-Liang, MD, Deputy Director
For Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

TO: Robert Justice, M.D., Director
Division of Drug Oncologic Products

SUBJECT: Phase IV Commitment - [redacted]

SPONSOR: Celgene Corporation

DRUGS: Thalidomide and dexamethasone

PID#: D060312

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The Division of Drug Oncologic Products (DDOP) requested the Division of Drug Risk Evaluation (DDRE) to assess the capacity of the ——————— to successfully conduct a proposed Phase IV epidemiologic investigation.

PROBLEM SUMMARY

Celgene Corporation has a Supplemental New Drug Application under review for thalidomide in combination with dexamethasone for newly diagnosed symptomatic multiple myeloma (MM) patients. This application is based on results from the Eastern Cooperative Oncology Group study E1A00. The results of E1A00 showed that MM patients receiving thalidomide in combination with dexamethasone are at significant risk for venous thromboembolic events (VTE).

These results also raised additional important clinical questions regarding thalidomide-associated VTE in this population. DDOP therefore asked Celgene to propose a plan to collect and submit information to answer the following 3 questions:

1. What is the failure rate for each of the different types of thromboembolic prophylaxis (e.g. antiplatelet or anticoagulant therapy) for MM patients treated with a thalidomide-containing regimen?

1. What is the failure rate for each type of DVT treatment (dose-adjusted heparin, low molecular weight heparin, coumadin) for those patients with MM and a DVT who continue to receive ongoing treatment with thalidomide?

2. What is the failure rate for each type of post-DVT thromoboembolic prophylaxis for those patients with MM and a DVT who continue to receive ongoing treatment with thalidomide?

Celgene has responded to these queries as follows:

> "Celgene has initiated formal discussions with . With the assistance of their epidemiology group, we propose to investigate the use of anticoagulation in the patients diagnosed with multiple myeloma who received thalidomide (approximately 2,150 patients), with attention to answering the three questions posed. Access to the individual patients' data will be available for those cases identified as being relevant."

Celgene has identified an epidemiology group called with which it wishes to collaborate in studying these three clinical questions. To determine whether this proposal is acceptable, DDOP needs to ascertain the qualifications and experience of the

For DDRE (ODS):

1. Please assess the capacity of the [redacted] to successfully conduct the proposed epidemiologic investigations.

DDRE Comment:

The incidence of myeloma[1] has remained stable over time (5.9 per 100,000 in 1992 – 5.5 per 100,000) in 2002), is higher in males (7.2 per 100,000) than in females (5.0 per 100,000), in blacks (7.0 per 100,000) more than whites (5.4 per 100,000) but particularly, the incidence is higher in individuals over 64 years of age (30.4 per 100,000) compared to those younger than 65 years (2.1 per 100,000).

[redacted] is qualified and has performed Phase IV epidemiology studies for many sponsors. They usually rely on their insurance claims databases to identify exposed populations and health outcomes using ICD-9 CM and CPT codes. They also have the capability of verifying health outcomes from the medical records. Therefore, in many instances, selection of this group for a Phase IV epidemiology study would be acceptable.

In this particular instance, however, use of the UHC claims database is less than ideal given that there is a significantly better choice.

- *Although the UHC database captures information on millions of claims, until December 31, 2006, the database covered mostly individuals younger than 65 years of age whereas most of the MM cases occur over the age of 65 years. The number of seniors in the UHC database may increase beginning January 1, 2006 since the American Association of Retired People (AARP) has been encouraging seniors to select UHC as their prescription medication provider for Part D Medicare drug coverage. Many have signed with UHC, but it is unclear when the information will be available for analysis.*
- *Information from the claims database would be limited only to MM individuals covered by UHC, currently only 2,150 proposed. Information on gender is available but information on demographic characteristics is not readily available in claims data although it could be obtained from the medical record.*
- *There is a relatively long lag time (as much as 6 months) between occurrence of an event and capture of the event in the database particularly when the patient is hospitalized.*
- *Use of ICD9-CM codes to identify claims is not efficient since claims may need to be verified and some may be miscoded and missed altogether.*

However, when no other data source exists, use of the UHC database is a good proxy.

DDRE Recommendation – Use of Patient Registry

---

[1] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Public-Use, Nov 2004 Sub (1973-2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.

The S.T.E.P.S. patient registry for Thalidomide provides a unique research opportunity. All users need to register at least once. The registration requirement provides an opportunity for real-time, instant cohort capture of nearly 100%, an unusual occurrence in epidemiology and one with a potential that could and should be maximized. The benefits of using the patient registry to establish a follow-up cohort are as follows:

- *Allows identification of nearly 100% of an exposed cohort prior to exposure. The UHC proposal claims to have 2,150 MM patients that use thalidomide for the study. The most recent sponsor's quarterly report[2] states that 4,814 new patients were registered in the S.T.E.P.S. registry during the fourth quarter of 2005 alone and of these 4,326 (90%) were oncologic patients and 3,071 (64%) were multiple myeloma patients. Use of the registry to identify a study cohort would yield more study subjects in one quarter than would the review of UHC database as proposed.*
- *Use of the registry also provides the ability to obtain informed consent for follow-up and physician contact at the time of registration.*
- *Use of the registry would also allow real-time follow-up to capture health problems of interest as they occur for the majority of exposed patients and hopefully prior to death.*
- *Cost of this follow-up may be lower, or at least no more than querying the UHC database and performing medical record review.*
- *Use of the registry may also allow a comparison of the following cohorts:*
    - *MM patients on thalidomide, dexamethasone, and use of anticoagulation;*
    - *MM patients on thalidomide and dexamethasone only;*
    - *MM patients on other therapy.*

Many non-profit organizations and academic institutions are capable of providing expertise in doing this type of research. It is conceivable that the sponsor is considering the [redacted] *to provide the research support needed to do a Phase IV study using the S.T.E.P.S. registry to identify exposed patients. Based on the information provided in the consult request, however, it does not appear that this is the case.*

2. We plan to have the company submit a protocol along with a detailed statistical analysis plan to answer the above questions as part of a phase 4 commitment. We will ask for a consult from ODS at the time this protocol and statistical analysis plan are provided.

Whatever course of action is selected, DDRE supports the Division's intention of requesting the sponsor to submit a protocol along with a detailed statistical analysis plan prior to implementation. DDRE (ODS) would be happy to review the protocol and provide recommendations.

---

[2]Celgene Corportation. NDA 20-785. THALOMID® (Thalidomde) Capsules. S.T.E.P.S® Quarterly Report (October 1, 2005 – December 31, 2005), March 17, 2006.

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/s/

Rita Ouellet-Hellstrom
4/27/2006 02:41:11 PM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
4/27/2006 05:32:27 PM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Mary Dempsey/Office of Drug Safety

FROM: Carl Huntley/OODP/DDOP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
4-5-06		21-430	Supplemental NDA	March 15, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Thalidomide (Thalomid)	High	Immune modulator	

NAME OF FIRM: Celgene

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
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- ☐ RESUBMISSION
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- X PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Celgene Corporation has a Supplemental New Drug Application under review for thalidomide in combination with dexamethasone for newly diagnosed symptomatic multiple myeloma (MM) patients. This application is based on results from the Eastern Cooperative Oncology Group study E1A00. The results of E1A00 showed that MM patients receiving thalidomide in combination with dexamethasone are at significant risk for venous thromboembolic events (VTE). These results also raised additional important clinical questions regarding thalidomide-associated VTE in this population. DDOP therefore asked Celgene to propose a plan to collect and submit information to answer the following 3 questions:

1. What is the failure rate for each of the different types of thromboembolic prophylaxis (e.g. antiplatelet or anticoagulant therapy) for MM patients treated with a thalidomide-containing regimen?

2. What is the failure rate for each type of DVT treatment (dose-adjusted heparin, low molecular weight heparin, coumadin) for those patients with MM and a DVT who continue to receive ongoing treatment with thalidomide?

3. What is the failure rate for each type of post-DVT thromoboembolic prophylaxis for those patients with MM and a DVT who continue to receive ongoing treatment with thalidomide?

Celgene has responded to these queries as follows: "Celgene has initiated formal discussions with [redacted]

[redacted]. With the assistance of their epidemiology group, we propose to investigate the use of anticoagulation in the patients diagnosed with multiple myeloma who received thalidomide (approximately 2150 patients), with attention to answering the three questions posed. Access to the individual patients' data will be available for those cases identified as being relevant."

Celgene has identified an epidemiology group called [redacted] with which it wishes to collaborate in studying these three clinical questions. In order to determine whether this proposal is acceptable, DDOP needs to ascertain the qualifications and experience of the [redacted].

For ODS:

1. Please assess the capacity of the [redacted] to successfully conduct the proposed epidemiologic investigations.
2. We plan to have the company submit a protocol along with a detailed statistical analysis plan to answer the above questions as part of a phase 4 commitment. We will ask for a consult from ODS at the time this protocol and statistical analysis plan are provided. Do you have any recommendations concerning these requests?

SIGNATURE OF REQUESTER Thanks, Carl Huntley	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND X Electronic
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Carl Huntley
4/5/2006 03:14:48 PM

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FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road
Beltsville, Maryland 20705

PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager

Total number of pages, including cover sheet 2
Date: 2-1-06

COMMENTS: Regarding sNDA 21-430 for Thalomid, this communication follows a teleconference held between Celgene and DDOP January 25, 2006.

You have a Supplemental New Drug Application under review for thalidomide in combination with dexamethasone for newly diagnosed ← multiple myeloma (MM) patients. This application is based on results from the Eastern Cooperative Oncology Group study E1A00. The results of E1A00 demonstrate that MM patients receiving thalidomide in combination with dexamethasone are at significant risk for venous thromboembolic events (VTE).

We have identified three clinical questions regarding thalidomide-associated VTE in patients with MM. Please provide us with a proposal and plan to collect and submit this information which will answer the following 3 questions:

1. What is the failure rate for each of the different types of thromboembolic prophylaxis (e.g. antiplatelet or anticoagulant therapy) for MM patients treated with a thalidomide-containing regimen?

2. What is the failure rate for each type of DVT treatment (dose-adjusted heparin, low molecular weight heparin, coumadin) for those patients with MM and a DVT who continue to receive ongoing treatment with thalidomide?

3. What is the failure rate for each type of post-DVT thromoboembolic prophylaxis for those patients with MM and a DVT who continue to receive ongoing treatment with thalidomide?

Thanks.
Regards,
-carl

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/s/

Carl Huntley
5/11/2006 11:35:52 AM
CSO

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FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road
Beltsville, Maryland 20705

PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager

Total number of pages, including cover sheet 4
Date: 1-26-06

COMMENTS: Regarding sNDA 21-430 for Thalomid, please see attached meeting minutes from the January 5, 2006 telecon.

Thanks.
Regards,
-carl

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 5, 2006
TIME: 4:00 PM
LOCATION: Room 2376, Telecon
APPLICATION: NDA 21-430
DRUG NAME: Thlidomid® (Thalidomide)
TYPE OF MEETING: Type B telecon

MEETING CHAIR: Ann Farrell, MD

MEETING RECORDER: Carl Huntley, R.Ph. MBA

FDA ATTENDEES:

Robert Justice, MD, Acting Division Director, DDOP
Ann Farrell, MD, Medical Team Leader, DDOP
Michael Brave, MD, Medical Reviewer, DDOP
Peiling Yang, Ph.D., Statistician, OPSS/OB/DBI
Carl Huntley, R.Ph., MBA, Regulatory Project Manager

CELGENE ATTENDEES (except for the IDMC representative)

John Patin, Executive Director, Biostatistics and Data Management
Kenton Wride, Senior Statistician, Clinical R&D
Zhinuan Yu, Senior Statistician, Clinical Operations
Graham Burton, M.D., SVP Regulatory Affairs and Pharmacovigilance
Megan Parsi, Director Regulatory Affairs
Jerry Zeldis, M.D., VP, Chief Medical Officer
Herbert Faleck, D.O., VP, Clinical Research and Development
Bob DeLap, M.D., VP, Global Medical Research
Marta Olesnyckyi, Clinical Research Scientist
Michelle Loveland, Manager, Project Management
[redacted] (Chairman, IDMC)

BACKGROUND:
On January 4, 2006, Celgene requested a teleconference with the Agency to discuss interim results from Thal-MM-003. On November 21, 2005, an independent Data Monitoring Committee (IDMC) meeting was convened to review interim data for Celgene Corporation Phase 3 THAL-MM-003 study. The IDMC determined that the study met the pre-determined stopping criteria boundary for efficacy and recommended early release of the information. The initial evaluation revealed a highly significant difference (p=0.000015) with respect to the primary endpoint, TTP, in favor of the thalidomide-dexamethasone treatment arm.
In addition, the IDMC noted that neither the overall toxicity findings nor the differences in toxicity between the two treatment arms were unexpected and excessive. The data set evaluated by the IDMC was based upon investigator assessments.

Based upon the results of the interim analysis and in accordance with the recommendations from the IDMC, Celgene proposes to provide un-blinded datasets to the investigators and to stop the

study. Thalidomide will be made available to all patients still participating in the study as judged clinically appropriate by the investigator. Celgene asks if the Agency concurs with the proposal to stop the trial based on the pre-specified criteria, to unblind participants, and provide the datasets to investigators.

MEETING OBJECTIVES:

To discuss the IDMC findings and to seek Agency concurrence of the recommendation by the IDMC to stop the THAL-MM-003 study.

DISCUSSION POINTS:

1. The Agency congratulated Celgene for the design and implementation of the study. The Agency agreed that it was an acceptable proposal to stop the study based on the IDMC recommendation and the fact that the results met the pre-specified criteria. The sponsor clarified what was meant by providing the un-blinded data sets to the investigators. Celgene meant that for their particular patients, those data would be available to the investigator (not the entire dataset).
2. The THAL-MM-003 study was discussed. The Agency agreed that this study could be a phase IV commitment.
3. The sponsor clarified that all available E1A00 data has been submitted in response to the Agency's request and they consider the submission complete. Based on this information, the Agency stated that the THAL re-submission letter dated November 23, 2005 would be classified as a type 2 submission, which meant a 6 month time clock, although a shorter review time was possible.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

See discussion above.

ATTACHMENTS/HANDOUTS:

None

The meeting concluded at 4:30 PM

Carl Huntley
Regulatory Project Manager

Ann Farrell, MD
Meeting Chair

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/s/

Ann Farrell
1/25/2006 05:34:56 PM

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Carl Huntley
1/26/2006 09:56:06 AM

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Division of Drug Marketing,
Advertisement, and Communications

Enforcement Branch II

Internal Consult

****Pre-decisional Agency Information****

To: Michael Brave, MD, Medical Officer, DDOP

From: Joseph A. Grillo, Regulatory Review Officer, DDMAC
Iris Masucci, Labeling Reviewer, DDMAC

CC: Carl Huntley, Project Manager, DODP

Date: October 27, 2005

Re: NDA # 21-430
MACMIS # 13660
Thalomid® (thalidomide) Capsules
Comments on draft Labeling

In response to your consult request via email on June 20, 2005, we have reviewed the draft Labeling and offer the following comments:

1 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Joseph Grillo
10/27/2005 01:00:11 PM
DDMAC REVIEWER

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Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

October 25, 2005

Robert Justice, M.D.
Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-430 Thalomid®
Thalidomide Capsules
Type 6 (sNDA)

RE: RESPONSE TO FDA REQUEST FOR ADDITIONAL INFORMATION

Dear Dr. Justice:

On September 19 and 20, 2005, the FDA sent facsimiles to Celgene Corporation with comments/requests from the Medical review team, regarding a number of patients enrolled in the ECOG E1A00 study with a complete response, near complete response, or partial response as defined by the criteria used by ECOG in this study (ECOG criteria). FDA requested additional information/data to justify claimed responses for 71 patients.

In review of the FDA queries, we determined that there are common features in a number of these queries. These requests include but are not limited to availability of specific urine or serum paraprotein measurements, and radiographical skeletal surveys to satisfy response designations.

Through recent discussions with ECOG, we confirmed that under certain circumstances, the above referenced paraprotein measurements and bone surveys were not considered necessary by ECOG to designate a patient as a "responder" based on the clinical importance of certain parameters needed to designate a patient as a "responder". Specifically, we have ascertained that:

1. If a patient presented at baseline with no measurable disease in the urine M-protein (<200 mg/24hr light chain), then post-baseline collection of urine M-protein data was not required. This reflects the intrinsic variability of this low paraprotein value. Hence, patients with this low amount of urine M-protein at baseline did not have post-baseline values recorded in the database.
2. Skeletal surveys were not required to confirm a PR or CR. The value of the skeletal survey is to confirm disease progression.
3. The 4-month response evaluation submitted by ECOG is the best response during the first 4 months of therapy, not the response at the end of the first 4 months. Such an analysis may favor the dexamethasone/ placebo arm since time to best

response for dexamethasone monotherapy is relatively early, typically less than 4 months and patients often begin to relapse by four months.

We requested ECOG to further clarify in writing their criteria for certain response designations. Please see the attached letter from ECOG describing the rationale for the following:

- Why a bone scan or bone survey was not needed at the point of a response (ex. PR at cycle#2)
- Why a serum PR did not always need to be accompanied by a paraprotein result for urine

As we continue to work with ECOG in the attainment of the additional responses to the remaining outstanding FDA requests, we hope this submission will help to address the comments and questions in your prior facsimile communications. Please be advised that a complete response document also has been drafted where specific FDA comments are provided in a tabular format together with any currently available additional relevant data that can be provided, and with Celgene's response for each patient. Celgene intends to submit this detailed response document to the Agency in the next few days, upon receipt of the additional information from ECOG.

If you have any questions, please do not hesitate to contact me at (908) 673-9566.

Sincerely,

Megan M. Parsi
Director, Regulatory Affairs
E-mail: megan.parsi@celgene.com
Enclosures

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Eastern Cooperative Oncology Group

Coordinating Center
Frontier Science
900 Commonwealth Avenue•Boston, MA 02215
(617) 632-3610•Fax: (617) 632-2990
Randomization: (617) 632-2022

Group Chair: Robert L. Comis, M.D.
Group Statistician: Robert Gray, Ph.D.

Jean MacDonald, Director of Research Operations
Mary Steele, Director of Group Administration

October 21, 2005

Jerome B. Zeldis, M.D., Ph.D.
Chief Medical Officer/VP Medical Affairs
Celgene Corporation

Dear Dr. Zeldis

Here are my responses to the query letter you sent me regarding assessment of response in multiple myeloma pertaining to the E1A00 ECOG clinical trial. Your queries by their nature pertain to myeloma in general and my responses are listed below.

1) Why a bone scan or bone survey was not needed at the point of a response (ex. PR at cycle#2)
Response:

1) Typically bone scans and bone surveys are highly unreliable to quantify or follow response in multiple myeloma. Bone lesions in myeloma take many years to heal and often even with significant healing no changes occur. Further due to technical reasons bone surveys can be variable from study to study. Therefore supporting bone survey confirmation of response is not required.

2) If a bone survey happened to be repeated in the first 4 cycles due to clinical reasons (presumably due to new symptoms since this was not required per protocol) and showed unequivocal progression then that information would be used in coding response. However, a bone survey is not done and was not required to be routinely performed to confirm lack of progression or to confirm response. As stated in section 6.11 paraprotein criteria supersede other criteria in determining response or progressive disease (PD) unless there is clear-cut, obvious progressive disease by other criteria. This fact and reasoning that a bone survey is not needed to confirm response due to the drawbacks and inadequacies listed earlier, is assumed in the ECOG response criteria and therefore not made as a requirement in the test schedule. The limitations of bone evaluations are well recognized and the fact that they are not required to document response has been subsequently made more explicitly clear in the current Blade (EBMT) myeloma response criteria which states that:

"Similarly, skeletal X-rays are not required for the definition of response, but if performed there must be no evidence of progression of bone disease. Follow-up X-rays to confirm continuing response are also not mandatory, although periodic radiological examinations are recommended. If radiological examinations are performed as part of routine follow-up, or for other clinical indications, and show evidence of progressive disease, this will constitute relapse or progression even in the absence of any other criteria." Br J Haematol 1998;102:1118.

3) In keeping with the same reasoning, even in cases of suspected disease progression Section 6.74 states that when progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from study

- Why a serum PR did not need to be accompanying with a paraprotein result of the urine.

Response:

1) The ECOG criteria pre-dates the EBMT criteria by many years. As a rule we follow the patient by the parameter that qualified as "measurable disease." (Section 3.1- Monoclonal protein (M-protein) ≥ 1.0g/dl on serum protein electrophoresis or ≥ 200mg of monoclonal light chain on a 24 hour urine protein electrophoresis) The rationale for defining "Measurable disease" using these levels (which are also used fairly commonly in almost all myeloma studies) was defined using these minimal levels of M protein is to be sure that a certain degree of reduction observed is unlikely to be due to chance or laboratory variation. For, eg., a 50% drop in serum M protein level from 0.5gm/dl to 0.25gm/dl could based on the nature of the test be simply due to a lab variation. Similarly, urine M protein measurement is a calculated value. The laboratory translates mg/dl to mg/day based on the volume of urine collected in a day to arrive at that figure. Thus levels of urine M protein below 200mg/day are actually based on very small amounts of M protein in mg/dL terms. Thus they are not considered reliable to follow for response. The Table on section 6.11 explains how we applied the response criteria. An M protein was considered to be present in the serum or urine only if it was "measurable" not merely positive or negative by immunofixation or electrophoresis.

2) The reasoning also has to do with biology. Urine paraprotein levels are increased in patients who either have a light chain only form of multiple myeloma or who secrete a free light chain in addition to the intact immunoglobulin. Patients who do not have this ability to secrete significant amounts of free light chain are unlikely to have acquired this ability in the first four month, particularly in the setting of a 50% or greater reduction in the serum protein level. In other words, it would be extremely unlikely that a patient who starts off with unmeasurable (<200mg/day) levels of urine M protein, and has a 50% or decrease in serum M protein would have developed progressive disease in urine. Thus responses in ECOG trials which used the ECOG response criteria have response assessed using the serum M protein levels alone in patients without measurable M protein levels in the urine at baseline. This was done to spare the need for a cumbersome 24 hour urinary M protein collection in patients who didn't have measurable disease to follow in the urine. Therefore section 7.0 did not require 24 hour urine collections to follow urinary M protein in patients with <200mg/day of urinary M protein.

Please let me know if you need further clarifications

Sincerely,

S. Vincent Rajkumar, MD
E1A00 Study Chair

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November 1, 2005

Robert Justice, M.D.
Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research, HFD-150
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NDA 21-430 Thalomid®
Thalidomide Capsules
Type 6 (sNDA)

RE: Response to Request for Additional Information

Dear Dr. Justice:

On September 19 and 20, 2005, the FDA sent facsimiles to Celgene Corporation with comments/requests from the Medical review team, regarding a total of 71 patients enrolled in the ECOG E1A00. FDA requested additional information/data to support the determinations of complete response, near complete response, or partial response (as defined by ECOG criteria) for these patients.

On October 24, 2005, Celgene provided additional information received from ECOG, clarifying and explaining relevant aspects of ECOG response assessments, in myeloma and in the E1A00 study.

As indicated in our letter of October 24th, we have had continuing discussions with ECOG to further address the details of the FDA requests. Attached is a response table, where specific FDA comments are summarized in a tabular format, along with Celgene's reply for each patient.

This table, together with the October 24th response, address FDA's September 19 and 20th comments, with the exception of the following patients for whom ECOG input is pending:

Patients: 10063, 10120, 10140, 10167

Celgene intends to submit the detailed responses regarding the above-mentioned remaining patients to the Agency in the next few days, upon receipt of the additional information from ECOG. .

If you have any questions, please do not hesitate to contact me at (908) 673-9566.

Sincerely,

Megan M. Parsi
Director, Regulatory Affairs
E-mail: megan.parsi@celgene.com
Enclosures

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1539 FAX: (301) 594-0499

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager
Phone: (301) 827-1539

Total number of pages, including cover sheet 1
Date: 10-4-05

COMMENTS: Regarding your sNDA 21-430 for Thalomid, Amendment to a Pending Application – Response to Action Letter dated May 13, 2005, we have the following comments/requests from our Medical Review Team.

We plan on sharing our findings of our review of the ECOG study E1A00 with the Cancer Therapy Evaluation Program/NCI. Will that be acceptable to you?

Regards,
-carl

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/s/

Carl Huntley
10/4/2005 09:25:23 AM
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 1, 2005

TO: sNDA 21-430

FROM: Michael Brave, M.D., Medical Officer
Ann Farrell, M.D., Clinical Team Leader

SUBJECT: Thrombotic risk associated with thalidomide in multiple myeloma

The clinical review team for sNDA 21-430 has recently reviewed the published medical literature regarding the risk of venous thromboembolism (VTE) during thalidomide treatment for multiple myeloma (MM). We identified eighteen relevant clinical reports.[1-18] The reported risk of VTE ranges from approximately 3 % to 5 % when thalidomide is used alone, reaches up to 8 % when thalidomide is combined with dexamethasone, and ranges from 8 % to 28 % when thalidomide was used in combination with standard chemotherapeutic agents such as alkylating agents or anthracyclines. These data suggest that the risk of VTE in MM patients nearly doubles during treatment with combination regimens containing both thalidomide and other chemotherapeutic agents, compared to when thalidomide is used alone

The causality determination for thromboembolic events is especially difficult in cancer patients who may have multiple other underlying conditions which would predispose them to develop a VTE. For example, postulated thrombogenic mechanisms in MM include paraprotein interference with fibrin function, procoagulant autoantibodies, inflammatory cytokines actions on endothelium, acquired activated protein C resistance, adhesion molecule upregulation, and direct endothelial injury or secretion of thrombogenic and angiogenic substances.[19]

The FDA previously noted that the use of thalidomide had been associated with thromboembolism. Consequently, a labeling change to strengthen the association between Thalomid and thrombosis which was made on October 10, 2003. The package insert was modified to read:

Thrombotic Events:
Thrombotic events have been reported in patients treated with THALOMID® (thalidomide). Patients with neoplastic and various inflammatory conditions being treated with THALOMID® (thalidomide) may have an increased incidence of pulmonary embolism, deep vein thrombophlebitis, thrombophlebitis, or thrombosis. It is not known if concomitant therapy with other medications, including anticancer agents, are a contributing factor.

Primary data from the Eastern Cooperative Oncology Group study E1A00 were submitted by Celgene Corporation to the FDA in May 2005 as part of supplemental New Drug Application 21-430. Two hundred and four patients comprised the E1A00 safety population. The reported rate of VTE was significantly higher in the Thal/Dex treatment arm (22.5 %) than among patients who received dexamethasone alone (4.9 %).

These findings are consistent with previous data from single-arm studies linking the use of thalidomide in MM to VTE, particularly when part of a combination regimen. Most VTE's noted were lower extremity deep venous thrombosis and pulmonary emboli. The clinical review team did not find evidence linking thalidomide use in MM to VTE in unusual sites (mesenteric, retinal, etc.).

Prophylactic anticoagulation prescribed in conjunction with thalidomide may lessen the potential for VTE. Amendments to recent clinical trial designs suggest that this practice is becoming used almost routinely in the academic community. However, these therapies are not without risk to patients. Anticoagulation for prophylaxis has been associated with severe and fatal bleeding (as outlined in the warfarin labeling). Cancer patients can be at risk both for an increased risk of bleeding and an increased risk of clotting based on their underlying disease (including the development of acquired bleeding and clotting disorders). Multiple myeloma patients in particular are at risk for falls and pathologic fractures which can become complicated by bleeding. Therefore, the decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

Within the past 9 months, we have discussed the question of conducting a phase 4 safety study studying antithrombotic prophylaxis with Oncologic Drugs Advisory Committee consultants (hematologists and oncologists) who treat cancer patients with thalidomide. These physicians did not recommend a phase 4 safety study for several logistical reasons, including the following:

1. A randomized trial of prophylactic anticoagulation to reduce the risk of VTE during thalidomide therapy for MM might, to be safe and ethical, need to exclude patients at risk for VTE (i.e. those with a family or personal history of VTE and perhaps those receiving concurrent cytotoxic chemotherapy). Evolving practice patterns suggest that some form of prophylaxis for high-risk patients has become common place.
2. Such a trial would likely also need to exclude patients at risk for complications of anticoagulation (i.e. those with histories of falling or pathologic fracture, history of bleeding problems, history of gastrointestinal or genitourinary bleeding).
3. Physicians differ in preferences for thromboembolic prophylaxis. One consultant mentioned a preference for using aspirin, an antiplatelet agent. The other consultant preferred to use an anticoagulant. Given the strong preference for antiplatelet or anticoagulant use, this reviewer questions whether the consultants would enroll in a randomized trial, particularly if the trial involves a regimen that they do not use.

This reviewer questions whether it would be ethical to randomize patients to a placebo arm given the high rate of deep venous thrombosis and embolism seen in the EA100 trial.

In light of this information, we propose the following:

1. The Thalomid label should be modified to include these data on VTE. We propose using the following language and placing this language in a "black box" for emphasis:

The use of Thalomid in multiple myeloma has been associated with an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used for this indication in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone. ——— data suggest that ——— patients who are appropriate candidates may benefit from concurrent prophylactic antithrombotic therapy.

2. The Warnings section of the label be strengthened with a bolded warning describing the thromboembolic events risk.

3. A "Dear Health Care Professional" letter should be distributed, notifying prescribers of this information.

---

[1] Arnulf B, Levy V, Leblond V, et al. Preliminary analysis of a double blind randomized study comparing thalidomide or placebo in combination with a VAD-like regimen in relapsing multiple myeloma. Hematol J 2003,4:S247 (abstr 356).

[2] Rajkumar SV, Gertz MA, Lacy MQ, et al. Thalidomide as initial therapy for early-stage myeloma. Leukemia 2003,17:775.

[3] Weber D, Rankin K, Gavino M, et al. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 2003,21:16.

[4] Dimopoulos MA, Zervas K, Kouvatseas G, et al. Thalidomide and dexamethasone combination for refractory multiple myeloma. Ann Oncol 2001,12:991.

[5] Anagnostopoulos A, Weber D, Rankin K, et al. Thalidomide and dexamethasone for resistant multiple myeloma. Br J Haematol 2003,121:768.

[6] Zangari Z, Siegel E, Barlogie B, Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. Blood 2002,100:1168.

[7] A. Palumbo, A. Bertola, P. Musto, et al. Oral melphalan, prednisone and thalidomide for newly diagnosed myeloma patients. Proc Am Soc Clin Oncol 2004, abstr 6549.

[8] Kropff MH, Lang N, Bispin G, et al. Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (Hyper CDT) in primary refractory or relapsed multiple Myeloma. Br J Haematol 2003,122:607.

[9] Arnulf B, Levy V, Leblond V, et al. Preliminary analysis of a double blind randomized study comparing thalidomide or placebo in combination with a VAD-like regimen in relapsing multiple myeloma. Hematol J 2003,4:S247(abstr 356).

[10] Osman K, Rajkumar SV. Deep venous thrombosis and thalidomide therapy for multiple myeloma. N Engl J Med 2001,344:1951.

[11] Zangari M , Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 2001,98:1614.

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/s/

Michael Brave
10/2/2005 09:38:48 PM
MEDICAL OFFICER

Ann Farrell
10/3/2005 07:54:10 AM
MEDICAL OFFICER

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

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PHONE: (301) 827-1539 FAX: (301) 594-0499

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager
Phone: (301) 827-1539

Total number of pages, including cover sheet 1
Date: 9-29-05

COMMENTS: Regarding your sNDA 21-430 for Thalomid, Amendment to a Pending Application – Response to Action Letter dated May 13, 2005, we have the following comments/requests from our Medical Review Team.

As part of the review of the submission for sNDA 21-430, and per CFR 312.53 c (4), we are validating/verifying the financial disclosure for investigators who participated in studies: Mayo 98-80-13, Thal MM-99-002 and the ECOG E1A00. Please provide the financial disclosure for the participating investigators for our review.
Thanks,
-carl

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/s/

Carl Huntley
9/29/2005 09:26:24 AM
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PHONE: (301) 827-1539 FAX: (301) 594-0499

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager
Phone: (301) 827-1539

Total number of pages, including cover sheet 1
Date: 9-26-05

COMMENTS: Regarding your sNDA 21-430 for Thalomid, Amendment to a Pending Application – Response to Action Letter dated May 13, 2005, we have the following comments/requests from our Medical Review Team.

Please provide information for each treatment arm regarding the number of patients, by treatment arm, which had to have a second dose reduction within the first 4 cycles and overall cycles.

Thanks,
-carl

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carl Huntley
9/26/2005 11:25:22 AM
CSO

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On Original

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1539 FAX: (301) 594-0499

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager
Phone: (301) 827-1539

Total number of pages, including cover sheet 10

Date: 9-20-05

COMMENTS: Regarding your sNDA 21-430 for Thalomid, Amendment to a Pending Application – Response to Action Letter dated May 13, 2005, we have the following comments/requests from our Medical Review Team.

The Clinical Review Team for sNDA 21-430 is attempting to verify which patients met the predefined primary endpoint of Study ECOG E1A00 (a complete response, near complete response, or partial response, as defined by ECOG criteria, within the first 4 cycles of treatment). We have discovered additional patients where data required justifying claimed responses appear to

be missing or inconstant with your claimed response. Please comment on the following 56 patients.

Patient 10004

1. This patient's myeloma subtype is missing from the database. Please provide this information.
2. Listing 16.2.6.2 of the Clinical Study Report indicates that this patient did not have a bone survey prior to study enrollment, whereas the dataset KLONST seems to suggest that the patient had 1-3 lytic lesions at entry. Please clarify this apparent discrepancy.
3. You have designated this patient as having attained a partial response. Please indicate the dates and disease parameters you believe support this designation.

Patient 10005

You have designated this patient as having attained a partial response by ECOG criteria. Please indicate the dates and data results parameters you believe support this designation.

Patient 10010

1. This patient's disease reportedly progressed by radiographic bone survey on study day 111 (October 29, 2002). Please clarify why the patient continued to receive protocol treatment despite this apparent disease progression.
2. Please indicate whether this patient had a measurement of 24-hour urine light chain excretion at baseline.

Patient 10015

You designate this patient as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10032

You designate this patient as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. We are also unable to locate the radiographic skeletal survey needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10034

You designate this patient as having attained a partial response by ECOG criteria. We notice that on study day 111 (December 10, 2002) a radiographic bone survey was interpreted as showing disease progression.

1. Please discuss when you believe this patient attained a partial response and which specific serum and urine paraprotein measurements support this designation.
2. Please discuss why this patient continued to receive protocol treatment after apparent disease progression on study day 111.

Patient 10035

You designate patient 10035 as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion

needed to satisfy this response designation. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10042
You designate this patient as having attained a partial response by ECOG criteria. We are unable to locate a second urine paraprotein measurement needed to confirm this response before study day 159 when a radiographic bone survey was interpreted as showing possible disease progression. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10045
You designate this patient as having attained a partial response by ECOG criteria. However, we note that on the patient's second visit, a radiographic bone survey was interpreted as showing disease progression. Please discuss why you believe that this patient attained a partial response in light of this radiographic report.

Patient 10046
You designate patient 10046 as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10048,
Listing 16.2.4.2 states "One lesion appeared to increase - see comment below." However, we find no comment below. Please provide this comment if available.

Patient 10050
The urine light chain is reportedly 0.0 at baseline. On visit 2, the urine light chain is 56.0 mg/24 h. The urine light chain decreases after that time to 0.00 on 2 occasions. Please clarify the initial urine light chain result is accurate as recorded. If this result is accurate, please explain the decision to continue protocol treatment despite apparent disease progression by urine paraprotein excretion criteria.

Patient 10052
You designate patient 10052 as having attained a partial response by ECOG criteria.

1. However, we are unable to locate specific serum and urine paraprotein data that would support this response designation. Please provide such data if available. If these data are not available, please discuss why you believe this patient attained a partial response.
2. Please explain why this patient appears to be missing from the KLDSAS dataset.

Patient 10053
You designate patient 10053 as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular

patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10062

You designate patient 10062 as having attained a partial response by ECOG criteria. We are unable to locate a serum paraprotein value needed to satisfy this response designation (i.e. 50% or less than baseline). Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10063

You designate patient 10063 as having attained a partial response by ECOG criteria. We are also unable to locate the radiographic skeletal survey needed to satisfy this response designation. Please indicate where this information is located in the application and the readings for this particular patient. If this information is not available, please state why you believe that patient 10063 attained a partial response.

Patient 10065

You designate patient 10065 as having attained a partial response by ECOG criteria.

1. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.
2. The first bone survey which we find for this patient (study day 113) was interpreted as "increased". Please discuss why, in light of this report, you believe this particular patient attained a partial response.

Patient 10069

You designate patient 10069 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation.

1. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.
2. Please define what is meant by a 24-hour urine paraprotein excretion value of 9999.99

Patient 10072

You designate patient 10072 as having attained a partial response by ECOG criteria.

1. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient 10072 attained a partial response.
2. The first bone survey which we find for this patient (study day 72) was interpreted as showing disease progression in the right femur. Please discuss why, in light of this report, patient apparently continued to receive protocol therapy.

Patient 10078
You designate patient 10078 as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10080
You designate patient 10080 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation (i.e. two samples obtained at least two weeks apart). Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10083
You designate patient 10083 as having attained a partial response by ECOG criteria. We are also unable to locate the radiographic skeletal survey needed to satisfy this response designation. Please indicate where this information is located in the application and the readings for this particular patient. If this information is not available, please state why you believe that patient 10083 attained a partial response.

Patient 10095
You designate patient 10095 as having attained a partial response by ECOG criteria. We are also unable to locate the radiographic skeletal survey needed to satisfy this response designation. Please indicate where this information is located in the application and the readings for this particular patient. If this information is not available, please state why you believe that patient 10095 attained a partial response.

Patient 10096
You designate patient 10096 as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10097
You designate patient 10097 as having attained a partial response by ECOG criteria. Serum and paraprotein data from Clinical Study Report Listing 16.2.6.2 seem to corroborate this claim; however, paraprotein data for patient 10097 appear to be missing from the dataset D_LAB. Please discuss your decision to designate this patient as having attained a partial response in light of this apparent discrepancy.

Patient 10099
You designate patient 10099 as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10100

You designate patient 10100 as having attained a partial response by ECOG criteria.

1. We are unable to locate a second measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.
2. The first bone survey which we find for this patient (study day 114) was interpreted as showing an enlarging mid-humeral lesion, qualifying as disease progression. Please discuss why, in light of this report, you believe this particular patient attained a partial response.

Patient 10105

You designate patient 10105 as having attained a partial response by ECOG criteria. The first bone survey which we find for this patient (study day 139) was interpreted as showing an increased lesions in both femurs, qualifying as disease progression. Please discuss why, in light of this report, you believe this particular patient attained a partial response.

Patient 10108

You designate patient 10108 as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10111

You designate patient 10111 as having attained a partial response by ECOG criteria. However, we note that on study day 126, a radiographic bone survey was interpreted as showing disease progression. We are unable to locate sufficient serum and urine paraprotein data prior to day 126 to satisfy the criteria for partial response. Please discuss why you believe that this patient attained a partial response in light of this radiographic report.

Patient 10114

You designate patient 10114 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10120

You designate patient 10120 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. In particular, we note that the 24-hour urine paraprotein excretion increased by > 25 % between study days 76 and 111, thus meeting the criteria for disease progression during that interval.

1. Please discuss why the patient continued treatment on protocol despite this apparent disease progression.
2. In light of #1, please clarify the specific serum and urine paraprotein values you believe support a designation of partial response for this patient.
3. Please clarify the meaning of 9999.99 mg/24 h as a urine paraprotein value on study day zero.

Patient 10121

You designate patient 10121 as having attained a partial response by ECOG criteria. We are unable to locate serum paraprotein measurements needed to satisfy this response designation (i.e. a reduction of at least 50 % compared to baseline). In addition, the bone marrow plasma cell burden increased from 17 % to 90 % between baseline and study day 96.

1. Please indicate the serum paraprotein values that you believe justify a partial response designation for patient 10121.
2. Please discuss why patient 10121 continued treatment on protocol despite this apparent disease progression by bone marrow criteria.

Patient 10122

You designate patient 10122 as having attained a partial response by ECOG criteria.

1. We note that on study day 152, a radiographic bone survey was interpreted as showing disease progression. Please discuss why you believe that this patient attained a partial response in light of this radiographic report.
2. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10124

You designate patient 10124 as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10026

You designate patient 10026 as having attained a partial response by ECOG criteria. We are unable to locate a baseline measurement of 24-hour urine paraprotein excretion. We are also unable to locate the measurements of 24-hour needed to satisfy the criteria for a partial response. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10128

You designate patient 10128 as having attained a partial response by ECOG criteria.

1. We note that on study day 160, a radiographic bone survey was interpreted as showing disease progression. Please discuss why you believe that this patient attained a partial response in light of this radiographic report.
2. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10137

You designate patient 10137 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10140
You designate patient 10140 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10141
You designate patient 10108 as having attained a partial response by ECOG criteria. We are unable to locate confirmatory measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10145
You designate patient 10145 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10152
You designate patient 10152 as having attained a partial response by ECOG criteria. We note that on study day 117, a radiographic bone survey was interpreted as showing disease progression. We are unable to locate sufficient serum and urine paraprotein data prior to day 117 to satisfy the criteria for partial response.

1. Please discuss why you believe that this patient attained a partial response in light of this radiographic report.
2. Please discuss why this patient apparently continued to receive protocol treatment despite apparent disease progression.

Patient 10153
You designate patient 10153 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10156
You designate patient 10156 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10159
You designate patient 10159 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10165
You designate patient 10165 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10167
You designate patient 10167 as having attained a partial response by ECOG criteria. We are unable to locate a serum paraprotein value, needed to satisfy this response designation (i.e. 50% or less than baseline). Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10506
You designate patient 10167 as having attained a partial response by ECOG criteria. We note that a radiographic bone survey on study day 24 was interpreted as showing disease progression. We are unable to locate serum paraprotein values, needed to satisfy a partial response designation (i.e. 50% or less than baseline, confirmed by a second sample at least two weeks later).

1. Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.
2. Please discuss why this patient apparently continued to receive protocol treatment beyond study day 24 despite apparent disease progression.

Patient 10507
You designate patient 10507 as having attained a partial response by ECOG criteria. We are also unable to locate the radiographic skeletal survey needed to satisfy this response designation. Please indicate where this information is located in the application and the readings for this particular patient. If this information is not available, please state why you believe that patient 10507 attained a partial response.

Patient 10510
You designate patient 10510 as having attained a partial response by ECOG criteria. We are unable to locate a serum paraprotein value, needed to satisfy this response designation (i.e. 50% or less than baseline). Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10521

You designate patient 10521 as having attained a partial response by ECOG criteria. We are unable to locate a second confirmatory measurement of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10522
You designate patient 10522 as having attained a partial response by ECOG criteria. We are also unable to locate the radiographic skeletal survey needed to satisfy this response designation. Please indicate where this information is located in the application and the readings for this particular patient. If this information is not available, please state why you believe that patient 10522 attained a partial response.

Patient 10528
You designate patient 10528 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10533
You designate patient 10533 as having attained a partial response by ECOG criteria. We are unable to locate serum paraprotein values, needed to satisfy a partial response designation (i.e. 50% or less than baseline, confirmed by a second sample at least two weeks later). Please indicate where this information is located in the application and the values that you believe support the response designated for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10534
You designate patient 10528 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Patient 10539
You designate patient 10539 as having attained a partial response by ECOG criteria. We are unable to locate measurements of 24-hour urine paraprotein excretion needed to satisfy this response designation. Please indicate where this information is located in the application and the values for this particular patient. If this information is not available, please state why you believe that this patient attained a partial response.

Thanks.

Regards,
-carl

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carl Huntley
9/20/2005 06:03:11 PM
CSO

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FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1539 FAX: (301) 594-0499

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager
Phone: (301) 827-1539

Total number of pages, including cover sheet 3

Date: 9-19-05

COMMENTS: Regarding your sNDA 21-430 for Thalomid, Amendment to a Pending Application – Response to Action Letter dated May 13, 2005, we have the following comments/requests from our Medical Review Team.

The Clinical Review Team for sNDA 21-430 is attempting to verify which patients met the predefined primary endpoint of Study ECOG E1A00 (a complete response, near complete response, or partial response as defined by ECOG criteria). In order to accomplish this, we are comparing the response data submitted in dataset D_RESP (RESP4M $\leq$ 3) against the raw data provided in Listing 16.2.6.2 of the Clinical Study Report. This is the method that Kyle McBride

and Kenton Wride recommended to Dr. Brave during their meeting in Rockville, Maryland on July 27, 2005.

We have discovered that for a significant number of patients, data required to justify claimed responses appear to be missing or inconstant with your claimed response. Areas that are problematic in this regard include the following:

1. Serum paraprotein measurements
    a. Six patients appear to have had no baseline serum paraprotein measurement. These were patients 10052, 10062, and 10146 in the Thal/Dex treatment arm and patients 10026, 10045, and 10140 in the dexamethasone-alone arm.
    b. Three patients appear to not to have had a serum paraprotein measurement at the time of a urine paraprotein response. These were patients 10052 and 10146 in the Thal/Dex treatment arm and patient 10140 in the dexamethasone-alone arm.
    c. Five patients appear not to have had their initial serum paraprotein response confirmed by a second measurement. These were patients 10506 and 10533 in the Thal/Dex treatment arm and patients 10026, 10045, and 10167 in the dexamethasone-alone arm.

2. Urine paraprotein measurements
    a. Fourteen patients appear to have had no baseline urine paraprotein measurement. These were patients 10010, 10062, 10114, 10122, 10137, 10145, and 10146 in the Thal/Dex treatment arm and patients 10005, 10096, 10099, 10153, 10155, 10165, and 10167 in the dexamethasone-alone arm.
    b. Three patient's serum paraprotein response appear to have been of inadequate magnitude to meet the ECOG definition of PR. These were patient 10062 in the Thal/Dex treatment arm and patients 10167 and 10510 in the dexamethasone-alone arm.
    c. Twenty-six patients appear not to have had a measurement of 24-hour urine paraprotein excretion at the time of a serum paraprotein response. These were patients 10010, 10015, 10022, 10032, 10046, 10052, 10059, 10062, 10108, 10114, 10122, 10137, 10156, and 10159 in the Thal/Dex treatment arm and patients 10005, 10035, 10065, 10078, 10096, 10099, 10124, 10153, 10155, 10165, 10167, and 10534 in the dexamethasone-alone arm.
    d. Seventeen patients appear not to have had their initial urine paraprotein response confirmed by a second 24-hour urine sample. These were patients 10038, 10055, 10069, 10080, 10111, 10141, 10145, 10146, 10166, 10521, 10528, and 10539 in the Thal/Dex treatment arm and patients 10026, 10029, 10053, 10064, and 10072 in the dexamethasone-alone arm.

3. Radiographic skeletal surveys
    a. Twenty patients appear not to have had baseline skeletal surveys. These were patients 10004, 10010, 10013, 10032, 10042, 10052, 10055, 10063, 10083, 10095, 10121, 10146, 10152, 10156, 10159, 10507, 10521, 10522, 10528, and 10539 in the Thal/Dex treatment arm.
    b. Eleven patients appear not to have had skeletal surveys documented at the time of paraprotein response. These were patients 10031, 10141, and 10145 in the Thal/Dex treatment arm and patients 10005, 10018, 10099, 10140, 10153, 10167, 10510, and 10534 in the dexamethasone-alone arm

c. Patients' skeletal surveys appear to have shown disease progression at the time of serum paraprotein response. These were patients 10048, 10059, 10069, 10100, 10108, 10111, 10122, 10137, and 10506 in the Thal/Dex treatment arm and patients 10026, 10045, 10065, 10072, 10105, and 10128 in the dexamethasone-alone arm.

4. Two patients' bone marrows appear to have shown disease progression at the time of paraprotein response. These were patients 10017 and 10121 in the Thal/Dex treatment arm.

In order to help us verify these responses, please provide:

a. The dates and values of paraprotein measurements, radiographic surveys, or bone marrow examinations that you believe demonstrate the response claimed for each patient listed above;
b. Please state where this information is contained within the datasets or clinical study report submitted.

Thanks.

Regards,
-carl

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/s/

Carl Huntley
9/19/2005 04:21:08 PM
CSO

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Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

September 16, 2005

Robert Justice, M.D.
Acting Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research / HFD-150
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

sNDA 21-430
THALOMID® (thalidomide)
50mg, 100mg, 200mg Capsules

RE: GENERAL CORRESPONDENCE – MANUSCRIPT FOR STUDY E1A00

Dear Dr. Justice:

Reference is made to the Type 6 sNDA #21-430 which was submitted for THALOMID® (thalidomide) Capsules as a treatment for patients with multiple myeloma, on December 22, 2003.

Enclosed is a copy of a manuscript published for study E1A00 conducted by ECOG. This manuscript has just become available to Celgene thus, we are forwarding it to FDA for your records.

The enclosed CD was certified to be virus-free using McAfee Security, VirusScan Enterprise 7.1 scan engine 4.4. created on June 23, 2005 by Celgene Corporation.

Number of CD(s): 1
Submission Size: 1.03 MB

Please address any comments or questions regarding this application to myself, at 908 653-9566 (FAX: 908-673-2763).

Sincerely,

Megan Parsi

Megan M. Parsi
Director, Regulatory Affairs
E-mail: megan.parsi@celgene.com

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-430

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Celgene Corporation	September 16, 2005
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(908) 673-9000	(908) 673-2763
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 86 Morris Avenue, Summit, NJ 07901	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-430

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	CODE NAME *(If any)*
Thalidomide	THALOMID®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Alpha-(N-phthalimido) glutarimide		
DOSAGE FORM: Capsule	STRENGTHS: 50 mg, 100 mg, 200 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Multiple Myeloma

APPLICATION DESCRIPTION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
General Correspondence – Manuscript for Study E1A00

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-785 IND 49,481
ID

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (i)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER:

ERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Megan Parsi	Megan Parsi, Director, Regulatory Affairs	September 16, 1005

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A Randomized Phase III Clinical Trial of Thalidomide Plus Dexamethasone versus Dexamethasone Alone in Newly Diagnosed Multiple Myeloma: A Clinical Trial Coordinated by the Eastern Cooperative Oncology Group

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Word Count: 3000

Abstract

Purpose: To determine if thalidomide plus dexamethasone yields superior response rates compared to dexamethasone alone as induction therapy for newly diagnosed multiple myeloma.

Patients and Methods: Patients were randomized to receive thalidomide plus dexamethasone or dexamethasone alone. Patients in Arm A received thalidomide 200 mg orally for four weeks; dexamethasone was administered at a dose of 40 mg orally on days 1-4, 9-12, and 17-20. Cycles were repeated every 4 weeks. Patients in Arm B received dexamethasone alone at the same schedule as in Arm A.

Results: Two hundred and seven patients were enrolled: 103 were randomized to thalidomide plus dexamethasone and 104 to dexamethasone alone. Eight were ineligible. The response rate with thalidomide plus dexamethasone was significantly higher than with dexamethasone alone, 63% versus 41%, respectively, (P=0.0017). The response rate allowing for use of serum monoclonal protein levels when a measurable urine monoclonal protein was unavailable at follow-up was 72% versus 50% respectively. The incidence rates of grade 3 or higher deep vein thrombosis (DVT), rash, bradycardia, neuropathy, and any grade 4-5 toxicity in the first 4 months were significantly higher with thalidomide plus dexamethasone compared to dexamethasone alone, 45% versus 21% respectively, P <0.001. DVT was more frequent in Arm A than Arm B (17% versus 3%); peripheral neuropathy was also more frequent (7% versus 4%, respectively)

Conclusion: Thalidomide plus dexamethasone demonstrates significantly superior response rates in newly diagnosed myeloma compared to dexamethasone alone. However, this must be balanced against the greater toxicity seen with the combination.

Key words: myeloma, therapy, thalidomide, corticosteroids

Multiple myeloma is a malignant plasma cell proliferative disorder that accounts for over 11,000 deaths each year in the United States.[1,2] For many years, melphalan and prednisone had remained the standard therapy for this disease.[3] Response rates with this therapy are approximately 50%; and median survival is approximately three years. Recently, autologous stem cell transplantation has been shown to be effective in the treatment of multiple myeloma in randomized clinical trials.[4,5] Patients eligible for stem cell transplantation typically avoid alkylator-based induction therapy to enable an adequate and safe stem cell harvest early in the disease course.

Vincristine, doxorubicin, dexamethasone (VAD) is typically used as pre-transplant induction therapy for patients who are considered candidates for stem cell transplantation.[2,6,7] However, VAD has several disadvantages including the need for an intravenous indwelling catheter, which predisposes patients to catheter related sepsis and thrombosis. Moreover, the activity of VAD primarily is due to the high-dose dexamethasone component, with vincristine and doxorubicin having minimal roles.[8] As a result, dexamethasone alone is a safer and better tolerated induction therapy for multiple myeloma, particularly in patients who will proceed to more definitive therapy with early autologous stem cell transplantation.

Thalidomide has shown significant single agent activity in relapsed refractory multiple myeloma.[9] In combination with dexamethasone, response rates increase to about 50% in relapsed refractory disease.[10] The combination of thalidomide plus dexamethasone has also shown high activity in newly diagnosed myeloma in three phase II clinical trials.[11-13] Response rates range from 65-70%, which are comparable to those obtained with VAD. Thalidomide and dexamethasone (Thal/Dex) has the advantage of being an oral regimen without the neurotoxicity, cardiotoxicity, alopecia, and other complications related to infusional VAD.

The goal of this clinical trial was to compare the response rate and efficacy of thalidomide plus dexamethasone versus dexamethasone alone in newly diagnosed multiple myeloma.

PATIENTS AND METHODS

Eligibility

Patients were eligible to enter on the study if they had previously untreated symptomatic multiple myeloma, bone marrow plasmacytosis (≥10% plasma cells or sheets of plasma cells) or a biopsy proven plasmacytoma, and measurable disease defined as serum monoclonal protein >1.0g/dL and/or urine monoclonal protein ≥200mg/24 hours. Patients also needed to have hemoglobin >7g/dL, platelet count >50,000 cells/mm^3, absolute neutrophil count >1,000 cells/mm^3, creatinine <3mg/dL, bilirubin 1.5mg/dL or lower, and ALT and AST less than or equal to 2.5 times upper limit of normal. No prior systemic therapy, with the exception of bisphosphonates, was permitted. Prior systemic glucocorticoids were not permitted for any illness in the last six months. Prior palliative localized radiation therapy was permitted provided at least four weeks had passed from the date of last radiation therapy. Also excluded were patients with grade 2 or higher peripheral neuropathy, active infection, current or prior deep vein thrombosis, and ECOG performance score of 3 or 4. Pregnant or nursing women were not eligible. Women of child-bearing potential who were unwilling to use a dual method of contraception and men who were unwilling to use a condom were not eligible. Patients with prior malignancy were eligible provided they had been treated with a curative intent and had been free of disease for the time period considered appropriate. The study was approved by the NIH Central Institutional Review Board as well as by Institutional Review Boards in the participating institutions. Patients were enrolled between June 2002 and April 2003.

Treatment Schedule

Patients in Arm A received thalidomide 200mg orally for four weeks. The dose of thalidomide was based on a previous phase II study using this combination in newly diagnosed

myeloma.[11] Dexamethasone was administered at a dose of 40mg orally on days 1-4, 9-12, and 17-20. Each cycle was repeated every 4 weeks. Patients in Arm B received dexamethasone alone at the same schedule as in Arm A. Dose adjustments were permitted for toxicity. Patients were expected to go off study after 4 cycles of therapy, but treatment beyond four cycles was permitted at physician's discretion. All patients received monthly infusions of pamidronate or zoledronic acid as part of supportive care. Patients who developed DVT or pulmonary embolism were required to stop thalidomide therapy temporarily; patients were allowed to resume treatment after therapeutic anticoagulation was achieved with a 50% dose reduction.

Response and Toxicity Criteria

The primary endpoint of this trial was best response within four cycles of treatment (4 months from the start of treatment). The response criteria used were standard ECOG response criteria. An objective response was defined as a 50% or higher decrease in the serum and urine monoclonal protein levels from baseline. Patients with measurable disease only in the urine needed to have a greater than 90% reduction in 24-hour urine monoclonal protein excretion to be considered a response. All responses needed to be confirmed at least two weeks apart by two consecutive determinations. For objective response criteria to be met, there must be no new bone lesions, no increase in existing lytic lesions, no recurrence or persistence of hypercalcemia, no increase in any existing plasmacytomas, and no new plasmacytomas. For patients in whom serum monoclonal protein was not measured, the appropriate serum immunoglobulin levels were used. Similarly, urinary light chain excretion measured by kappa or lambda light chain assays was permitted when follow-up urine monoclonal protein level was not determined. A complete response was defined as a complete disappearance of the monoclonal protein in the serum and

urine by immunofixation studies and less than 3% plasma cells on bone marrow examination. Patients appearing to meet CR criteria except for the lack of repeat bone marrow examination, presence of 3-6% plasma cells or clusters of plasma cells on bone marrow examination were considered to have near complete response (NCR). Meeting objective response criteria, but not the criteria for CR or NCR was defined as partial response (PR). Disease that does not satisfy the criteria for response, complete response, or progression was classified as no response.

Disease progression required two of the following four criteria: 1) increase in serum monoclonal protein 50% or higher above the lowest response level or a rise in level by more than 2g/dL, 2) increase in urine monoclonal protein by 50% above the lowest remission value or increase in excretion by 2000mg/24 hours or higher, 3) increase in size of soft tissue plasmacytoma by more than 50%, and 4) definite appearance of bone lesions or increase in the size of existing bone lesions by more than 50%. For patients meeting only the serum or the urine monoclonal protein criteria, hypercalcemia, anemia, increase in bone marrow plasma cell percentage by greater than 50% or generalized bone pain also constituted progression. The NCI CTC, version 2, was used to grade adverse effects.

Statistical Design and Analysis

The primary endpoints of this study were best response within 4 months/4cycles and toxicity within 4 months/4cycles. This study was designed to detect a 20% improvement in response rate in the thalidomide plus dexamethasone arm. It was assumed that the 4-month response rate would be 60% with dexamethasone, and 80% on with thalidomide plus dexamethasone. In order to give 90% power while maintaining an overall one-sided 0.05 significance level, the design required enrolling 184 eligible patients (194 total assuming a 5% ineligibility rate). This allowed

for two interims and one final analysis. The two interim analyses were scheduled to take place when response information was available on 61 patients and 123 patients, and the final analysis was planned when response information was available on 184 eligible patients. The nominal significance level for declaring a significant increase in response rate on the thalidomide plus dexamethasone arm at full planned information was 0.047. All toxicities were monitored. The proportion of patients with a rash, deep vein thrombosis (DVT), neuropathy, or bradycardia of grade 3 or higher, or a toxicity of any type of grade 4 or higher were planned to be specifically compared between the two arms.

One-sided Fisher's exact tests were used to test for difference in response rate and specified toxicity rates between the arms. Two-sided Fisher's exact tests were used to compare other characteristics between the two arms. Two-sided Wilcoxon rank sum tests were used to compare continuous characteristics between the arms. The study crossed the boundaries for declaring a significant increase in response rate as well as increased toxicity on the thalidomide plus dexamethasone arm at a planned interim analysis.

RESULTS

Patient characteristics are listed on Table 1. Two hundred seven patients were registered to the study. Eight patients were declared ineligible: no measurable disease at baseline (3 patients); no baseline urine protein electrophoresis (1 patient); no baseline urine protein electrophoresis and no baseline serum electrophoresis (1 patient); no biopsy of plasmacytoma (1 patient); no data sent (1 patient); bone marrow biopsy inadequate (1 patient). Patients were well matched between the two arms as listed on Table 1. One hundred and seven (54%) of patients had measurable levels of M protein in serum alone, 27 (14%) had measurable levels in urine

alone, 55 (28%) in both serum and urine, and 10 (5%) had measurable levels in the serum and unknown levels in the urine at baseline.

Response to Therapy

Based on standard ECOG criteria, the best response within four cycles of therapy was significantly higher with thalidomide plus dexamethasone compared to dexamethasone alone; 62 of 99 patients (63%) versus 41 of 100 patients (41%), respectively, P=0.0017. Eighteen (9%) of patients had a measurable urine protein (>200 mg/day) at baseline that was unavailable for assessment at follow-up or had urine follow-up but not enough to confirm response; the median serum M protein in these patients was 4.5 gm/dL (range, 2.1-9.0 gm/dL). When response was assessed using serum monoclonal protein levels in these 18 patients in whom a measurable urine protein was unavailable at follow-up, the adjusted response rates were 72% with thalidomide plus dexamethasone versus 50% with dexamethasone alone. The four-month responses occurred rapidly with the median time to response among ECOG criteria responders being 1.1 months in both arms; range, 0.7-4.1 months with thalidomide plus dexamethasone versus 0.7-2.9 months with dexamethasone alone.

Complete responses occurred in 4% of patients within four cycles of therapy with thalidomide plus dexamethasone, and in 0% of patients in the dexamethasone alone arm. Disease progression within four cycles of therapy was noted in 2% of patients with thalidomide plus dexamethasone and 5% of patients with dexamethasone alone.

At present, the status on whether a stem cell harvest had been performed is known on 79% of patients. Of these patients, 37% have undergone a stem cell harvest; 29 of 79 patients

(37%) in the thalidomide plus dexamethasone arm, and 30 of 79 patients (38%) in the dexamethasone alone arm. Stem cell harvest was successful in 90% of patients in each arm.

Overall survival curves for the two arms are provided in Figure 1; however, since patients were allowed to discontinue protocol therapy, survival was not an end-point for the study and the study was not powered to compare differences in survival between arms.

Toxicity and deaths

The most common grade 1-2 non-hematologic toxicities were fatigue (67% with thalidomide plus dexamethasone and 51% with dexamethasone alone) and hyperglycemia (67% with thalidomide plus dexamethasone and 71% with dexamethasone alone). The frequency of major grade 3 or higher non-hematologic toxicities, including treatment related deaths, that occurred during the course of the trial are listed on Table 2. Grade 3-4 neutropenia was seen in 9% of patients receiving thalidomide plus dexamethasone, and 6% of patients receiving dexamethasone alone.

Grade 3 or higher non-hematologic toxicities were seen with 67% of patients within four cycles with thalidomide plus dexamethasone and 43% with dexamethasone alone ($P < 0.001$, one-sided). The rate of grade 3 or higher non-hematologic toxicities after excluding DVT was 62% versus 43%, in the two arms respectively. The incidence of grade 3 (or higher) DVT, rash, sinus bradycardia, neuropathy, and toxicity of any type grade 4 or higher occurring within 4 cycles were specifically monitored for a planned comparison between the two arms. The incidence of these specifically monitored toxicities were 45% with thalidomide plus dexamethasone versus 21% with dexamethasone alone, $P < 0.001$ (Table 3).

There were 7 deaths in the thalidomide plus dexamethasone arm within four cycles compared to 11 deaths in the dexamethasone alone arm. Among the 7 deaths within 4 months of treatment start, on the thalidomide plus dexamethasone arm, 4 were determined to be a result of toxicity (3 due to infections and one suicide) possibly, probably, or definitely related to treatment. Among the 11 deaths, within 4 months of treatment start, on the dexamethasone arm, 4 were determined to be a result of toxicity (one each due to infection, respiratory failure, stroke, and gastrointestinal bleeding) possibly, probably, or definitely related to treatment.

As expected, DVT occurred more frequently with thalidomide plus dexamethasone compared to dexamethasone alone, 17% versus 3%, respectively, $P<0.001$ (one-sided). On the thalidomide plus dexamethasone arm, the incidence of DVT was not significantly associated with age; DVT occurred in 12% of patients less than age 65 compared to 22% in those 65 and older, $P=0.29$. There was also no significant association between incidence of DVT and response to therapy, $P=1.0$. Forty-two percent of all incidences of DVT occurred within the first two months of therapy; 9 of 23 (39%) patients with thalidomide plus dexamethasone and 2 of 3 (67%) patients with dexamethasone alone.

DISCUSSION

Thalidomide has been reintroduced into clinical practice as an anti-cancer drug.[10,14,15] In the first clinical trial conducted at the University of Arkansas, 25% of patients with advanced relapsed refractory multiple myeloma achieved a partial response to therapy.[9,16] Subsequently, numerous clinical trials have confirmed the single agent activity of thalidomide.[17,18] Thalidomide alone produces a response rate of 25-35% in patients with relapsed refractory disease. Weber and colleagues made the interesting observation that patients who had previously failed thalidomide and dexamethasone as single agents could respond again when the two drugs were combined.[19] This led to several clinical trials with thalidomide plus dexamethasone in relapsed multiple myeloma.[20,21] Response rates with this combination are approximately 50% in the relapsed refractory setting.

Three phase II trials have been conducted with the thalidomide plus dexamethasone combination in newly diagnosed multiple myeloma. In the Mayo Clinic trial, 50 patients were treated and 64% responded to therapy.[11] Similar response rates were seen in the MD Anderson clinical trial and the Italian clinical trial, respectively.[12,13] As a result of these phase II trials, the use of thalidomide and dexamethasone has increased significantly in standard practice. Recently Cavo and colleagues reported a matched case-control study of 200 patients, which showed a significantly higher response rate with oral Thal-Dex therapy compared to intravenous VAD; 76% versus 52%, respectively.[22]

This clinical trial shows that the addition of thalidomide to dexamethasone significantly increases the 4-month response rate. The response rate seen with thalidomide and dexamethasone in this trial are similar to those obtained with complex intravenous regimens including VAD.[6] Thus, thalidomide plus dexamethasone appears to be an oral alternative to

infusional, intravenous chemotherapy. However, the trial shows that thalidomide plus dexamethasone does increase the rate of the specifically monitored toxicities and grade 3 or higher non-hematologic toxicity in a significant manner. The occurrence of increased DVT with thalidomide plus dexamethasone therapy has been previously reported by us and others.[23-25] When the trial was designed and initiated, the benefit of routine prophylaxis was not well established. Based on the high rate of DVT seen in this trial, and recent results using thrombosis prophylaxis,[26] we recommend routine DVT prophylaxis be used in all patients starting therapy with thalidomide plus dexamethasone with either a prophylactic dose of low molecular weight heparin (equivalent of enoxaparin 40 mg once daily), or full dose anticoagulation with warfarin (targeting a therapeutic INR 2-3). In patients considered to have a high bleeding risk, aspirin (81 mg or 325 mg enteric-coated tablets) once daily can be used instead.

There does not seem to be any adverse effect of the addition of thalidomide on the ability to harvest stem cells. Based on the results of this trial, thalidomide plus dexamethasone or dexamethasone alone would both be suitable induction regimens for the treatment of multiple myeloma.

The increased response rates with thalidomide plus dexamethasone need to be balanced against the increased toxicity. In our opinion, for patients in whom a delay of 1-2 months to assess response to dexamethasone alone is possible because of low tumor burden and minimal symptoms, therapy can be initiated on dexamethasone alone. If response is not observed within 1-2 months, thalidomide can be added to the regimen. Alternatively thalidomide plus dexamethasone can be used from the outset with routine prophylactic anticoagulation after reviewing the risks and benefits with the patient. For patients with more aggressive disease including those with painful lytic lesions, impending spinal cord compression, or other

symptomatic disease, thalidomide plus dexamethasone with prophylactic anticoagulation should be preferred over dexamethasone alone as initial therapy. Although the trial had no age restrictions, it should also be noted that patients with performance status of 3-4, serum creatinine ≥3 mg/dL, hemoglobin ≤7g/dL and those with active infections were excluded from the study and the safety and efficacy of thalidomide plus dexamethasone in these patients cannot be determined from this trial.

One limitation of the present trial was that overall survival comparisons were not possible because the trial was intended to study pre-transplant induction therapy. However, an ongoing multicenter study comparing these two regimens in which stem cell transplantation is reserved for relapsed disease, will shed light on these outcome measures.

Although thalidomide plus dexamethasone has emerged as an oral alternative to intravenous induction regimens for myeloma, more effective and safer regimens are needed. Recent studies show that lenalidomide, an analog of thalidomide may be safer and more effective than thalidomide.[27] A combination trial with lenalidomide plus dexamethasone has already shown improved activity with lower toxicity in a phase II clinical trial.[28] Large phase III trials are ongoing in the United States headed by ECOG and SWOG to investigate the role of lenalidomide plus dexamethasone in newly diagnosed multiple myeloma. Similarly, high activity has been observed with bortezomib-based induction in several phase II trials. Future randomized trials should compare these active induction regimens to determine the optimum initial therapy for multiple myeloma.

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Figure Legends

Figure 1. Overall survival estimates of patients enrolled in the trial by the Kaplan-Meier method. Straight lines represent patients treated with thalidomide plus dexamethasone (Arm A) and dotted lines represent patients treated with dexamethasone alone (Arm B).

Table 1. Characteristics of Eligible Patients

Patient Characteristic	Thalidomide plus dexamethasone (n=99)	Dexamethasone (n=100)	P-value
Age – median, (range) years	65 (38,83)	65 (38,82)	0.86
Sex – no. of patients (%)			0.25
Male	50 (51)	59 (59)	
Female	49 (49)	40 (40)*	
International Staging System (%)			0.64
I/II	54 (83)	43 (78)	
III	11 (17)	12 (22)	
Missing	34	45	
ECOG Performance status- no. of patients (%)			0.27
0	42 (42)	38 (38)	
1	48 (48)	45 (45)	
2	9 (9)	17 (17)	
Serum monoclonal protein size gm/dL – median (range)	3.7 (0-9.0)	3.3 (0-11.2)	0.43
Type of M protein - no. of patients (%)			
IgG	62 (63)	58 (58)	
IgA	21 (21)	22 (22)	
IgM	0 (0)	1 (1)	
Biclonal	0 (0)	1 (1)	
Light-chain only	16 (16)	17 (17)	
Missing	0	1	
Urine monoclonal protein size mg/24hr median (range), n	91.1 (0-20494)	219.5 (0-14100)	0.16
Urine monoclonal protein size			0.24
≥200 mg/24hr	31 (41)	35 (51)	
<200 mg/24hr	45 (59)	33 (49)	
Missing	23	32	
Serum creatinine - no. of patients (%)			0.33
>2 mg/dL	3 (3)	7 (7)	
≤ 2 mg/dL	96 (97)	93 (93)	
Hemoglobin - no. of patients (%)			0.54
<10 gm/dL	32 (32)	28 (28)	
≥10 gm/dL	67 (67)	72 (72)	
Platelets - no. of patients (%)			0.68

$<100 \times 10^9$/L	3 (3)	2 (2)	
$\geq 100 \times 10^9$/L	96 (97)	98 (98)	
Serum calcium - no. of patients (%)			0.28
>11 mg/dL	2 (2)	6 (6)	
≤11 mg/dL	96 (97)	93 (93)	
Missing	1	1	
Radiographic Bone Abnormalities			0.14
Absent	20 (20)	30 (30)	
Present	79 (80)	69 (70)	
Missing	0	1	

* Gender data was missing in one patient

Table 2. Major Grade 3 or Higher Non-Hematologic Toxicities

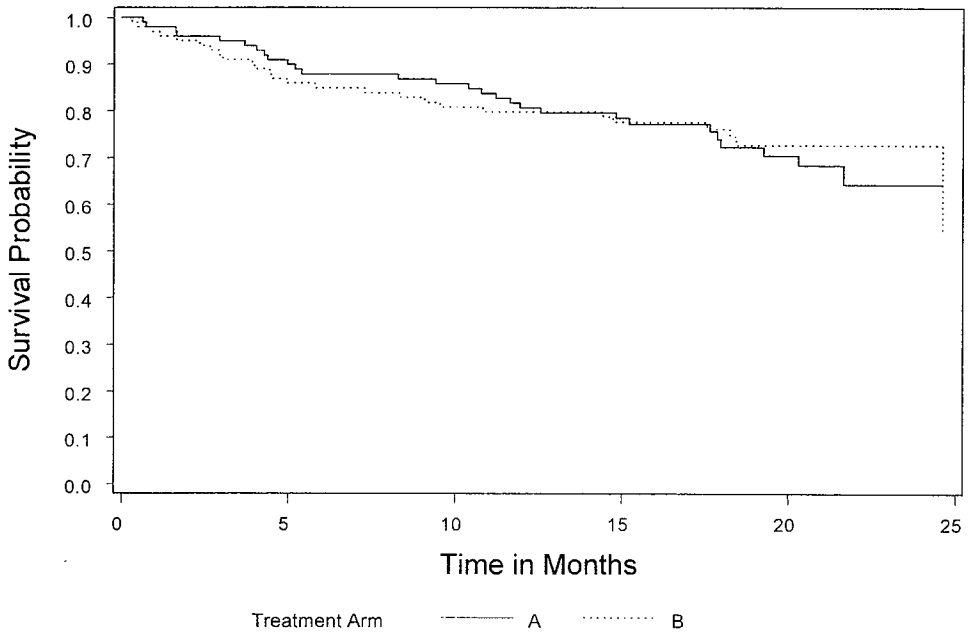
Toxicity	Treatment Arm	
	Thalidomide plus dexamethasone (n=102)	**Dexamethasone alone (n=102)**
	No. of patients	No. of patients
Treatment related deaths	5	4
Thrombosis/embolism	20	3
Hyperglycemia	15	15
Fatigue	15	10
Dyspnea	11	10
Hypocalcemia	8	3
Confusion	8	2
Constipation	8	1
Neuropathy-motor	7	4
Muscle weakness	6	9
Edema	6	2
Pneumonitis/pulmonary infiltrates	5	4
Hyponatremia	4	7
Hypotension	4	3
Dehydration	4	1
Neuropathy-sensory	4	1
Rash/desquamation	4	0
Nausea	4	0
Hypoxia	3	3
Depressed level of consciousness	3	2
Anorexia	3	1
Seizure	3	0
Syncope	3	0
Infection w/o neutropenia	2	5
Conduction abnormality	2	0
Insomnia	0	5
Hypertension	0	3
Anxiety/agitation	0	3

Table 3. Specifically Monitored Grade 3 or Higher Toxicities

Toxicity	Thal/Dex (n=102) No. of patients (%)	Dex (n=102) No. of patients (%)
Deep vein thrombosis (Grade >=3)	17 (17%)	3 (3%)
Skin Rash (Grade >=3)	4 (4%)	0 (0%)
Sinus bradycardia (Grade >=3)	1 (1%)	0 (0%)
Peripheral Neuropathy (Grade >=3)	7 (7%)	4 (4%)
Toxicity of Any Type (Grade >=4)	35 (34%)	18 (18%)
Total **	**46 (45%)**	**21 (21%)**

** Rows do not add to total as patients could have more than one of these toxicity types

Figure 1.



FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1539 FAX: (301) 594-0499

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager
Phone: (301) 827-1539

Total number of pages, including cover sheet 2
Date: 8-8-05

COMMENTS: Regarding your sNDA 21-430 for Thalomid, Amendment to a Pending Application – Response to Action Letter dated May 13, 2005, we have the following comments/requests from our Medical Review Team.

The FDA is attempting to verify financial disclosure for the investigators who participated in studies ECOG E1A00, Mayo 98-80-13, and Thal MM-99-002.

Your current sNDA, resubmitted May 13, 2005, contains no financial disclosure statements for the investigators who conducted Study E1A00. The submission instead makes the following statement:

"The Pharmaceutical Management Branch, Cancer Therapy Evaluation Program/DCTD/NCI/NIH is responsible for maintaining the investigator registration documents for NCI sponsored trials"

"The study noted above, was approved February 5, 2002. CTEP started collecting Financial Disclosure Forms (FDF) in March 2002. The FDF was made a requirement for active registration of all NCI investigators as of May 31, 2002."

"Form 1572, Investigator Registration Forms, the Supplemental Form for Investigator Registration and the Financial Disclosure Forms are available on request by the FDA for all investigators who participated in Protocol E1A00."

Your original submission of this sNDA, dated December 22, 2003, contains no financial disclosure statements for the investigators who conducted Studies Mayo 98-80-13 and Thal MM-99-002 (NDA 21-430, volume 1.01 of 1.45, section 19.0, Financial Information).

Appropriate financial certification and disclosure is critical for the NDA review process. As the Applicant of sNDA 21-430, it is your responsibility to submit the appropriate documentation (CFR §54.4(g)). Please provide these statements for all three registration trials – ECOG E1A00, Mayo 98-80-13, and Thal MM-99-002 – as soon as possible.

Thanks.

Regards,
-carl

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/s/

Carl Huntley
8/9/05 01:03:31 PM
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FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1539 FAX: (301) 594-0499

TO: Megan Parsi
Director, Regulatory Affairs
Fax: 908-673-2763

FROM: Carl Huntley
Project Manager
Phone: (301) 827-1539

Total number of pages, including cover sheet 1
Date: 7-14-05

COMMENTS: Regarding your sNDA 21-430 for Thalomid, Amendment to a Pending Application – Response to Action Letter dated May 13, 2005, we have the following comments/requests from our Medical Review Team.

Please inform the Division as to the status of Celgene's Protocol THAL-MM-003. Please include in your response how many patients have accrued to date, whether early results from the study have been published or presented, and when you anticipate submitting results of that study to the FDA.
Thanks,
-carl

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/s/

Carl Huntley
7/14/05 11:01:45 AM
CSO

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ATTACHMENT

MEMO OF FILING MEETING

DATE: June 28, 2005

BACKGROUND: This type 6 NDA re-submission, (NDA 21-430) was submitted on May 13, 2005 following our October 22, 2004 approvable letter. The new date will be November 13, 2005. This NDA seeks approval for the use of thalidomide in the treatment of [redacted] multiple myeloma. The proposed labeling is "THALOMID is indicated for the treatment of patients with multiple myeloma [redacted]
Orphan Drug Designation for Thalomid use in patients with Hansen's Disease was granted on October 14, 1998 (#98-1155).

ATTENDEES: Robert Justice, Ann Farrell, Michael Brave, Raji Sridhara, and Valeria Freidlin.

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Michael Brave
Secondary Medical:	Ann Farrell
Statistical:	Valeria Freidlin
Pharmacology:	Haleh Mahloogi
Statistical Pharmacology:	
Chemistry:	Hari Sarker
Environmental Assessment (if needed):	
Biopharmaceutical:	Roshni Ramchandani
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Leslie Ball/Gan
Regulatory Project Management:	Carl Huntley
Other Consults:	DDMAC (Grillo), DMETS (Dallas),
ODS (Lu)	

Per reviewers, are all parts in English or English translation?	YES	X	NO	☐

If not, explain:

CLINICAL	FILE	X	REFUSE TO FILE	☐

• Clinical site inspection needed?	YES		NO	X

• Advisory Committee Meeting needed? YES, date if known		NO	X

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A	☐	YES	☐	NO	☐

CLINICAL MICROBIOLOGY	N/A	X	FILE	☐	REFUSE TO FILE	☐	
STATISTICS	N/A	☐	FILE	X	REFUSE TO FILE	☐	
BIOPHARMACEUTICS		FILE	X	REFUSE TO FILE	☐		
• Biopharm. inspection needed?				YES	☐	NO	☐
PHARMACOLOGY	N/A	☐	FILE	X	REFUSE TO FILE	☐	
• GLP inspection needed?				YES	☐	NO	X
CHEMISTRY		FILE	X	REFUSE TO FILE	☐		
• Establishment(s) ready for inspection?				YES	☐	NO	☐
• Microbiology				YES	☐	NO	☐

ELECTRONIC SUBMISSION:
Any comments: In review

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing

X No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. X Convey document filing issues/no filing issues to applicant by Day 74.

Carl Huntley
Regulatory Project Manager, HFD-150

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **DDMAC /HFD-42**
\ttention: Joseph Grillo

FROM: HFD-150/Carl Huntley

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6-20-05		21-430	Type 6 re-submission	May 13, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Thalomid (Thalidomide)	This will be a priority review	IMID	The Div. goal date is 10/28/05 PDUFA date is 11/13/05

NAME OF FIRM: Celgene

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please note that this is an electronic submission. NDA 21-430. This is a re-submission of an approvable letter finalized October 22, 2004. The clinical reviewer is Dr. Brave.

SIGNATURE OF REQUESTER Thanks, Carl Huntley	METHOD OF DELIVERY (Check one) e- MAIL
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carl Huntley
6/20/05 04:25:53 PM

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Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901
Tel 908-673-9000
Fax 908-673-9001

May 13, 2005

Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
Center for Drug Evaluation and Research, HFD-150
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

NDA 21-430 Thalomid®
Thalidomide Capsules
(Type 6 sNDA)

RE: Amendment to a Pending Application – Response to Action Letter

Dear Dr. Pazdur:

Reference is made to the sNDA 21-430 for Thalomid® capsules that was submitted on December 22, 2003, for the treatment of patients with multiple myeloma. Reference is also made to FDA's letter dated October 22, 2004, upon completion of the review of the original application.

As suggested in the October 22nd FDA letter, we have deleted all data and reference to Study UARK-98-003 and have incorporated data from Study E1A00, a randomized Eastern Cooperative Oncology Group (ECOG) study that compared thalidomide plus dexamethasone to dexamethasone alone in previously untreated multiple myeloma patients. As requested, the final clinical study report for E1A00 is submitted, along with the required Case Report Forms (CRF).

The proposed labeling has been updated to reflect the safety and efficacy information relevant to the new patient population studied by ECOG. The key sections of the labeling that have been revised include, but are not limited to; Clinical Studies, Indication and Usage, Incidence in Multiple Myeloma Controlled Clinical Trials and the Dosage and Administration section.

Appended to this cover letter is Celgene's complete response to the deficiencies, recommendations, comments and issues noted in the above referenced FDA letter.

Celgene has not submitted any marketing authorization application outside the United States. However, the thalidomide application submitted by Pharmion Corporation to Turkey has been approved. Accordingly, a copy of the approved Turkish labeling text is included in Item 3 of this application.

This amendment is being submitted electronically to facilitate the Agency's review of the application. The information contained on the enclosed CD-ROM is compliant with the following guidelines:

- Guidance for Industry: Regulatory Submissions in Electronic Format; General Considerations (January 1999)"
- Guidance for Industry: Regulatory Submissions in Electronic Format; NDAs (January 1999)"

Submission Size: 384 MB
Number of CDs: 1

The CD was certified to be virus-free using McAfee Virus Scan Enterprise 7.1.

Orphan Drug Designation for Thalomid use in patients with multiple myeloma was granted on October 14, 1998 (Application #98-1155). Therefore, this application qualifies for the orphan Exception under Section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act and is not subject to an application fee, although new clinical data are being submitted. A complete Prescription Drug User Fee Cover Sheet (Form FDA 3397) is provided in Item 18.

As described in the Financial Information section of this application (Item 19), all regulatory documents for the investigators that have participated in the ECOG E1A00 study are on-file at NIH, National Cancer Institute.

As provided in the Patent Information Section (Item 13), Celgene Corporation would expect that a 7-year exclusitivity be granted for the use of Thalomid in multiple myeloma from the date of approval.

It should be noted that Celgene will continue to complete the Thal-MM-003 study as our Phase IV commitment.

We look forward to your review of this amendment. Please address any comments or questions regarding this application to me at (908) 673-9566 (FAX 908-673-2763).

Sincerely,

Megan M. Parsi

Megan M. Parsi
Director, Regulatory Affairs
E-mail: megan.parsi@celgene.com
Enclosures

Deficiency 1

Your application failed to provide substantial evidence of effectiveness. Three single arm studies were submitted (MAYO-98-80-13, THAL-MM-99-002, UARK-98-003), and FDA identified problems with each study as outlined below.

The FDA could not rely upon results of the largest study, the 146–patient University of Arkansas study (UARK 98-003). The sponsor or investigator did not follow requisite Federal regulations designed to assure data integrity. Among the deficiencies noted were failure to provide investigators and the Institutional Review Board with major amendments to the protocol, failure to meet the sponsor's general responsibilities, and failure to maintain adequate record keeping. Because of these deficiencies, critical data are either missing or insufficiently recorded and/or validated.

The remaining data in the application are from 62 patients enrolled in the other two studies. The confirmed response rate in the 62 patients in the two evaluable studies was only 13%, and there were no complete responses. The response rate is substantially lower than that claimed in your initial application package and represents only 8 confirmed responses. This contrasts with literature rates of 28% to 48% in similar populations, leaving uncertainty as to the actual effect of the drug. Only one study provided case report forms that could be evaluated for quality and reporting completeness.

Response

As requested, Celgene has deleted all data and references to the UARK 98-003 study and incorporated data from the ECOG E1A00 study. The randomized E1A00 study is now considered the pivotal study in this submission, particularly for thalidomide use in previously untreated patients. The two open-label studies, Mayo-98-80-13 and Thal/MM-99-002, support the use of thalidomide to treat the relapsed and refractory multiple myeloma patients.

Deficiency 2

Additionally, there were unresolved problems regarding our 74- day filing letter including discrepancies between the E-mail and hard copy responses.

Response

As noted in our correspondence dated October 21, 2004, according to our records, copies of all responses previously submitted via e-mail, have been sent to the FDA Document Room for filing in the NDA 21-430 application.

Deficiency 3

Safety information concerning thalidomide use cannot be extrapolated from the erythema nodosum leprosum (ENL) safety database to the multiple myeloma population because the thalidomide dose used for ENL treatment is lower than that used for multiple myeloma treatment.

Response

Please refer to this submission's Integrated Summary of Safety (ISS) that contains the safety information from all three studies (ECOG E1A00, MAYO-98-80-13, and THAL/MM-99-002) conducted in patients with multiple myeloma. The safety data from these studies have also been incorporated into the proposed label.

Recommendation 1

Characterize the reversibility of thalidomide-induced neuropathy.

Response

No formal clinical trial has been conducted to study the reversibility of thalidomide-induced peripheral neuropathy.

The incidence of thalidomide-induced neuropathy continues to be evaluated in patients participating in the on-going THAL-MM-003 study.

Recommendation 2

We recommend that you conduct the following studies to provide an adequate understanding of the metabolism and excretion of thalidomide. These data will provide the basis for determining whether studies and/or dosage adjustments would be necessary in patients with organ dysfunction:

- *In vitro* hepatic metabolism:
  We recommend that you perform *in vitro* studies in hepatic preparations to evaluate the potential influence of non-microsomal enzymes involved in thalidomide metabolism. If no other enzymes are detected, a hepatic impairment study is not necessary.

Response

Celgene had previously determined the microsomal metabolism of thalidomide in human microsomes, cloned human cytochrome P-450 isozymes and Hansen's disease patients (Study # 002168A). No significant metabolism was observed.

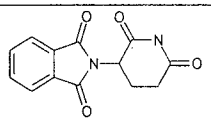
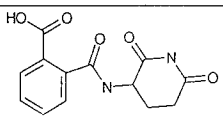
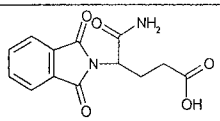
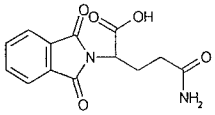
An *in vitro* metabolism study has been initiated (XBL 05631; *In vitro* Metabolism of Thalidomide in Human Hepatocytes in the Presence and Absence of a Non-specific P450 Inhibitor 1-Aminobenzotriazole, XenoBiotic Laboratories Inc., Plainsboro, NJ) to determine if there is any non-microsomal metabolism (eg. sulfation, glutathione conjugation, cysteine conjugations, *O*-methylation). The final study report is estimated to be completed in 4Q05.

- Activity of metabolism
  We recommend that you identify thalidomide's major metabolites in urine or multiple myeloma patients. You should screen *in vitro* these metabolites for pharmacological activity. If metabolites are active, you should plan to evaluate their pharmacokinetics. If no active metabolites are identified in the urine, a renal impairment study will not be required.

Response

The only thalidomide metabolites detected in the urine (Lu et al. 2003 Clin. Can. Res. 9:1680-1688) or plasma (Chung et al. 2004, Clin. Can. Res. 10:5949-5956) of multiple myeloma patients were the hydrolysis products *N*-(*o*-carboxybenzoyl)-glutamic acid imide, phthaloylisoglutamine and phthaloylglutamine. These hydrolysis products were synthesized and tested *in vitro* for pharmacological activity using three assays, each measuring a different aspect of thalidomide's known activity: 1) inhibition of tumor necrosis factor-alpha (TNF-α) production by human peripheral blood mononuclear cells (Sampaio et al. 1991 J. Exp. Med. 173:699), a measure anti-inflammatory activity; 2) elevation of interleukin (IL)-2 production by T cells (Haslett et al. 1998 J. Exp. Med. 187:1885), a measure of T cell costimulation, and; 3) inhibition of migration of

endothelial cells (Celgene Study Report 5239-92-5239-188), a measure of anti-angiogenic potency. Results from these studies are shown in the following table:

CC number	Compound Structure	Compound Name	MW	(1) TNF-α production at 50 μg/mL (% inhibition)	(2) IL-2 production at 50 μM (% elevation)	(3) VEGF-induced HUVEC migration (% inhibition)
2001		Thalidomide	258	52**	2	1 μM: 56%* 10 μM: 54%* 100 μM: 35%
1085		N-(o-carboxybenzoyl) glutamic acid imide	276	9.2	9	1 μM: 23% 10 μM: 26% 100 μM: 5.5%
1016		Phthaloylisoglutamine	276	5.9	11	1 μM: –4.6% 10 μM: 30% 100 μM: 39%
1007		Phthaloylglutamine	276	-14	11	1 μM: –7% 10 μM: 3.7% 100 μM: 35%
Conclusion				Only thalidomide is active	No compound is active	Thalidomide is more potent

* $p<0.05$, **$p<0.01$ vs. non-drug treated control

1) Thalidomide inhibited TNF-α production by 52% ($p<0.01$) at 50 μg/ml, while the hydrolysis products *N*-(*o*-carboxybenzoyl)-glutamic acid imide, phthaloylisoglutamine and phthaloylglutamine inhibited TNF-α production by only 9.2%, 5.9, and –14%, respectively, which is not statistically significant. Therefore, the hydrolysis products are at least 5-fold less active than thalidomide at inhibiting TNF-α production.

2) As illustrated in the table above, elevation of T cell IL-2 production was not significantly affected by any compound, including thalidomide, while the internal positive control (3-amino-phthalimido-glutarimide) did have activity in this model as expected (average EC_{50} of 10 nM).

3) Thalidomide inhibited migration of human umbilical vein endothelial cells (HUVEC) induced by vascular endothelial growth factor (VEGF) by 56% at 1 μM ($p<0.05$), 54% at 10 μM ($p<0.05$), and 35% at 100 μM. In comparison, the hydrolysis product *N*-(*o*-carboxybenzoyl)-glutamic acid imide inhibited HUVEC migration by 23% at 1 μM, 26% at 10 μM, and 5.5% at 100 μM; Phthaloylisoglutamine inhibited HUVEC migration by –4.6% at 1 μM, 30% at 10

μM, and 39% at 100 μM. Phthaloylglutamine inhibited HUVEC migration by –7% at 1 μM, 3.7% at 10 μM, and 35% at 100 μM. Although some activity has been observed with the hydrolysis products, none of the inhibitory activity seen was statistically significant. Therefore, thalidomide is more potent than these hydrolysis products for this antiangiogenic activity.

In summary, thalidomide was more potent than its hydrolysis products *N*-(*o*-carboxybenzoyl)-glutamic acid imide, phthaloylisoglutamine and phthaloylglutamine in two out of the three *in vitro* models of pharmacological activity, namely, in the TNF-α inhibition model and anti-angiogenesis assays. No significant activity was observed with any of these compounds, including thalidomide, in the IL-2 production assay.

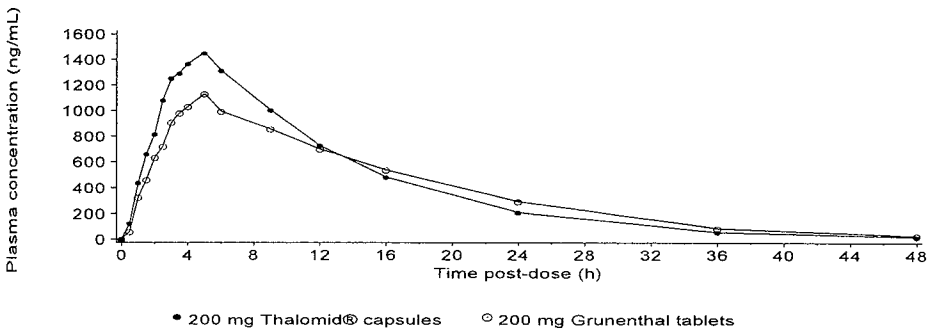
Recommendation 4

Pharmacokinetics in multiple myeloma patients:
The bioequivalence simulation approach does not demonstrate bioequivalence between the capsule (Celgene) and the tablet (Chemie Grunenthal) formulations. Pharmacokineteics in multiple myeloma patients treated with the capsule remains unclear. We recommend that you examine thalidomide's pharmacokinetics in multiple myeloma patients, either in a prospective study or in your ongoing Phase 3 studies. This approach will allow the examination of exposure-response relationships for both toxicity and effectiveness.

Response

1. Regarding the bioequivalence simulation, Celgene has now completed a clinical study comparing the Grunenthal Tablets and Celgene's Thalomid® Capsules in healthy volunteers. The study confirms the previously submitted simulation. The final report from this study (THAL-BA-001: A Phase 1, Open-Label, Randomized, Balanced, Two-Period Crossover Study to Investigate the Relative Bioavailability of Single Oral Doses in Two Different Formulations in Healthy Male Subjects) was submitted to IND 49,481 as Serial #188 on April 22, 2005.

   Figure 1 - Geometric Mean Plasma Concentrations of Thalidomide Following Single Oral Doses (Linear Scale) of Thalomid® Capsules and Grunenthal Tablets. (Celgene Study Thal-BA-001)



   The extent of absorption of these two products was not statistically different; although the C_{max} following Thalomid® was higher than after Chemie Grunenthal's tablets.

2. Aside from the data discussed above, based on the Agency recommendation, Celgene plans to conduct a 14-day study of Thalomid® pharmacokinetics in multiple myeloma patients. This trial will characterize both the initial 100 mg single-dose and the Day-14 dose (steady-state) pharmacokinetic profile of Thalomid® when given orally to subjects diagnosed with multiple myeloma. Its purpose will include isolating

potential major metabolites in urine (e.g. >10% of administered dose) of thalidomide after a single, oral and multiple oral doses and to study the safety of thalidomide in multiple myeloma patients administered 100 mg QD for up to 14 days. This trial is anticipated to begin in the latter part of 2005.

Comment 1

The half-life of thalidomide is 6 hours, and the regimens studied were based on daily dosing. The drug is eliminated prior to the next dose. Effectiveness might be improved by using alternate dosing schedules. Please provide any additional information that would clarify whether alternate dosing regimens have been evaluated or are planned to be evaluated.

Response

As stated in the current package insert, thalidomide frequently causes drowsiness and somnolence. Therefore, in the DOSAGE AND ADMINISTRATION section of the label, it is recommended that thalidomide capsules be taken at bedtime. Accordingly, Celgene does not have any plans to further evaluate alternate dosing regimens.

Comment 2

Consider the impact of drug loss that might occur if dialysis occurs in the absorptive phase following a thalidomide dose. Please consider delaying dialysis for at least 4 hours post dose.

Response

Thalomid® is generally taken near bedtime while hemodialysis sessions are generally scheduled during the day, thus providing a natural separation of these events. In an independent study conducted by Dr. G.A. Kaysen (University of California Davis Medical Center) in 6-patients with end-stage renal disease, it is concluded that the drug-concentration time curves were not statistically significantly different between days patients were on and off of dialysis. Therefore, it was recommended that no dosage adjustment was considered necessary for renally impaired patients on dialysis (*A Pharmacokinetic Study of 200 mg Q HS of Thalomid® in Six Patients Undergoing Renal Dialysis*; submitted in the original sNDA, Volume 1.03, Page 600031).

The results from this study are described in the CLINICAL PHARMACOLOGY section of the proposed label, under Pharmacokinetics Data in Special Populations, Patients with Renal Insufficiency.

Comment 3

The articles you submitted do not adequately support your conclusion that thalidomide [redacted] If you choose to pursue this mechanism of action in product labeling, you will need to submit additional information to support your conclusions.

Response

In the "Mechanism of Action" section of the proposed package insert, the statement, [redacted] has been modified to, [redacted]

The statement regarding inhibition of cell proliferation is supported by Hideshima et al. 2000[10], who demonstrated that thalidomide inhibited DNA synthesis in MM.1S and Hs Sultan cells by 15-20% (Figure 1A and 1B), caused G_0/G_1 cell cycle arrest in MM.1S and multiple myeloma patient cells (Figure 5A), and increased apoptosis in MM.1S cells (Figure 5B). The statement regarding inhibition of IL-6 and VEGF production is supported by Gupta et al. 2001[11], who demonstrated that thalidomide reduced VEGF and IL-6 secretion triggered by HS Sultan cells to bone marrow stromal cell binding by 87% ($P<0.001$) and 94% ($P<0.001$), respectively (Figure 7a and g). Reductions in secretion of VEGF after addition of thalidomide was also noted in co-cultures of BMSCs and RPMI8226, U266, MM1 and MM2 cells (Figure 7c-f). IL-6 secretion was also decreased in co-cultures of BMSCs and MM.1S, RPMI8226, U266, MM1, and MM2 cells in the presence of thalidomide (Figure 7 h-l).

Copies of the above-referenced publications (i.e., Hideshima et al. 2000 and Gupta et al. 2001), are provided in the "Publication" Section of this application, for your ease of review.

Comment 4

We note your inclusion of rodent carcinogenicity study results in the proposed product label for thalidomide in the MM indication. A final determination regarding study conclusions and the suitability of the study findings for inclusion in future product labeling will be forthcoming.

Response

In October 2004, we were notified by the Division of Special Pathogen and Immunology Drug Products that their review of the carcinogenicity studies would be completed in February 2005. They also informed Celgene that there might be a recommendation to slightly modify the wording of this section, however, we have not yet received any written notification regarding the FDA's proposed language.

Issue 1

Describe in detail any significant changes or findings in the safety profile

Response

There are no pending supplemental applications providing for a change in the safety profile of thalidomide. Accordingly, the currently approved US labeling for THALOMID®(thalidomide) 50 mg, 100 mg, and 200 mg Capsules prescribing information version THALPI.008 CG 2/04 remains unchanged. In addition, there are no previously unidentified adverse events presented in the ISS of this submission.

Issue 2

When assembling the sections describing discontinuations due to adverse events, serious adverse events and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

Response

In the ISS (Integrated Summary of Safety), the new safety data are presented for Study ECOG E1A00. However, because Study ECOG E1A00 evaluated the effects of thalidomide in combination with dexamethasone in newly diagnosed multiple myeloma patients, a direct comparison of the adverse event profile with Studies 98-80-13 and THAL/MM-99-002 was not possible. Therefore, safety data from Study ECOG E1A00 are presented in parallel with safety data from Studies 98-80-13 and THAL/MM-99-002.

An overall adverse event profile for Study ECOG E1A00 is presented in Section 6.1.1.1 (Table 21) of the ISS. This section provides the most common adverse events occurring in ≥10% of patients in either treatment group. The adverse event profile for patients in the thalidomide/dexamethasone combination arm is consistent with the known adverse events profile for thalidomide.

Section 6.2.1 (Table 24) of the ISS presents NCI CTC Grade 3 and Grade 4 adverse events for Study ECOG E1A00 that occurred in ≥2% of patients in either treatment group.

Section 6.6.1 (Table 29) of the ISS presents data on dose reductions that occurred in Study ECOG E1A00, although this study did not capture specific adverse events leading to the dose reduction. Section 6.7.1 of the ISS presents data on treatment discontinuation due to adverse events. Specific adverse events leading to discontinuation were not captured in Study ECOG E1A00, however, Data Listing 16.2.1 (see Appendix 16.2) of the ECOG E1A00 final study report identifies patients for whom the reason for discontinuation was noted as toxicity/side effect (adverse events) on the CRF.

Serious adverse events were not specifically captured for Study ECOG E1A00, however expedited adverse events were captured on CIOMS forms using the AdEERS system and forwarded to NCI and ECOG. For thalidomide related adverse events, ECOG forwarded

CIOMS forms to Celgene Corporation's Drug Safety Group. Safety narratives for expedited adverse events, for which sufficient information was available, are included in the ECOG E1A00 clinical study report.

Section 9 of the ISS includes adverse event profiles for Study ECOG E1A00 based on age, gender, and race.

Issue 3

Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

Response

Section 6.7.1 of the ISS presents data on treatment discontinuation due to adverse events. As specific adverse events leading to discontinuation were generally not captured in Study ECOG E1A00, no direct comparisons across all studies can be made. However, as noted above, there are no previously unidentified adverse events presented in the ISS. Data Listing 16.2.1 (see Appendix 16.2) of the ECOG E1A00 final study report identifies patients for whom the reason for discontinuation was noted on the CRF, as toxicity/side effect (adverse events).

Issue 4

Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

Response

The case report forms (CRFs) for patients who either died or dropped out due to an adverse event during the study (in the first 4 cycles of treatment) are included in Item 12 of this submission. ECOG has designed the CRFs to capture the data by cycle number rather than visit numbers. Therefore, due to ECOG's CRF presentation style, the case report forms have been bookmarked by cycle number and by domain accordingly.

Additionally, included in the ECOG E1A00 final study report are narrative summaries for the above referenced patients as well as those who experienced serious adverse events during the study. As indicated in our response to Issue 2, these safety narratives are provided for the expedited adverse events for which sufficient information was made available through ECOG.

Issue 5

Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

Response

As provided in our previous responses above and as discussed in the ISS, there are no new data that suggests a substantial change in the incidence of common, but less serious, adverse events.

Issue 6

Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Response

Pharmion has filed an application for the use of thalidomide capsules as follows:

Countries approved	Date approved
Australia	October 9, 2003
New Zealand	October 2003
Turkey	June 2004
Israel	Recently approved September 2004 but labeling not yet available

As a condition of registration, the Pharmion Risk Management Program (PRMP) is mandatory in Australia, New Zealand, Turkey and Israel. Prescribers and pharmacies are required to register with the PRMP in order to prescribe or dispense thalidomide, and patients are required to complete an informed consent process and to participate in a confidential surveillance registry. The PRMP is based on the *S.T.E.P.S.* ® program developed by Celgene Corporation in cooperation with the US Food and Drug Administration.

Thalidomide Pharmion is authorized in Australia, New Zealand and Turkey. Pharmion also makes thalidomide available in many European countries on a compassionate use basis. It is indicated for the treatment of multiple myeloma after failure of standard therapies, and for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). Thalidomide is not indicated as monotherapy for ENL in the presence of moderate to severe neuritis.

The worldwide experience of the safety of thalidomide has been provided in THALOMID® NDA Number 20-785 Periodic Adverse Event Annual Report July 17, 2003-July 16, 2004 Section III Patient Exposure. Another copy of this report is included in the "Other" Section of this submission for your ease of reference.

Calculation of patient exposure to Pharmion thalidomide 50 mg is based upon data obtained through the Pharmion Risk Management Program (modeled after the Celgene *S.T.E.P.S.* ® Program) that requires patients, physicians and pharmacists to be registered in order to receive the product. During the period 10 April 2004 through 09 October 2004, 5,969 patients were exposed to Pharmion thalidomide 50 mg corresponding to approximately 506,627 patients days of exposure (18,325 prescriptions). The total number of patients has increased in comparison with the previous 6-monthly period (3,961 patients treated from 10 October 2003 to 09 April 2004).

US PATIENT EXPOSURE:

Because Thalomid® is approved for marketing only under the *S.T.E.P.S.*® program restricted distribution system, it is possible to monitor the number of patients for whom it has been prescribed. The U.S. marketing launch occurred on September 23, 1998 and the first post-marketing prescription was filled on October 01, 1998. The new enhanced program started July 31, 2001.

Total prescriptions data and patient registration data is only available from July 1, 2003 to June 30, 2004. Additional data will become available at the time of the submission of the periodic report in September 2005, covering the period from July 1, 2004 to June 30, 2004. Since July 1, 2003 through June 30, 2004 there were —— total prescriptions (both new prescriptions and refills) for a total of —— patients. For July 1, 2003 to June 30, 2004 total new registered patients (active and inactive) are as follows: —— female of which —— are child bearing potential, and —— are males.

Appears This Way
On Original

Issue 7

Provide English translations of current approved foreign labeling not previously submitted

Response

Since the submission of the original sNDA, thalidomide has been approved in Turkey in June 2003. Accordingly, copies of the approved Turkish SmPC, along with its English translation, are enclosed in Item 3 of this application, in "Foreign Marketing History".

Please also be advised that an application for thalidomide capsules has also been submitted to Israel. This application was approved in September 2004; however, the labeling is still under negotiation and is therefore unavailable at this time.

The other two countries that have approved thalidomide for commercial use are Australia and New Zealand. Copies of the labeling used in these countries have previously been submitted to sNDA 21-430.

MEMORANDUM Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 29, 2004

From: Carl Kraus, MD
Medical Officer,
Division of Special Pathogen and Immunologic Drug Products, HFD-590

Through: Renata Albrecht, MD
Director
Division of Special Pathogen and Immunologic Drug Products, HFD-590

Through: Edward Cox, MD MPH
Acting Director
Office of Drug Evaluation IV, HFD-104

To: Anne Trontell, MD, MPH
Deputy Director
Office of Drug Safety, HFD-400

Subject: A Synopsis of the Elements of the *S.T.E.P.S.*® Program

Background

Thalomid® (thalidomide) and its Approval

Thalomid® (thalidomide) (Celgene, Corp.) was approved by the US FDA in July 1998 under the restricted distribution provisions of Subpart H, 21 CFR §314.520. Approval under subpart H restricted distribution requires that postmarketing restrictions are implemented to provide for the safe use of the drug product. Specifically, Subpart H states the following:

§ 314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:
(1) Distribution restricted to certain facilities or physicians with special training or experience; or
(2) Distribution conditioned on the performance of specified medical procedures.
(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

The approved indications for Thalomid® are the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. The required risk management program instituted by Celgene Corporation for the distribution of Thalomid® is the System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.®*).

Thalomid® Prescribing Patterns

The major specific safety concern for thalidomide is teratogenicity and the risk management goals are the prevention of fetal exposures to thalidomide. An evaluation of recent usage patterns of Thalomid® under the *S.T.E.P.S.®* program revealed that almost 90% of the prescribing of Thalomid® is for oncologic conditions. Between September 1998 and April 2003, approximately ——— patients were prescribed Thalomid® (a total of approximately ——— prescriptions). Of these ——— patients, approximately 4000 patients were females of childbearing potential. Evaluation of the distribution of Thalomid® recipients by gender finds a slight predominance of male patients. The mean age for patients receiving Thalomid® in the *S.T.E.P.S.®* program is approximately 65 years of age.

A Synopsis of the *S.T.E.P.S.®* Program

Elements of *S.T.E.P.S.®* Program

The *S.T.E.P.S.®* program includes a number of tools to manage the risks of Thalomid®. The key elements of the *S.T.E.P.S.®* program include the following:

- Product labeling informing of the risks of thalidomide and containing elements of the *S.T.E.P.S.®* program
- Required registration of all prescribers, patients, and pharmacists who prescribe, receive, or dispense Thalomid® (thalidomide)
- Six risk groups based on age, gender, and reproductive status
- A patient acknowledgement / informed consent form
- Authorization validation prior to dispensing Thalomid®
- A required telephonic survey (utilizes an interactive voice response system (IVR)) that patients and prescribers must complete.
- Required pregnancy testing in females of childbearing potential
- Compliance with measures to prevent pregnancy and thereby prevent fetal exposure to Thalomid®
- Educational materials – a brochure and a video tape
- Patient counseling
- Limiting prescriptions to a 28-day supply that is provided in blister packs with safety information on the blister card as well as prohibition of telephone prescriptions and automatic refills

- Distribution of Thalomid® from Celgene to registered pharmacies
- Any suspected fetal exposures to Thalomid must be reported immediately
- Quality assurance activities of the *S.T.E.P.S.®* program - ongoing evaluation of the *S.T.E.P.S.®* program

In the sections that follow further information is provided on the elements of the *S.T.E.P.S.®* program that are listed above.

Product Labeling

The Thalomid® product labeling provides Warnings regarding the teratogenicity of thalidomide, the elements of the patient acknowledgement / informed consent form, and describes other elements of the *S.T.E.P.S.®* program. The label explicitly states the requirement for enrollment in *S.T.E.P.S.®* prior to institution of drug therapy. Statements concerning risk to the fetus by mention of "birth defects", "fetal abnormalities", or "teratogenicity" if thalidomide is taken during pregnancy are present in several sections of the Thalomid® label. At the top of the Thalomid® label is a boxed Warning entitled "WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS." Overall, such statements are present in the following sections of the label: Warnings (including the boxed Warning), Contraindications, Precautions, and Adverse Reactions. The Thalomid® label refers to the *S.T.E.P.S.®* program with explicit mention of the requirement for enrollment prior to thalidomide therapy. The complete Thalomid® (thalidomide) package insert also provides additional information on Thalomid® including other information such as additional Warnings and Precautions, information on Adverse Events, Indications and Usage, and Dosage and Administration.

Required Registration of Prescribers, Patients, and Pharmacies

All prescribers, patients, and pharmacies are required to register in the *S.T.E.P.S.®* program in order to prescribe, receive, or dispense Thalomid®. Physician registration requires a DEA# or Social Security Number as well as the designation of a *S.T.E.P.S.®* coordinator for that prescriber (this may be the prescriber). The registration form is faxed to the prescriber and when completed faxed back to Celgene Corporation. A pharmacy registers by having a designated pharmacist complete a similar registration form that is returned to Celgene. (For patient registration information, please see "Patient Acknowledgement/ Informed Consent" below).

Six Risk Groups

The *S.T.E.P.S.*® program divides patients into six risk groups in order to provide risk group appropriate information to prevent fetal exposure to thalidomide. For example, adult females not of childbearing potential are required to participate in the Interactive Voice Response System (IVR) survey once every six months whereas females of childbearing potential (FCBP) are required to participate monthly.

The six risk groups are as follows:

- Adult females of childbearing potential
- Adult females not of childbearing potential
- Female children of childbearing potential
- Female children not of childbearing potential
- Adult males
- Male children

Patient Acknowledgement / Informed Consent Form

The risk group appropriate patient acknowledgement / informed consent form can be generated using computer software that is supplied with the materials for prescribers registered in the *S.T.E.P.S.*® program. Prescribers are expected to provide these risk group specific forms to the patient, provide counseling on the risks and benefits of therapy, provide mandatory contraceptive counseling, pregnancy testing for females of childbearing potential and then fax the completed acknowledgement / informed consent forms to Celgene Corporation. When computer generated forms cannot be used, risk group appropriate forms can be provided by fax to the prescriber. The patient is registered with *S.T.E.P.S.*® upon receipt of the acknowledgement / informed consent form by Celgene.

Authorization Validation

After the risk group appropriate patient acknowledgement / informed consent form has been completed and faxed to Celgene Corporation the patient is then instructed to complete the patient phone survey while the prescriber completes the physician phone survey. Upon completion of the survey, the physician obtains an authorization number that is placed on the prescription which the patient then presents to the pharmacist. Without the authorization number Thalomid® cannot be dispensed. (Please see below, IVR system).

Required Telephonic Survey Utilizing an IVR System

A brief, automated, telephone-based survey that utilizes IVR technology (IVR=interactive voice response system). The survey questions are tailored to each of the specific risk group as are the intervals for completing the required IVR surveys. All patient risk groups complete the survey with each 28-day interval, except for adult females not of childbearing potential who complete the IVR survey every 6 months. Prescribers complete the IVR survey with each prescription (maximum dispense of a 28-day supply). At the end of the successful completion of the prescriber survey a number to be written on prescription form is generated (the authorization number).

The risk group specific IVR survey is a series of 4 to 6 questions for each participant (Prescriber and Patient) intended to acquire essential information and to perform a focused query for at-risk behavior or program non-compliance. The prescriber and patient must answer all questions in the IVR survey appropriately before a Thalomid® prescription is "activated". When a response to the IVR system signals an at-risk behavior, the prescriber or patient is transferred from the IVR system to a Celgene *S.T.E.P.S.*® intervention specialist for real-time intervention prior to dispensing of Thalomid® (specialists are available 8a-8p M-F & Sat).[1] The response that triggered the intervention is further addressed and remediated as appropriate.

If the patient and prescriber responses are appropriate to all questions in the IVR, the Thalomid® prescription is "activated." Then a registered pharmacist can call the IVR system, enter the number from the prescription, and the pharmacist then receives authorization to dispense the "activated" Thalomid® prescription. To reflect the temporal restriction with regard to recent pregnancy testing. Thalomid® prescriptions are required to be filled within seven days of issue. Conventional methods (paper, fax, telephone) are available when the IVR cannot be used (paper forms are also available in fourteen languages). When a paper based process is used, the handling process is the same as for the IVR (i.e., real-time intervention).

Required Pregnancy Testing

Females of childbearing potential are required to have a negative pregnancy test within 24 hours prior to initiating Thalomid® therapy. Testing occurs weekly for the first 4 weeks, and then q-28 days thereafter while on Thalomid®, unless menses are irregular in which case pregnancy testing is performed on a biweekly basis. The prescriber enters the date and result of the last pregnancy test into the IVR system with each Thalomid prescription (i.e., every 28-days). Therapy

[1] Incorrect responses that occur at off-hours result in an inactivated prescription that is followed-up during hours of staffing.

with Thalomid® must be discontinued immediately if a pregnancy occurs in a patient receiving Thalomid® therapy.

Compliance with Measures to Prevent Pregnancy

Females of childbearing potential must use at least one highly effective method of birth control and one additional method of birth control.[2] These methods of contraception must be initiated at least four weeks before beginning Thalomid® therapy, must be continued during Thalomid® therapy, and continued for four weeks following discontinuation of Thalomid® therapy. Females of childbearing potential must use these birth control methods unless the patient completely abstains from heterosexual sexual contact. Male patients receiving Thalomid® must agree to abstain from heterosexual sexual contact or use a latex condom when he engages in sexual contact with a woman who can become pregnant or who is pregnant.

Educational Materials – Brochure and Video Tape

Patients must review the Thalomid® patient brochure and/or view the videotape regarding the safe use of Thalomid®.

Patient Counseling

Patients are to receive counseling to review the safe use of Thalomid® at the time of initial *S.T.E.P.S.*® enrollment and subsequently at each prescription refill.

Limiting Prescriptions to a 28-day Supply

Thalomid® prescriptions are limited to a duration of 28-days to allow for appropriate interval follow-up. Telephone prescriptions are not permitted. A new prescription is required for further dispensing (i.e. automatic refills are not permitted).

Distribution of Thalomid® from Celgene to Registered Pharmacies

Thalomid® is directly shipped from Celgene to registered pharmacies. This allows Celgene to compare the amount of Thalomid® shipped to pharmacies with the amount of Thalomid® that specific pharmacies have been authorized to dispense.

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[2] Highly effective = hormonal, IUD, tubal ligation, partner's vasectomy; Effective = latex condom, diaphragm, cervical cap

Any Suspected Fetal Exposures to Thalomid Must be Reported Immediately

Prescribers must report any suspected fetal exposure to Thalomid immediately to the FDA and Celgene Corporation. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The label provides the FDA MedWatch phone number (800-FDA-1088) and also includes an "800" number for Celgene Corporation. Any suspected fetal exposures to Thalomid® also receive additional follow-up.

Quality Assurance Activities of the *S.T.E.P.S.*® Program

Ongoing assessments of the *S.T.E.P.S.*® program and a separate voluntary follow-up survey are performed as part of the quality assurance activities of the *S.T.E.P.S.*® program.