

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-430

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type Supplemental (type 6) NDA
Submission Number 21-430
Submission Code N-000

Letter Date November 23, 2005
Stamp Date November 23, 2005
PDUFA Goal Date May 23, 2006

Reviewer Name Michael Brave, M.D.
Review Completion Date May 18, 2006

Established Name Thalidomide
(Proposed) Trade Name Thalomid
Therapeutic Class Immune modulator
Applicant Celgene corporation

Priority Designation Priority

Formulation Oral capsule
Dosing Regimen 200 to 400 mg orally once daily
Indication Multiple myeloma
Intended Population Adult multiple myeloma patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends accelerated approval of thalidomide in combination with dexamethasone (Thal/Dex) for previously untreated, symptomatic multiple myeloma (MM) patients. This recommendation is based on primary data from one prospective multicenter clinical trial – Eastern Cooperative Oncology Group (ECOG) study E1A00.

Study E1A00 randomized 207 patients to 4 cycles of Thal/Dex versus dexamethasone alone, after which patients were encouraged to undergo stem cell transplantation off study. Response rates based on serum or urine paraprotein measurements were significantly higher in combination arm (51.5% compared with 35.6% for dexamethasone alone; $p = 0.025$). Median overall survival (OS) was similar in both treatment groups (75.4 weeks for Thal/Dex and 76.6 weeks for dexamethasone-alone).

The incidence of grade 3 or 4 adverse events (AEs) in Study E1A00 was 84.3% on the Thal/Dex treatment arm, and 73.5% on the dexamethasone-alone arm. The most common toxicities with thalidomide in newly diagnosed MM patients were somnolence, constipation, neuropathy, venous thromboembolism (VTE), and rash, as previously described. The risk of thalidomide-induced VTE was significantly higher in the Thal/Dex treatment arm than among patients who received dexamethasone alone (22.5% and 4.9%, respectively; $p = 0.002$).

Prophylactic antithrombotic therapy prescribed in conjunction with thalidomide may lessen the potential for VTE. However, the chief risk of this approach is bleeding. MM itself predisposes patients to both acquired bleeding and clotting disorders, and MM patients 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.

The Applicant also sponsored a multicenter clinical trial, Thal-MM-03, which randomized 470 newly diagnosed patients to Thal/Dex versus dexamethasone-alone until progression or unacceptable toxicity. An Independent Data Monitoring Committee interim efficacy analysis found the primary time to progression endpoint to be superior in the Thal/Dex treatment arm, surpassing the prespecified O'Brien-Fleming boundary for unblinding the trial. These data have not yet been submitted to the sNDA.

The risk-benefit ratio favors the approval of thalidomide for these indications. These indications would increase the available options for MM patients.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Thalidomide, like other chemotherapy agents, should be administered under supervision of a qualified physician with experience in administering chemotherapy.

The thalidomide label should be updated with a boxed warning reflecting the significantly increased risk of VTE seen with thalidomide combination therapy in this population. In addition, Celgene should send a Dear Health Care Provider letter concerning this finding.

1.2.2 Required Phase 4 Commitments

1. The sponsor should 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 glucocorticoid alone as induction therapy in patients with previously untreated multiple myeloma* when completed.
2. The sponsor should conduct an epidemiologic study to address the efficacy of anticoagulant and antiplatelet prophylaxis and treatment using the System for Thalidomide Education and Prescribing Safety (STEPS) patient registry database.

1.2.3 Other Phase 4 Requests

All patients in the E1A00 study should be followed for 5 years or death following completion of their therapy. A final study report should be submitted to the Agency.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Please see my previous clinical review dated November 9, 2005 for an overview of Study E1A00.

1.3.2 Efficacy

The primary efficacy endpoint of Study E1A00 was best overall response (OR) by ECOG criteria during the first 4 cycles of treatment. The Applicant's derived response rates for the intention-to-treat (ITT) population were 60.2% on the Thal/Dex arm and 38.5% on the dexamethasone-alone arm (2-sided Fisher Exact $p = 0.002$). FDA-adjudicated ECOG response rates, based on a serum or urine response without mandatory skeletal radiography, were lower than those claimed in the application package but remained statistically superior in favor of the combination arm (51.5% compared with 35.6% for dexamethasone alone; $p = 0.025$).

1.3.3 Safety

One hundred two patients who received thalidomide in Study E1A00 provided safety information for thalidomide in MM.

Mortality was similar in each arm within 30 days of the last treatment (10.7% on Thal/Dex versus 8.9% on dexamethasone alone). At the November 18, 2004 clinical data cutoff point mortality was also comparable in each treatment arm (29.4% on Thal/Dex versus 25.5% on dexamethasone alone).

All patients developed at least 1 treatment-emergent AE. The incidence of treatment-emergent grade 3/4 toxicity was 84.3% on the Thal/Dex arm and 73.5% on the dexamethasone-alone arm. Consistent with published literature, the incidence of all-grade and grade 3/4 fatigue, constipation, peripheral neuropathy, VTE, and rash were higher in the Thal/Dex treatment arm than with dexamethasone alone. In addition, there was a statistically significant difference in the reported rate of VTE in the Thal/Dex treatment arm compared to dexamethasone alone (22.5% and 4.9%, respectively; $p = 0.002$).

E1A00 was not designed to assess reversibility of toxicity following dose reduction. No systemic allergic or hypersensitivity reactions were reported. Overall clinical safety data are adequate for marketing approval for this indication.

1.3.4 Dosing Regimen and Administration

In the registration study, patients received thalidomide as a single daily oral dose, at bedtime, on a continuous schedule. Based on submitted data, the recommended dose of thalidomide in combination with dexamethasone for newly diagnosed MM is 200 mg daily. Thalidomide should be administered at bedtime to minimize sedation.

1.3.5 Drug-Drug Interactions

This registration study was not designed to specifically evaluate drug-drug interactions with thalidomide.

1.3.6 Special Populations

Of 202 patients in the safety population of Study E1A00, 111 (55%) were male and 90 (45%) were female (the gender of patient 10006 was not recorded). The mean age of the E1A00 safety population was 64 years, with 104 (51%) over age 65 and 98 (49%) age 65 or younger.

Neither gender nor age appeared to correlate with thalidomide responsiveness. The overall risk of grade 3/4 toxicity as well as risks of each of the most common individual grade 3/4 toxicities (sedation, constipation, neuropathy, rash, and VTE) appeared to be somewhat higher among patients over age 65 and among those whose baseline serum creatinine was > 1.5 mg/dL.

No pharmacokinetic or safety data are available in subjects below the age of 18 years. Pediatric patients were specifically excluded from Study E1A00. Because MM is virtually nonexistent in children, the pediatric population is not relevant to this sNDA.

Thalidomide undergoes spontaneous hydrolysis and has no known active metabolites. Its biologic effect is therefore thought to be independent of renal and hepatic function, and the current product label recommends no dose adjustments for patient age, renal or hepatic function.

Study ECOG E1A00 required that patients have baseline serum creatinine < 1.5 mg/dL and bilirubin < 3.0 mg/dL for entry, and all patients met these requirements. Only 11 patients in E1A00 had baseline serum creatinine 2.1 to 2.9 mg/dL.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Please see my previous clinical review dated November 9, 2005.

2.2 Currently Available Treatment for Indications

Please see my previous clinical review dated November 9, 2005.

2.3 Availability of Proposed Active Ingredient in the United States

Please see my previous clinical review dated November 9, 2005.

2.4 Important Issues With Pharmacologically Related Products

Please see my previous clinical review dated November 9, 2005.

2.5 Presubmission Regulatory Activity

2.5.1 Prior to submission of sNDA 21-430 (1960 – December 2003)

Please see my previous clinical review dated November 9, 2005.

2.5.2 Since submission of sNDA 21-430 (December 23, 2003 – present)

Dec. 23, 2003 Celgene submitted a sNDA for thalidomide as a treatment for patients with MM after failure of standard therapies under 21 CFR §314.500 Subpart H – Accelerated Approval of New Drugs for Serious or Life Threatening Conditions. Three single arm studies were submitted (Mayo 98-80-13, THAL-MM-99-002, and UARK-98-003). The FDA did not rely upon results of the largest study, the 146-patient University of Arkansas study (UARK 98-003). The remaining data in the application were from 62 patients enrolled in the other two studies. The Agency decided that two studies did not provide sufficient data for approval at that time. The confirmed response rate in those 62 patients

was only 13%, and there were no complete responses. This response rate was substantially lower than that claimed in the application package, and contrasted 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. Safety information concerning thalidomide could not be extrapolated from the ENL safety database to the MM population because thalidomide doses used for MM were higher than those used for ENL.

- May 13, 2005 Celgene resubmitted sNDA 21-430 for thalidomide based on data from ECOG Study E1A00. On reviewing that study, this reviewer found significant quantities of data needed to confirm which patients in the ITT population had met primary efficacy endpoint were either missing or uninterpretable. Because of this problem, efficacy could not be verified.
- Nov. 10, 2005 The Agency took an approvable action on sNDA 21-430.
- Nov. 23, 2005 Celgene completed submission of sNDA 21-430, based on responses to FDA queries.

2.6 Other Relevant Background Information

Please see my previous clinical review dated November 9, 2005.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

There were no CMC, microbiology, pharmacology, animal toxicology, biopharmaceutics, or clinical pharmacology components included in this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources used were those for my previous clinical review dated November 9, 2005. In addition, I incorporated the Applicant's response to the Agency's queries into a reanalysis of efficacy in Study E1A00.

4.2 Tables of Clinical Studies

Please see my previous clinical reviews dated November 9, 2005.

4.3 Review Strategy

Please see my previous clinical review dated November 9, 2005.

4.4 Data Quality and Integrity

Please see my previous clinical review dated November 9, 2005.

4.5 Compliance with Good Clinical Practices

Please see my previous clinical review dated November 9, 2005.

4.6 Financial Disclosures

Please see my previous clinical review dated November 9, 2005.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There were no clinical pharmacology studies for this application. Please see the original reviews for NDA 20-785 and the review associated with this supplement.

5.2 Pharmacodynamics

There were no clinical pharmacology studies for this application. Please see the original reviews for NDA 20-785 and the review associated with this supplement.

5.3 Exposure-Response Relationships

Please see full discussion under Integrated Review of Efficacy.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

Please see my previous clinical review dated November 9, 2005.

6.1.2 General Discussion of Endpoints

Endpoints for clinical studies of MM in general are discussed in my November 9, 2005 clinical review. The primary endpoint of Study EA100 was the best overall response during 4 treatment cycles based on ECOG Myeloma Response Criteria.

Reviewer's Comment: A 2-week interval between initial and confirmatory paraprotein measurements used to define CR or PR is shorter than the 2 months used by SWOG or 6 weeks recommended by the EBMT.

6.1.3 Study Design

Please see my previous review dated November 9, 2005.

6.1.4 Efficacy Findings

This reviewer reviewed the submitted data and analyzed the efficacy endpoint (serum or urine paraprotein). The results are summarized in Reviewer's Table 1.

Reviewer's Table 1: Study E1A00 overall response rates

Overall response rate (ECOG CR + PR)		P (2-sided Fisher Exact)
Thal/Dex (n = 103)	Dex alone (n = 104)	
53 (51.5 %)	37 (35.6 %)	0.025

Reviewer's Comment: This revised analysis found determined that the response rate in the Thal/Dex arm is statistically superior to that in the dexamethasone-alone arm.

6.1.5 Clinical Microbiology

Not applicable to this efficacy supplement.

6.1.6 Efficacy Conclusions

Protocol E1A00 was a prospective randomized controlled trial of Thal/Dex versus dexamethasone alone in patients with newly diagnosed MM. Treatment arms appeared well balanced with respect to demographic and disease characteristics and compliance with assigned treatment appeared acceptable (see my November 9, 2005 review for details). The Applicant claimed that the primary objective of the study, a difference in prespecified definition of OR rate at 4 months, was met.

My analysis suggests that Thal/Dex results in a statistically significant difference in OR rate compared with dexamethasone alone. OS was similar in both treatment arms, 75.4 weeks and 76.6 weeks for the Thal/Dex and dexamethasone-alone arms, respectively. OS was expected to be similar because 4-month mortality in newly diagnosed MM patients tends to be low, and trial E1A00 was not designed or powered to evaluate this endpoint.

7 INTEGRATED REVIEW OF SAFETY

Please see my previous clinical reviews dated October 22, 2004 and November 9, 2005.

8 ADDITIONAL CLINICAL ISSUES

I searched existing published medical literature, and found 15 open-label, phase II studies that evaluated the safety and efficacy of thalidomide in a total of 610 patients with relapsed or refractory MM plus seven open-label, phase II studies that evaluated thalidomide in combination with dexamethasone in 363 total patients with newly diagnosed MM. Data from these studies suggest that single-agent thalidomide induces an overall rate of paraprotein response, defined as a single (unconfirmed) > 50% reduction, of 33% in relapsed/refractory MM and 64% in combination with dexamethasone in newly diagnosed MM. These data support the conclusion of Study E1A00 that thalidomide has activity in MM.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.1.1 Efficacy

The Applicant submitted primary data from one multicenter, open-label, randomized clinical trial evaluating the use of thalidomide in MM. Response rates in Study E1A00, based on a serum or urine paraprotein without radiographic or bone marrow confirmation, were significantly higher in the combination arm (51.5% compared with 35.6 % for dexamethasone alone; 2-sided Fisher exact $p = 0.025$). Study ECOG E1A00 was not designed or powered to detect an OS difference, and OS was similar in both treatment groups (75.4 weeks for Thal/Dex and 76.6 weeks for dexamethasone-alone).

9.1.2 Safety

Most patients in Study E1A00 experienced at least one grade 3-4 AE (84.3% on the Thal/Dex treatment arm, and 73.5% on the dexamethasone-alone arm). The most common toxicities with thalidomide, somnolence, constipation, neuropathy, VTE, and rash, have been previously described. Study E1A00 was not designed to evaluate the reversibility of thalidomide-induced neuropathy.

I reviewed the published medical literature regarding the risk of VTE during thalidomide treatment for MM and identified several relevant clinical reports. 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 is used in combination with standard chemotherapeutic agents such as alkylating agents or anthracyclines. The higher rate of VTE in Study E1A00 reported in the Thal/Dex treatment arm than among patients who received dexamethasone-alone (22.5% and 4.9%, respectively; $p = 0.002$) is consistent with this literature. Although the causality of such events can be difficult to determine in cancer patients in whom multiple confounding variables may be present, the increased incidence of VTE in ECOG E1A00 is particularly significant because it was a prespecified endpoint.

Prophylactic antithrombotic therapy prescribed in conjunction with thalidomide may lessen the potential for VTE. Amendments to recent clinical trial designs suggest that this practice may be common in clinical trials. However, the chief risk of this approach is bleeding. MM itself predisposes patients to both acquired bleeding and clotting disorders, and MM patients 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.

9.2 Recommendation on Regulatory Action

This reviewer recommends accelerated approval of thalidomide for patients with MM. This indication would increase the available options for therapy of patients this disease. Data from Study Thal MM-03, once mature, should confirm the clinical benefit of thalidomide in this population

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The thalidomide label should be updated with a boxed warning reflecting the significantly increased risk of VTE seen with thalidomide combination therapy in this population. In addition, Celgene should send a Dear Health Care Provider letter concerning this finding.

9.3.2 Required Phase 4 Commitments

1. The sponsor should 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 glucocorticoid alone as induction therapy in patients with previously untreated multiple myeloma* when completed.
2. The sponsor should conduct an epidemiologic study to address the efficacy of anticoagulant and antiplatelet prophylaxis and treatment using the STEPS patient registry database. This commitment and the completion dates agreed upon are listed below.

9.3.3 Other Phase 4 Requests

All patients in the E1A00 study should be followed for 5 years or death following completion of their therapy. A final study report should be submitted to the Agency.

9.4 Labeling Review

The review team's proposed labeling will include revisions to the indications and precautions sections. The following proposed language regarding VTE should be placed in a "black box" for emphasis:

The use of Thalomid[®] (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used 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 (p = 0.002). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

9.5 Comments to Applicant

None

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10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

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Clinical Review
Michael Brave, M.D.
sNDA 21-430
Thalidomide (Thalomid)

REFERENCES

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**CLINICAL REVIEW OF PROPOSED CHANGES TO
APPROVED THALOMID[®] LABEL**

Application Type: Supplemental (type 6) NDA
Submission: NDA 21-430
Submission Code N-000

Letter Date: November 23, 2005
Stamp Date: November 23, 2005
PDUFA Goal Date: May 25, 2006

DSPTP Reviewer: E.M. O'Shaughnessy, M.D.

Established Name: Thalidomide
Trade Name: Thalomid[®]
Therapeutic Class: Immune modulator
Applicant: Celgene Corporation

Formulation: Oral capsule
Dosing Regimen: 200 to 400 mg orally once daily
Indication: Multiple Myeloma
Intended Population: Adult human

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Thalidomide, Thalomid® – Review of Proposed Labeling Changes

Background

Thalidomide and its approval

Thalomid® (thalidomide) (Celgene, Corp.) was approved by the US FDA on July 16th, 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.

- 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:
- Distribution restricted to certain facilities or physicians with special training or experience; or
- Distribution conditioned on the performance of specified medical procedures.
- The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

Approved Indications for Thalidomide, Thalomid®

The currently 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.

Safety Program

The major specific safety concern for thalidomide is teratogenicity and the risk management goals are the prevention of fetal exposures to thalidomide.

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.*®).

An evaluation of 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 77,000 patients were prescribed Thalomid® (a total of approximately 400,000 prescriptions). Of these 77,000 patients, approximately 4000 (~5%) 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.

NDA 21-430 and NDA 20-785

NDA 21-430 belongs to the division of Division of Drug Oncology Products (DDOP). NDA 21-430, a supplemental (type 6) NDA, was submitted to the Division of Drug Oncology Products, Office of Oncology (DDOP) in November, 2005. This NDA was filed to support a treatment indication for multiple myeloma.

NDA 20-785/S-031 belongs to Division of Special Pathogens and Transplant products (DSPTP). This supplement was submitted on May 23, 2005, to harmonize the thalidomide label in 590 with the new label proposed for the multiple myeloma indication. This supplement also provided revised labeling for the Carcinogenicity, Mutagenicity and Impairment of Fertility subsection of the PI.

DDOP took an approvable (AE) action on 11/10/05, requesting revision of the label. DSPTP took an AE action on November 23, 2005, based on recommendations from DDOP. The sponsor submitted a complete response to the AE letter from DDOP on December 6, 2005. This submission contains revised labeling as requested in the AE letter. An approval (AP) action will be taken for both NDA 21-430 and 20-795/S-031 in May 2006.

All the postmarketing study commitments (listed in the approval letter, 7.16.1998) for thalidomide (NDA20-785) have been fulfilled, see letter dated 5.22.2006 from DSPTP to Celgene Corporation.

REVIEW OF PROPOSED CHANGES TO APPROVED THALOMID[®] LABEL**Introduction**

Three documents were consulted for this review i.e. the clinical review (5.18.06) completed by M. Brave, M.D. in DDOP, the revised labeling changes in the thalidomide label (NDA21-430), and a synopsis of the S.T.E.P.S. program in a memorandum by C Kraus, M.D. (1.29.04).

A labeling review and labeling negotiations have been conducted by the reviewers in DDOP. Additions and revisions to the clinical sections of the current thalidomide label are addressed in this brief review.

The medical officer in DSPTP defers to the clinical reviewer in DDOP regarding the analysis of efficacy and safety of thalidomide for the treatment of patients with multiple myeloma. The clinical reviewer in DDOP recommends accelerated approval of thalidomide in combination with dexamethasone for previously untreated, symptomatic patients with multiple myeloma. The most common toxicities reported in the clinical trials were somnolence, constipation, neuropathy, venous thromboembolism, and rash. There was a higher rate of venous thromboembolism in patients receiving thalidomide in combination with dexamethasone treatment arm compared to those who received dexamethasone alone.

Current Approved Thalomid[®] label

The currently approved 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.

Proposed Changes to Approved Thalomid[®] Label

One of the major changes to the label is a new box warning reflecting the significantly increased risk of venous thromboembolism with thalidomide combination therapy in the population studied in this submission. The original boxed warning regarding the potential for causing severe, life-threatening human birth defects remains the same.

1. WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.

There are no new changes to this section. Thalomid[®] (thalidomide) is approved for marketing only under a special restricted distribution program approved by the food and drug administration. The System For Thalidomide Education And Prescribing Safety (*S.T.E.P.S.*) is adequately addressed in the boxed warning as in the prior approved label. *S.T.E.P.S.* will continue to be implemented for patients with multiple myeloma and all patients receiving thalidomide.

2. WARNING: THROMBOEMBOLIC EVENTS

The clinical data supporting this new boxed warning was reviewed by M. Brave M.D. in DDOP.

The clinical reviewers in DSPTP defer to Oncology regarding the content of this section.

The use of Thalomid[®] (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used 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 (p = 0.002). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

INDICATIONS AND USAGE

The clinical reviewers in DSPTP defer to Oncology regarding the additional indication in this section of the label.

Multiple Myeloma

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 (see **CLINICAL STUDIES section**). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.*

CONTRAINDICATIONS

Based on Dr. Brave's review, the clinical reviewer in DSPTP agrees with the additional information in this section of the label.

“Thrombotic Events:

*The use of Thalomid[®] (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used 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 ($p = 0.002$). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment (See **BOXED WARNINGS**).”*

ADVERSE REACTIONS

Based on Dr. Brave's review, the clinical reviewer in DSPTP agrees with the additional information in this section of the label.

“Adverse events in Multiple Myeloma Controlled Clinical Trial

The safety analysis was conducted on 204 patients who received study drug in the randomized trial. Table 7 lists the most common treatment – emergent signs and symptoms (occurring at $\geq 10\%$) that were observed. The most frequently reported adverse events were constipation, sensory neuropathy, confusion, hypocalcemia, edema, dyspnea, thrombosis / embolism, and rash/desquamation (occurring in $\geq 20\%$ of patients and with a frequency $\geq 10\%$ in patients treated with Thalomid[®]/dexamethasone compared with dexamethasone alone).

Twenty-three percent of patients (47/204) discontinued due to adverse events; thirty percent (31/102) from the Thalomid[®]/dexamethasone arm and sixteen percent (16/102) from the dexamethasone alone arm.” See Table – in the label.

Medical Officer's (DSPTP) Conclusions

The clinical reviewer agrees with the changes to the current proposed label for thalidomide (Thalomid®). The required risk management program, *S.T.E.P.S.*®, to prevent fetal exposure to thalidomide will continue to be implemented.

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends taking an approvable action for thalidomide in combination with dexamethasone (Thal/Dex) for previously untreated, symptomatic multiple myeloma (MM) patients. This recommendation is based partly on primary data from one multicenter Eastern Cooperative Oncology Group (ECOG) clinical trial E1A00 in which 207 patients were randomized to Thal/Dex versus dexamethasone alone. Response rates based on a serum or urine paraprotein response resulted in a statistically significant difference in favor of the combination arm (46.6 % compared with 27.9 % for dexamethasone alone; $p = 0.003$). Median overall survival (OS) was similar in both treatment groups (75.4 weeks for Thal/Dex and 76.6 weeks for dexamethasone-alone). However, a final decision regarding approvability of this application is pending review of the sponsor's responses to the review team's queries regarding the data. Celgene submitted additional information on November 1 and informed the review team that additional data is forthcoming. After review of all new data and reanalysis, if the application's results continue to show a statistically significant difference in favor of the thalidomide combination for best response within the first 4 cycles, thalidomide may be given accelerated approval (AA) for the treatment of newly diagnosed patients with multiple myeloma.

[]

In Study E1A00, the incidence of grade 3 or 4 adverse events (AEs) was 84.3 % on the Thal/Dex treatment arm, and 73.5 % on the dexamethasone-alone arm. A total of 34 grade 3 or 4 AEs were reported among the 62 patients enrolled on studies Mayo 98-80-13 and Thal MM-99-002. The most common toxicities with thalidomide in both newly diagnosed and relapsed/refractory MM patients were somnolence, constipation, neuropathy, venous thromboembolism (VTE), and rash, have been previously described. In Study E1A00, the risk of thalidomide-induced VTE was higher in patients concurrently receiving dexamethasone, and the thalidomide label should be updated accordingly with a boxed warning. In addition, Celgene should send a Dear Health Care Provider letter concerning the increased risk of VTE seen with thalidomide combination therapy.

These data are further supported by existing published literature. I searched existing medical literature and found 16 open-label, phase II clinical studies that evaluated the safety and efficacy of thalidomide in a total of 779 patients with relapsed or refractory MM and 7 open-label, phase II studies that evaluated thalidomide in combination with dexamethasone in a total of 363 patients with newly diagnosed MM. Data from these studies suggest that thalidomide induces an overall rate of paraprotein response, defined as a single (unconfirmed) >50% reduction of 13 to

58 % in relapsed/refractory MM and 32 to 76 % in combination with dexamethasone in newly diagnosed MM.

The chief toxicities of thalidomide reported in these studies were sedation, peripheral neuropathy, constipation, rash, and VTE. The three trials for which primary data were submitted were not designed to evaluate the reversibility of thalidomide-induced neuropathy.

The risk-benefit ratio potentially favors the eventual approval of thalidomide for these indications. These indications could increase the available options for MM.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Thalidomide, like other chemotherapy agents, should be administered under supervision of a qualified physician with experience in administering chemotherapy.

1.2.2 Required Phase 4 Commitments

Study Thal-MM-003 is an ongoing, Celgene-sponsored multicenter study that should provide clinical benefit as required by AA regulations. This study is randomizing newly diagnosed MM patients to Thal/Dex versus dexamethasone-alone until progression or unacceptable toxicity. Four hundred and seventy patients have been randomized into the study and enrollment is closed. The last patient was enrolled on April 11, 2005. An interim analysis is planned when 50% of the 282 patients required for the primary analysis have progressed. The primary study endpoint is time to progression (TTP), and secondary endpoints are OS, response rate, duration of response, and time to first skeletal-related event.

1.2.3 Other Phase 4 Requests

All patients in the E1A00 study should be followed for 5 years or death following completion of their therapy. A final study report should be submitted to the Agency.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Thalidomide (α -phthalimidoglutarimide) is a small-molecule glutamic acid derivative with multiple proposed mechanisms of action. This sNDA contains primary data from one

All patients in Study E1A00 developed at least 1 treatment-emergent AE. The incidence of treatment-emergent grade 3/4 toxicity was 84.3 % on the Thal/Dex arm and 73.5 % on the dexamethasone-alone arm. Consistent with published literature, the incidence of all-grade and grade 3/4 fatigue, constipation, peripheral neuropathy, VTE, and rash were higher in the Thal/Dex treatment arm than with dexamethasone alone. In addition, there was a statistically significant difference in the reported rate of VTE in the Thal/Dex treatment arm compared to dexamethasone alone (22.5 % versus 4.9 %; $p = 0.002$).

None of the three registration trials were designed to assess reversibility of toxicity following dose reduction. No systemic allergic or hypersensitivity reactions were reported. Overall clinical safety data are adequate for marketing approval for this indication.

1.3.4 Dosing Regimen and Administration

Study E1A00 randomized patients with newly diagnosed MM to thalidomide 200 mg/day for 28 days (1 treatment cycle) plus dexamethasone 40 mg/day on days 1-4, 9-12, and 17-20 versus dexamethasone alone on days 1-4, 9-12, and 17-20 of the 28-day cycle. Patients with stable disease or better at the end of the first cycle continued treatment for a total of 4 cycles (16 weeks). Patients who had not progressed at 4 weeks were offered either standard MM therapy, including stem cell transplantation if eligible, or additional thalidomide with or without dexamethasone in an extension phase at the investigator's discretion until progression.

Reviewer's Comments:

1. In EA100 and most published clinical studies, patients received thalidomide as a single daily oral dose, at bedtime, on a continuous schedule.
2. Based on submitted data, the recommended dose _____
_____ in combination with dexamethasone for newly diagnosed MM is 200 mg daily. In both settings, thalidomide should be administered at bedtime to minimize sedation.

1.3.5 Drug-Drug Interactions

This registration study was not designed to specifically evaluate drug-drug interactions with thalidomide.

1.3.6 Special Populations

Of 202 patients in the safety population of Study E1A00, 111 (55%) were male and 90 (45%) were female (the gender of patient 10006 was not recorded). The mean age of the E1A00 safety population was 64 years, with 104 (51%) over age 65 and 98 (49%) age 65 or younger.

Neither gender nor age appeared to correlate with thalidomide responsiveness. The overall risk of grade 3/4 toxicity as well as risks of each of the most common individual grade 3/4 toxicities (sedation, constipation, neuropathy, rash, and VTE) appeared to be somewhat higher among patients over age 65 and among those whose baseline serum creatinine was > 1.5 mg/dL.

No pharmacokinetic or safety data are available in subjects below the age of 18 years. Pediatric patients were not included any of the three registration studies because MM is virtually nonexistent in children. The pediatric population is therefore not relevant to this sNDA.

Thalidomide undergoes spontaneous hydrolysis and has no known active metabolites. Its biologic effect is therefore thought to be independent of renal and hepatic function, and the current product label recommends no dose adjustments for patient age, renal or hepatic function. Study ECOG E1A00 required that patients have baseline serum creatinine < 1.5 mg/dL and bilirubin < 3.0 mg/dL for entry, and all patients met these requirements. Only 11 patients in E1A00 had baseline serum creatinine 2.1 to 2.9.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Thalidomide (α -phthalimidoglutarimide) is a small-molecule glutamic acid derivative that contains a chiral center and two amide rings. Its molecular formula is $C_{13}H_{10}N_2O_4$ and molecular weight is 258.23. Marketed pharmaceutical thalidomide is a racemic mixture containing an equal proportion of R and S isomers. Thalidomide is  soluble in water, and no intravenous preparation is available.

Thalidomide spontaneously undergoes nonenzymatic hydrolysis. The resulting products are further transformed (e.g. oxidation, reduction, conjugation, methylation, hydration, dehydration, decarboxylation, tautomerization, and decomposition) to over 200 metabolites, none of which have known biologic activity.¹ Numerous metabolites are renally excreted and nonabsorbed drug is eliminated in feces.² Thalidomide does not significantly interact with P-glycoprotein.³

Thalidomide induces G₁ growth arrest and apoptosis of cultured MM cells.⁴ Multiple mechanisms of action have been postulated to explain this observation. These are summarized in Reviewer's Table 1.

Reviewer's Table 1: Postulated mechanisms of action for thalidomide in MM

Physiologic System	Reported rationale	References
Angiogenesis	Thalidomide inhibits basic fibroblast growth factor induced angiogenesis in the rabbit microcorneal assay and downregulates angiogenesis genes in MM cell culture.	6-10

α_1 -acid glycoprotein	Thalidomide binds α_1 -acid glycoprotein, a physiologic immune response regulator.	10
TNF- α	TNF- α is a proinflammatory cytokine. Thalidomide responsiveness in MM is associated with high circulating TNF- α levels and a TNF- α promotor region “high-producer” polymorphism. The thalidomide S-isomer reduces TNF- α production (IC ₅₀ 50 mg/mL) and the half-life of TNF- α mRNA in monocyte cultures (from 30 to 17 min).	12-16
IL-6	Thalidomide reduces IL-6 production by peripheral blood mononuclear cells.	16
Bone marrow stroma	Thalidomide reduces myeloma cell adhesion to stroma.	17
Lymphocytes	Thalidomide costimulates natural killer cells and T lymphocytes and decreases the ratio of circulating CD4 ⁺ to CD8 ⁺ T cells.	19-21
DNA	Thalidomide may induce free-radical mediated DNA oxidation.	21

2.2 Currently Available Treatment for Indications

Melphalan and cyclophosphamide are approved as single-agent therapy for MM. Carmustine is approved in combination with prednisone. Bortezomib has regular approval for patients who have received at least one prior therapy. Zoledronic acid and pamidronate are approved as adjuncts to standard antineoplastic therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Thalidomide has been marketed in the United States under the S.T.E.P.S[®] program since July 1998. It is approved for the acute treatment and maintenance therapy of the cutaneous lesions of erythema nodosum leprosum (ENL).

2.4 Important Issues with Pharmacologically Related Products

There are no FDA-approved pharmacologically related products.

2.5 Presubmission Regulatory Activity

Thalidomide has a long regulatory history. It was first synthesized in 1957,²² and the following year was approved in Europe. By 1959, thalidomide was marketed in 48 countries as a mild sedative and antiemetic, available in many areas without a prescription. A US marketing application was submitted to the Agency in 1960 for use as a sedative (NDA _____) but was not approved because of emerging reports about neuropathy.^{23,24} While the Agency was awaiting answers to these concerns, the link between thalidomide use and an epidemic of congenital

malformations that was occurring in Europe was recognized and the drug was withdrawn from marketing in 1961. An estimated 5,000 to 6,000 infants, however, were born with characteristic thalidomide-induced deformities (phocomelia or amelia of the limbs, frequently combined with cardiovascular, gastrointestinal, respiratory, or urogenital defects). The tragedy played a part in the debate around the 1962 Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act that resulted in specific effectiveness requirements for drugs.²⁵

A serendipitous observation in 1965 of improvement during thalidomide use in patients with ENL²⁶ was subsequently confirmed by clinical trials. A Dermatologic and Ophthalmologic Drug Advisory Committee on September 4-5, 1997, considering evidence presented by the FDA, Celgene, and representatives of the Canadian Thalidomide Victims Association, voted 6-1 that thalidomide was effective treatment for ENL.

On September 9-10, 1997, an open public scientific workshop was held to discuss the potential benefits and risks of thalidomide. The Agency recognized that pregnancy and fetal exposure prevention programs and appropriate product labeling were critical to create an informational context that reinforced the correct use of thalidomide, understanding the impossibility of guaranteeing that the drug would always be used correctly and that no human embryopathy would ever occur.²⁷

On July 16, 1998, the FDA approved thalidomide 50 mg capsules (NDA 20-785) for the acute treatment and maintenance therapy of the cutaneous lesions ENL. This was the first time that the restricted distribution provisions of CFR 314.520 were invoked. Requirements included:

- a. Restriction to prescribers and pharmacies registered with the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)[®] program;
- b. Individual patient informed consent and completion of printed and video educational materials;
- c. Agreement by patients to comply with provisions of program, including not sharing medication or donating blood or sperm;
- d. For women with childbearing potential, agreement to use two methods of birth control, and mandatory monthly or biweekly pregnancy testing;
- e. For men taking thalidomide, agreement to use barrier contraception when sexually active with a woman of childbearing potential;
- f. Restriction on prescribing or dispensing more than a 28 day supply of drug.

This education, control and tracking system differed from the “primary prevention program” introduced in 1988 for the teratogenic vitamin A analogue isotretinoin (Accutane[®]) in that participation in the thalidomide program was mandatory rather than voluntary.

The following four thalidomide label revisions and reformulations have subsequently been effected.

1. September 9, 2001
 - a. Safe handling guidelines for health care professionals were added.

- b. The term *reproductive heterosexual sexual intercourse* was replaced by the simpler term *sexual contact* in the pregnancy prevention section, and warnings were added informing men of the presence of thalidomide in semen and the need to use latex condoms.
 - c. Warnings were added that seizures and Stevens-Johnson syndrome had been reported in postmarketing surveillance.
2. January 17, 2003
 - a. The 50 mg capsule was reformulated and 100mg and 200 mg capsules were introduced.
 - b. Capsules were distributed in individual 28-dose blister packs.
3. September 15, 2003: The informed consent form was redesignated a *patient-physician agreement form* to underscore its use in risk management and not for research purposes and to provide.
4. October 27, 2003
 - a. A statement was added that VTE had been reported with increased frequency among patients with neoplastic and inflammatory conditions receiving thalidomide and that the role of concomitant medications including anticancer agents was uncertain.
 - b. A warning to avoid cutaneous exposure or drug inhalation was added.
 - c. A statement was added that cases of bradycardia, some requiring medical intervention, had been reported.
 - d. The subsection “Important Non-Thalidomide Drug Interactions/Drugs That Interfere with Hormonal Contraceptives” was expanded.
 - e. “Other Adverse Events Observed in Post-Marketing Use” and “Other Adverse Events Observed in HIV-seropositive Patients” subsections were added.

In October 2003, Australia became the first country to approve thalidomide for “the treatment of multiple myeloma after failure of standard therapies”.²⁸ Thalidomide is also now approved for this indication in New Zealand, Turkey, and Israel. Thalidomide is distributed for MM outside the United States by the Pharmion Company.

On December 23, 2003, Celgene submitted a supplemental new drug application (sNDA) for thalidomide as a treatment for patients with MM after failure of standard therapies under 21 CFR §314.500 Subpart H – Accelerated Approval of New Drugs for Serious or Life Threatening Conditions. Three single arm studies were submitted (Mayo 98-80-13, THAL-MM-99-002, and UARK-98-003). The FDA did not rely upon results of the largest study, the 146-patient University of Arkansas study (UARK 98-003). The remaining data in the application were from 62 patients enrolled in the other two studies. The Agency decided that two studies did not provide sufficient data for approval at that time. The confirmed response rate in those 62 patients was only 13 %, and there were no complete responses. This response rate was substantially lower than that claimed in the application package, and contrasted 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.

Safety information concerning thalidomide could not be extrapolated from the ENL safety database to the MM population because thalidomide doses used for MM were higher than those used for ENL.

On May 13, 2005, Celgene resubmitted this sNDA for thalidomide based on data from ECOG Study E1A00.

2.6 Other Relevant Background Information

MM is the prototypic tumor of terminally differentiated plasma cells. It has a yearly incidence of nearly 14,000 patients in the United States, accounts for about 10% of hematologic malignancies, and is the second most frequent hematologic malignancy among older individuals.²⁹ Median overall survival is 3 to 5 years with conventional chemotherapeutic approaches, and few if any patients are cured. Recently proposed classifications grouping MM patients into classes based on their cytogenetic and genomic expression profiles have not been standardized.³⁰

The malignant plasma cells in MM produce a patient-specific monoclonal immunoglobulin heavy and/or light chain (paraprotein, M-protein or M-component) that is detectable by serum and/or urine electrophoresis (EP) in all patients except the 1-2% with non-secretory disease. Typical clinical and laboratory features include bone pain, anemia, renal insufficiency, hypercalcemia, increased susceptibility to infection, and constitutional symptoms. Less common complications include spinal cord compression by extramedullary plasmacytomas or vertebral collapse, peripheral neuropathy, amyloidosis and hyperviscosity syndrome.

Oral melphalan plus prednisone (MP), introduced over 30 years ago,³¹ remains a first-line therapy for older patients,³² controlling symptoms and reducing tumor mass by $\geq 50\%$ in about half of cases.³³ Responding patients survive longer than non-responders (43 versus 19 months) with no survival advantage for complete responders over partial responders, and no evidence that even a small subgroup is cured.^{34,35}

Monthly cycles of MP are administered until a plateau is attained, after which randomized trials show no survival advantage from maintenance therapy.³⁶ Interferon- α prolonged this plateau phase in some^{37,38,39,40} but not all^{41,42} randomized trials and offered no survival advantage.

The combination of vincristine, doxorubicin, and dexamethasone (VAD) is active in 65 % of previously untreated patients and over 50 % of those refractory to standard-dose MP.⁴³ Responses require a mean of 21 days, versus 6 to 8 weeks for MP, with less myelotoxicity. Unfortunately, median survival of patients treated up-front with VAD is similar to that achieved with MP^{44,45} or simply high-dose dexamethasone alone.⁴⁶ An advantage of first-line VAD for patients in whom transplantation is a consideration is that it avoids exposure to melphalan, which can impair stem-cell mobilization.^{47,48}

Bortezomib, a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells, received accelerated approval under 21 CFR §314 Subpart H in May 2003 as a single agent for the treatment of MM patients who have received at least two prior therapies and

have demonstrated disease progression on the last therapy. Safety and efficacy were evaluated in an open-label, single-arm study of 202 MM patients who had received at least two prior therapies and had demonstrated disease progression on the last therapy, and a smaller dose-finding study of 54 patients provided additional supportive information. The primary end point in the larger study was response rate, and 188 patients who met the inclusion criteria were included in the FDA efficacy analysis. CRs were confirmed in 5 patients and PRs in 47 patients for an OR rate of 28%. The dose finding study of 54 patients showed a higher OR rate for patients given 1.3 mg/m² compared with 1.0 mg/m² twice weekly for two of the 3-week schedule, but the study was too small for statistical dose-response comparisons. The most commonly reported adverse events were asthenic conditions (including fatigue, malaise, and weakness) in 65%, nausea (64%), diarrhea (51%), appetite decreased (including anorexia; 43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (37%, including peripheral sensory neuropathy and peripheral neuropathy aggravated), pyrexia (36%), vomiting (36%), and anemia (32%).⁴⁹

Bortezomib was converted to full approval in March 2005. This conversion was based on a prospective phase 3, international, randomized (1:1), stratified, open-label clinical trial enrolling 669 patients, designed to determine whether bortezomib resulted in improvement in TTP compared to high-dose dexamethasone in patients with progressive MM following 1 to 3 prior therapies. A preplanned interim analysis after a median follow-up for surviving patients (n = 534) of 83 months showed that compared to patients in the dexamethasone arm, those in the bortezomib arm had a superior OR rate (38 versus 18 %; p < 0.001), TTP (median 6.2 versus 3.5 months (p < 0.001), and OS (80 versus 66 %; p < 0.05).⁵⁰

High-dose chemotherapy with autologous stem cell support induces serum and urine IF-negative CRs in 30 % of patients, and CR correlates with survival.⁵¹ Randomized trials have established autotransplantation as a preferred option for patients under age 60 with stage II or III disease.^{52,53,54,55} Outcome is best for younger patients with favorable cytogenetics, brief duration of standard-dose therapy and low initial serum β_2 -microglobulin level.⁵⁶ Some^{57,58,59} but not all⁶⁰ long-term follow-up data suggest that at 8 to 10 years, a plateau in the survival curve appears at about 10 %.

Allogeneic stem cell transplantation for MM produces higher rates of CR (35 to 45%) and molecular remission (30 % of patients in CR) than autografting.^{61,62} First-year mortality, however, approaches 50 %, compared with < 5 % for autologous transplantation, and case-matched comparisons suggest inferior long-term survival.⁶³ Fewer than 10 % of MM patients are candidates for allogeneic transplantation, although the recent development of reduced intensity nonmyeloablative transplantation (e.g. melphalan < 140 mg/m² + total body irradiation 2 Gy, fludarabine, or cyclosporine) followed by donor lymphocyte infusion to sustain a graft-versus-myeloma effect may increase this proportion.^{64,65,66}

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please see the original review for NDA 20-785.

3.2 Animal Pharmacology/Toxicology

Please see the Pharmacology/Toxicology review for this sNDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data submitted for this sNDA were generated by ECOG study E1A00, which randomized patients with newly diagnosed MM to 4 cycles of open-label Thal/Dex versus dexamethasone-alone, and two open-label, single-arm studies (Mayo 98-80-13 and Thal MM-99-002) in patients with relapsed or refractory MM. Study E1A00 enrolled 207 patients and was conducted at 82 centers in the United States. Please see my previous review for details of the other 2 studies.

4.2 Tables of Clinical Studies

Reviewer's Table 2: Studies for which Applicant submitted primary data to support sNDA

Dates Open	Design	Primary Objectives	Dose and Regimen	Patient Population	n
ECOG E1A00: A Randomized Phase III Trial of Thalidomide (NSC #66847) Plus Dexamethasone Versus Dexamethasone in Newly Diagnosed Multiple Myeloma					
6/6/02 – 4/18/03	Multicenter, open label, randomized	Determine the response rate and toxicities	Dexamethasone 40 mg/d on days 1-4, 9-12, and 17-20 +/- thalidomide 200 mg/d every 28 days for up to 4 cycles	Newly diagnosed MM	207

4.3 Review Strategy

The applicant submitted the entire application electronically through the Electronic Document Room. All primary demographic, dosing, and AE data were submitted through datasets. Raw response data were submitted as patient listings. ECOG-adjudicated response data were submitted as derived datasets.

Using this submitted material, this reviewer

- Examined the E1A00 study report and amendments;
- Examined listings for all Applicant-claimed responders in study E1A00;
- Subjected datasets to queries using JMP;
- Examined patient case report forms (CRFs), selected at random.

In addition,

- I reviewed the regulatory history of NDA 21-430 and the thalidomide Annual Report.
- I searched the published literature using Medline and compared this information against primary data submitted by the Applicant.

4.4 Data Quality and Integrity

Interpretation of the data provided in this submission was limited by the designs of the E1A00 registration study in the following ways:

- All treatment was administered in an open-label fashion.
- Compliance data were not collected.
- Patient numbers provided insufficient power for statistically significant analyses of efficacy or safety in most subgroups (female, elderly, etc.).
- In study E1A00, time to progression data were confounded by subsequent therapy.

4.5 Compliance with Good Clinical Practices

Study E1A00 was conducted under IND ~~submitted~~ submitted by the ECOG. It was not Celgene sponsored. The Applicant claims that the study adhered to Good Clinical Practice (GCP), as required by the following Guidelines, Regulations, and Directives in operation at the time:

- Declaration of Helsinki, concerning medical research in humans;⁶⁷
- United States 21 Code of Federal Regulations, parts 50 and 56, concerning Informed Patient Consent and IRB approval;
- European Directive 75/318/European Ethics Committee (as amended) on the approximation of laws of Member States relating to analytical, pharmacotoxicological, and clinical standards and protocols in respect of the testing of medicinal products;
- International Conference on Harmonization: E6 Guidance for Good Clinical Practice, May 9, 1997.

The applicant certified that no services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act were used in connection with this application.

This clinical reviewer found:

- The informed consent document adequately explained the voluntary nature of the trial and its risks and benefits;
- Protocol violations were relatively few considering the size of the trial;
- No clustering of efficacy or AE findings seemed to be site-specific.

Reviewer's Comment: My findings corroborated the Applicant's claims that the trial was conducted in accordance with acceptable ethical standards. The FDA Division of Scientific Investigation therefore did not perform site audits to directly verify these claims.

4.6 Financial Disclosures

The Applicant submitted financial disclosure statements through FDA form 3454 regarding the conduct organization of Studies ECOG E1A00, Mayo 98-80-13, and Thal MM-99-002. The Applicant states the following:⁶⁸

"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators...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 or other sorts as defined in 21 CFR 54.2(f)"

Reviewer's Comment: Appropriate financial disclosures were provided for clinical investigators and for members of the Adjudication Committee. None of the disclosures raise questions about financial conflict of interest.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There were no clinical pharmacology studies for this application. Please see the original reviews for NDA 20-785 and the review associated with this supplement.

5.2 Pharmacodynamics

There were no clinical pharmacology studies for this application. Please see the original reviews for NDA 20-785 and the review associated with this supplement.

5.3 Exposure-Response Relationships

Please see full discussion under Integrated Review of Efficacy.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

6.1.2 General Discussion of Endpoints

The first objective response criteria for MM, developed in 1968 by the Committee of the Chronic Leukemia and Myeloma Task Force (CLMTF) of the U.S. National Cancer Institute, defined serum and urine paraprotein responses as reductions of at least 50% compared to baseline.^{69,70} In 1972 the Southwest Cancer Chemotherapy Study Group, now SWOG, raised the response criteria to require 75% and 90% reductions in serum and urine paraprotein, respectively (reductions in serum paraprotein synthetic rate between 50% and 74% were considered “improved”), included mandatory measurement of indirect disease manifestations, and added a requirement that the response be maintained for at least 2 months.⁷¹

The introduction of more effective chemotherapy regimens such as vincristine/doxorubicin/dexamethasone (VAD) and high-dose chemotherapy in the late 1980s and 1990s, with reports of normalization of serum and urine electrophoretic patterns and bone marrow plasma cell counts, allowed for the first time inclusion of a complete response (CR) category. The EBMT, the Autologous Blood and Marrow Transplant Registry, and the International Bone Marrow Transplant Registry in 1998 proposed a new standard response classification system – the EBMT or Bladé criteria.⁷² The definition of CR^{EBMT} required that there be no evidence of serum or urine monoclonal proteins by immunofixation (IF) as well as electrophoresis (EF). CR^{EBMT} and PR^{EBMT} require that the paraprotein response be confirmed 6 weeks later (two samples). As with previous systems, radiographic bone lesions must not progress, known plasmacytomas must disappear, the bone marrow, if examined, must contain fewer than 5% plasma cells, and otherwise unexplained hypercalcemia must not develop. The EBMT also proposed requirements for minimal response, plateau, relapse, and progression (not included in Reviewer’s Table 3).

Reviewer’s Table 3. Standard MM response criteria

	M Component		Radiographic	Other Disease Manifestations
	Serum	Urine		
CLMTF Response	≥50% reduction	≥50% reduction if initially >1 g/24h, and to <0.1 g/24h if initially 0.5 to 1.0 g/24h	≥50% reduction in size of known plasmacytomas; healing of skeletal lesions	May be helpful in grading response: rise in Hb (2 g/dL); weight gain (4 kg); normalization of serum calcium, renal function, serum albumin and normal Ig levels; <5% marrow plasma cells if initially >20%
SWOG Objective	Decrease in	≥90% reduction	Stable size and	Improved bone pain and performance

response	synthetic index by $\geq 75\%$ and to ≤ 2.5 g/dL	and to ≤ 0.2 g/24h	number of lytic skull lesions	status; normal serum calcium; Hb > 9 g/dL; serum albumin > 3 g/dL
Improvement	50 – 75% decrease in synthetic index			
EBMT CR	Negative IF	Negative IF	Disappearance of known plasmacytomas; stable size and number of lytic lesions	$< 5\%$ marrow plasma cells
PR	$\geq 50\%$ reduction	$\geq 50\%$ reduction or to < 200 mg/24h	Stable size and number of lesions 50% reduction in size of known plasmacytomas	25 – 50% fewer marrow plasma cells

Given its greater sensitivity, an IF-negative CR implies less residual disease and should perhaps be associated with a better prognosis. A retrospective analysis of 344 autologous transplant patients, performed after publication of the EBMT criteria, suggested that patients attaining a negative IF have longer overall and disease-free survival than those with a negative EF but positive IF.⁷³

6.1.3 Study Design

Title:

A randomized phase III trial of thalidomide (NSC # 66847) plus dexamethasone versus dexamethasone in newly diagnosed multiple myeloma

Study Objectives:

The primary objective was to evaluate the response rate and toxicity of Thal/Dex versus dexamethasone-alone in patients with newly diagnosed MM.

Secondary objectives were to evaluate

- Time to best confirmed response
- Time to first confirmed response
- Time to disease progression
- Overall survival
- Toxicity/AEs by treatment regimen

Study Design:

E1A00 was an open-label, international randomized multicenter study.

Reviewer's comment: The study could not be blinded because adverse effects of thalidomide are readily apparent.

Inclusion Criteria:

- Age ≥ 18 years
- Recent diagnosis of symptomatic MM confirmed within 4 weeks of randomization by
 - Bone marrow with $\geq 10\%$ plasma cells or sheets of plasma cells or biopsy-proven plasmacytoma
 - Monoclonal paraprotein ≥ 1.0 g/dL on serum protein electrophoresis (SPEP) or ≥ 200 mg of monoclonal light chain on a 24 hour urine protein electrophoresis (UPEP)
- Laboratory values within 4 weeks of randomization
 - Absolute neutrophils $\geq 1000/\mu\text{L}$
 - Hemoglobin ≥ 7 g/dL
 - Platelets $\geq 50,000/\mu\text{L}$
 - Serum creatinine < 3 mg/dL
 - Serum bilirubin < 1.5 mg/dL
 - Serum ALT and AST < 2.5 times the upper limit of normal
- ECOG performance status ≤ 2
- Females of childbearing potential and their male partners must refrain from sexual intercourse or use dual barrier of contraception (e.g., intrauterine device, birth control pills, tubal ligation, or partner's vasectomy plus either condom, diaphragm, or cervical cap) starting four weeks prior to, while taking, and four weeks after discontinuation of thalidomide therapy.
- Females of childbearing potential assigned to thalidomide must have a negative serum pregnancy test 28 days prior to randomization, 24 hours prior to initiation of treatment, weekly for the first four weeks of treatment, and then every four weeks if menstrual periods are regular or every two weeks if not.
- Patients with history of prior malignancy were eligible if treated with curative intent and free of disease for a time period appropriate for the specific cancer.

Exclusion Criteria:

- Smoldering myeloma or monoclonal gammopathy of undetermined significance
- Prior systemic therapy for MM with the exception of bisphosphonates
- Systemic dexamethasone or glucocorticoid therapy for any illness within 6 months prior to study
- Prior palliative, localized radiation therapy was permitted provided at least 4 weeks had elapsed from the date of the last radiation therapy to the date of registration.
- Grade ≥ 2 peripheral neuropathy due to other medical conditions at the time of randomization
- Active infection at the time of randomization
- History of current or previous deep vein thrombosis and receiving anticoagulant therapy
- Pregnant or breastfeeding

Reviewer's Comment: The inclusion and exclusion criteria define a population of otherwise relatively healthy patients with symptomatic, secretory MM. These criteria were selected to result in a high proportion of potential post-study stem cell transplantation candidates. This setting is one in which thalidomide is being evaluated by other groups of clinical investigators (see Section 8.6 of this review). The population was therefore appropriate for this study.

Treatment Arms:

Patients who met all inclusion/exclusion criteria were randomized 1:1 to Thal/Dex versus dexamethasone-alone. Thalidomide was administered as 200 mg/day for 28 days (1 treatment cycle). It was recommended that patients take thalidomide at night to reduce the effects of drowsiness. Patients in both treatment arms received identical dexamethasone dosing schedules – 40 mg by mouth daily on days 1-4, 9-12, and 17-20 every 28 days.

Reviewer's Comment: This dexamethasone monotherapy schedule is based on literature and used commonly in the community. It is therefore an acceptable control arm.

Patients with stable disease or better continued treatment for a total of 4 cycles (16 weeks), at which time, they were considered for stem-cell transplant. Patients who had not progressed yet were not candidates for stem-cell transplantation received either standard MM therapy or continued initial protocol therapy in an extension phase at the investigator's discretion until progression. Patients that progressed discontinued study treatment and were followed until death.

Schedule Modifications:

Reviewer's Table 4: Thalidomide dose adjustment for toxicity

CTC Category	Toxicity	Initial Action	Dose at Resumption
Dermatology	Grade 2/3 rash	Hold until resolves to baseline or grade \leq 1	50% reduction ¹
	Grade 4 rash	Off study	None
Hematologic	Grade 3 neutropenia	Consider G-CSF	
	Grade 4 neutropenia	Hold until ANC \geq 500/ μ L	50% reduction
	Grade 4 thrombocytopenia	Hold until resolves to baseline or grade \leq 2	50% reduction
Neurology	Grade 2 motor	Hold until resolves to grade \leq 1	50% reduction ^{1,2}
	Grade 3 motor	Off study	None
	Depressed level of consciousness grade \geq 3	Hold until resolves to baseline or grade \leq 1	50% reduction ¹
Gastrointestinal	Constipation grade \geq 3	Hold until grade \leq 1	Add prophylactic measures and lower dose ¹
Constitutional	Fatigue grade \geq 3	Hold until resolves to baseline or grade \leq 1	50% reduction

Other	Grade \geq 3	Hold until resolves to baseline or grade \leq 1	50% reduction
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¹ If the patient is on 100 mg/day of thalidomide when the toxicity occurs the dose should be lowered to 50 mg/day. The dose may subsequently be increased by 50 mg/day weekly as tolerated up to 200 mg. Patients who cannot tolerate 50 mg/d should discontinue protocol therapy.

² Thalidomide should be stopped if there is recurrence of dose-limiting peripheral neuropathy on the lower dose or failure to resolve to \leq grade 1.

Reviewer's Comments:

1. The sponsor defined grade 4 thrombocytopenia as $< 10,000/\mu\text{L}$ whereas the NCI CTC definition is $< 25,000/\mu\text{L}$.
2. Treatment was held until thrombocytopenia returned to baseline or grade < 2 because patients with baseline platelet counts as low as $50,000/\mu\text{L}$ were eligible.

Reviewer's Table 5: Dexamethasone dose adjustment for toxicity

CTC Category	Toxicity	Initial Action	Dose at Resumption
Neurology	Confusion or mood alteration grade > 2	Hold until resolves to grade ≤ 1	50 % reduction
Gastrointestinal	Dyspepsia, gastric/duodenal ulcer, gastritis grade 1/2	Add H ₂ blockers, sucralfate, or omeprazole	If persists, 50 % reduction
	Dyspepsia, gastric/duodenal ulcer, gastritis grade ≥ 3	Hold until symptoms adequately controlled	
	Acute pancreatitis	Discontinue	None
Musculoskeletal	Muscle weakness grade ≥ 2	Hold until resolves to baseline or grade ≤ 1	25 % reduction
Metabolic	Hyperglycemia grade ≥ 3	Insulin or oral hypoglycemics Baseline or grade ≤ 1	25 % reduction

Concomitant Medications:

All patients, regardless of treatment randomization, received the following:

- Pamidronate 90 mg intravenously over 2-4 hours at study entry and on weeks 4, 8, 12, and 16 (zoledronic acid at 4 mg intravenously over 15 minutes was permitted as a substitute)
- Palliative localized radiation therapy, if indicated
- Routine prophylaxis with laxatives
- Routine prophylaxis with H₂ antagonists (plus sucralfate or omeprazole if necessary)
- Antiemetic therapy as necessary
- Routine daily prophylaxis with a quinolone antibiotic (additional antibacterial, antifungal or antiviral therapy was permitted if infections occurred)
- Red cells and platelet transfusions, as indicated

- Erythropoietin if transfusion-dependent chronic anemia

Prohibited Medications:

- Concomitant use of glucocorticoids
- Allopurinol and sulfamethoxazole/trimethoprim (due to concerns of rash)

Scheduled Visits and Observations:

Baseline

The protocol recommended that each patient have a radiographic bone survey and nerve conduction velocity measurement within 42 days of randomization. Each patient was also to have a history and physical examination, complete blood count, chemistry profile (alkaline phosphatase, AST, ALT, calcium, creatinine, glucose, sodium, potassium, bilirubin, and uric acid), SPEP, quantitative immunoglobulins, 24-hour UPEP, serum and urine immunoelectrophoresis (IEP) and IF, bone marrow aspirate and biopsy, serum β_2 -microglobulin, C-reactive protein, radiographic bone survey, LDH, and serum pregnancy test (if indicated) within 28 days of randomization.

Prior to each cycle

Each patient was to have a repeat history and examination, blood counts, chemistry profile, SPEP, and quantitative immunoglobulins.

After 4 cycles of treatment or at discontinuation

All baseline studies were repeated.

Follow-up

Visits were scheduled every 3 months for 2 years, every 6 months between 2 and 5 years, and every 12 months between 6 and 7 years after study entry. At those visits, the history and physical examination, blood counts, chemistry profile, SPEP, quantitative immunoglobulins, 24-hour UPEP, and serum and urine IEP and IF were repeated.

Study Endpoints:

The best OR rate during the first four cycles of treatment was determined by criteria outlined in Reviewer's Table 6. If detectable at baseline, both serum and urine paraprotein levels had to be followed and both had to be within the ranges designated by the response category. Responses required verification by 2 consecutive paraprotein determinations separated by at least 2 weeks.

Reviewer's Table 6: Response criteria used for study E1A00

Category	M Component		Other Disease Manifestations
	Serum	Urine	
CR	Negative IF	Negative IF	CR or PR
PR			<ul style="list-style-type: none"> • Normal quantitative serum Ig • Bone marrow biopsy with < 5 % marrow plasma cells • No new or increase in existing bone lesions • No recurrent or persistent
<ul style="list-style-type: none"> • If initially abnormal in serum and urine 	$\leq 50\%$ pretreatment	< 50 % pretreatment	
<ul style="list-style-type: none"> • If initially abnormal in serum only 	$\leq 50\%$ pretreatment	< 150 mg/24 h	

• If initially abnormal in urine only	< 1.0 g/dL	< 10 % pretreatment	hypercalcemia • No new or increase in plasmacytoma
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A third category, near complete response (NCR) was added to designate patients meeting all criteria for CR except repeat bone marrow was lacking, contained 3-6 % plasma cells, or contained < 3 % plasma cells but still in sheets or clusters. Responding patients were further classified as being in *plateau* if serum and urine paraprotein values were stable (< 20 % variation) or disappeared for at least 4 weeks.

Reviewer’s Comment:

1. The sponsor identifies these endpoints as “ECOG Myeloma Response Criteria, modified to exclude references to non-secretory myeloma”. These particular response criteria are not widely used or generally recognized as reproducible, accurate, or predictive of clinical benefit.
2. A 2-week interval between initial and confirmatory paraprotein measurements used to define CR or PR is shorter than the 2 months used by SWOG or 6 weeks recommended by the EBMT.
3. A 4-week interval to define *plateau* is shorter than the 3 months recommended by the EBMT.
4. The need for supportive care (e.g. palliative radiotherapy, antibiotics, or transfusion) was not a prespecified endpoint.

Patients meeting two or more of the following criteria were considered to have relapsed or progressed:

- Increase in serum paraprotein to ≥ 50 % above nadir or a rise of 2.0 g/dL (and to > 1.0 g/dL if constituting the sole protein manifestation of relapse)
- Increase in 24-h urine paraprotein to 50 % above nadir or an increase of 2 g (and to ≥ 250 mg)
- Increase in soft tissue plasmacytomas by 50 % (the sum of the products of the cross diameters of each measurable lesion)
- Definite new lytic bone lesions or 50 % increase in size of the existing bone lesions
- Hypercalcemia > 12 mg/dL without other cause
- Anemia (decrease in hemoglobin > 2 g/dL to a level < 11 g/dL in men or < 10 g/dL in women) not due to chemotherapy, interferon, or myelodysplastic syndrome
- Increase in bone marrow plasma cell percentage by > 50 %
- Generalized bone pain

Reviewer’s Comment: The EBMT recommends that progression be declared when the serum or 24-hour urine paraprotein values increase by 25 %. The ECOG used a higher threshold for declaring progression; therefore, potentially more patients could be labeled as having stable disease. The use of nonstandardized criteria makes it difficult to compare results across studies.

Statistical Considerations:

Primary efficacy analyses were performed for all randomized patients (the intent to treat population). The primary efficacy variable was best ECOG response (CR + NCR + PR) during the first 4 cycles of treatment. A one-sided Fisher Exact test was used to test the null hypothesis of equal response rates in the two treatment arms versus the alternative of a superior response rate in the Thal/Dex arm. A sample size of 194 patients (97 per treatment arm) was chosen to provide 90 % power to detect an improvement in response rate from 60 % with dexamethasone-alone to 80 % with Thal/Dex, while maintaining an overall one-sided 0.05 significance level, allowing for interim analyses. Median time to OR was provided with 95% confidence intervals. Kaplan-Meier estimation was used to characterize time to progression and OS.

Reviewer's Comment: As the sponsor used a one-sided Fisher's exact test, for easier comparisons of the primary efficacy results statistical reviewer also used the 1-sided test. However, the statistical reviewer used the 0.025 significance level instead of the 0.05 significance level used by the sponsor (a 1-sided test with 0.025 significance is equivalent to a 2-sided test with 0.05 significance). This approach is preferable in regulatory settings because it promotes consistency with two-sided confidence intervals that are generally appropriate for estimating the sample size for detecting the difference between two treatments (ICH E9 Document).

Safety analyses were performed for all patients who received at least one dose of study medication. AEs were summarized by worst grade NCI CTC, treatment cycle, and relationship to study medication. AEs leading to death or to discontinuation from treatment, those classified as NCI CTC grade 3 or higher, and treatment-related events were monitored. When AEs or event frequencies were judged to be clinically important, a Chi-square test without continuity correction was used to analyze the difference between the treatment groups.

Reviewer's Comment: The decision whether to use a Chi-square test to analyze differences in AE rates between treatment arms relied on the investigator's judgment as to the clinical importance of those events. This design introduced an element of variability and potential bias.

The proportion of patients with rash, VTE, neuropathy, grade > 3 bradycardia, or any grade 4 toxicity within four treatment cycles was compared between treatment arms using a 1-sided Fisher Exact test. Anticipated rates of these events combined were 30 % with Thal/Dex and 15 % with dexamethasone alone. If the probability of having at least one of these events was at least 20 % higher on the Thal/Dex treatment compared to dexamethasone-alone, combination therapy would be declared too toxic and the trial would be stopped. The sample size provided 91% power to detect this difference (Applicant's Table 7)

Applicant's Table 7: Power calculation for toxicity assessment

True Thal/Dex Toxicity Rate	Probability of Declaring Thal/Dex too Toxic
35 %	91 %
30 %	73 %
25 %	46 %

One interim analysis to compare response and toxicity rates in both treatment arms was performed when safety information was available for 192 patients (93% of information) and best OR information was available for 109 patients (53% of information) who had completed four treatment cycles. For response rates, the *p*-value corresponding to the O'Brien-Fleming upper boundary for stopping in favor of the alternative hypothesis was set at 0.0111. For toxicity, the *p*-value corresponding to the Pocock upper boundary for stopping in favor of the alternative hypothesis was set at 0.04998.

Study Amendments:

The study was amended 6 times. These amendments are listed in Reviewer's Table 8.

Reviewer's Table 8: Amendments to Study E1A00

Number	Date	Changes Effectuated
1	4/02	<ul style="list-style-type: none"> Clinical Trials Support Unit incorporated prior to activation
2	1/03	<ul style="list-style-type: none"> Corrected Community Co-Chair's last name (title page) Added Sec. 10 and App VIII, renumbered Secs. 10-13 (Index) Added sentence regarding zoledronic acid as alternative (Schema, 1.0, 5.11, 5.12, 5.31, 5.32, 5.42, App I) Clarified pamidronate dose schedule (Schema, Secs. 5.11, 5.12, 5.31, 5.32, 5.42) Clarified use of treatment beyond four cycles (Schema, Secs. 5.11, 5.12, 7.1, App I) Removed extra "to", changed "prior" to "within" (Sec. 3.1) Amended prior therapy (Secs. 3.3, 3.4, 3.5, 3.10) Added web registration info (Sec. 4.0) Updated section references to reflect new numbering (Sec. 4.52) Added Sec. 4.53 Added zoledronic acid to Commercial Agents List (Sec. 5.21) Clarified use of radiation therapy (Sec. 5.41) Replaced Follow-up Sec. 5.5 with new Section 5.6, Duration of Follow-up Added note about dating of pre-study chemistries, clarified requirement and corrected time frame for serum and urine M-protein, Added ALT to chemistry group, deleted "bone marrow aspirate and biopsy with percent plasma cells", changed final column header and added footnote to reflect new long term follow-up (Sec. 7.0) Updated lab sample submission (Sec. 7.2); Changed "Nursing Implications" to "Nursing/Patient Implications" (Secs. 8.110, 8.210, 8.311) Deleted statement regarding separate Accountability Record (Sec. 8.18) Added Sec. 8.4; Updated Study Monitoring (Sec. 9.0); Added Section 10.0 Added note re: sample submission (Sec. 11.0) Added missing subsection number, added note re: where lab studies will take place (Sec. 11.1) Clarified sample submission schedule (Sec.11.2); Renamed Sec. 11.31 "Peripheral Blood" Revised and reformatted 11.32 and 11.33; Deleted 11.34; Updated RTBK (Sec. 12.0)

		<ul style="list-style-type: none"> Added references 48 and 49 (Sec. 14.0) Added “decrease in blood supply to the brain (stroke)” side effect for thalidomide to consent Added side effects for zoledronic acid Added new length of follow-up info to consent; changed CTSU from “clinical” to “cancer”; Amended sample collection on consent (App I) Updated ECOG website address (App. II); clarified sample submission wording (App. III) Amended CTSU correlative studies section (App. VII), added zoledronic acid to list of Commercial Agents Updated references from Sec. 10.0 to Sec. 11.0 (App. VII) Added App VIII
3	1/03	<ul style="list-style-type: none"> Corrected references to Phase 2 Mayo Clinic Study (Sec. 1.0) Corrected CRADA collaborator to be Celgene (App. V)
4	2/03	<ul style="list-style-type: none"> Updated to the new Adverse Event Reporting Requirements (Sec. 5.2) Updated Records to be kept to reflect AE changes (Sec. 12.0) Updated CTSU Appendix to reflect AE changes (App. VII)
5	4/03	<ul style="list-style-type: none"> Deleted sentence regarding CTEP’s providing free thalidomide (schema, Sec. 5.11); Fixed typos (Secs. 3.11, 3.21) Clarified “steroids” to be “systemic glucocorticosteroids” (Sec. 3.4) Updated randomization procedures with CTSU info and web registration (Secs. 4.1, 4.4) Replaced scheduled bone marrow biopsy and aspirate, deleted in error in addendum #2 (Sec. 7.1) Deleted outdated note re: express shipping (Sec. 8.18) Added note re: drug package inserts (Secs. 8.1, 8.2, 8.3, 8.4); Updated gender and ethnicity table (Sec. 9.0); Changed “7 Days” to “7 Working Days” (Sec. 12.0)
6		<ul style="list-style-type: none"> Added information regarding possible increased risk of renal dysfunction in multiple myeloma when thalidomide is given with zoledronic acid

Reviewer's Comment: The amendments were relatively clerical in nature and did not substantially alter patient eligibility, treatment, or study results.

6.1.4 Efficacy Findings

6.1.4.1 Study E1A00

Patient Characteristics:

Two hundred and seven patients were randomized to study E1A00 between June 6, 2002 and April 18, 2003 – 103 to the Thal/Dex treatment arm and 104 to dexamethasone-alone. The study was conducted at 113 institutions within the United States Centers contributing the highest numbers of patients were The Rochester Mayo Clinic (15; 7 %), followed by the Medical College of Wisconsin (11; 5 %) and the Marshfield Clinic (7; 3 %). No other center contributed more than 4 patients (2 %).

Reviewer's Comment:

1. No single center or group of centers appeared to contribute a dominant number of patients to the overall study.

The 207 patients enrolled onto Study E1A00 had the following demographic and disease characteristics.

Reviewer's Table 9: Baseline characteristics of ITT population

Characteristic	Thal/Dex (N = 103)	Dex (N = 104)
Demographic		
Male/female/missing (%)	51/49/0	59/40/1
Median age, years (range)	65 (37-83)	68 (38-83)
Caucasian (%)	90	90
General health		
ECOG score 0/1/2/missing (%)	42/49/9/1	38/46/16
Concurrent chronic disease (yes/no/missing; %)	63/35/2	53/36/1
History of deep venous thrombosis (y/n/missing; %)	0/102/1	0/104
Multiple myeloma		
Stage I/II/III/missing (%)	14/46/40/1	16/42/42/0
Lytic lesions 0/1-3/>3/missing (%)	27/23/33/17	13/18/40/29
Serum M-component present/absent/missing (%)	92/7/1	97/2/1
Urine M-component present/absent/missing (%)	30/46/24	25/49/25
Heavy chain IgG/IgM/IgA/biclonal/missing (%)	61/20/0/0/19	58/21/1/1/19
Light chain κ/λ (%)	57/27/16	51/38/11
β ₂ -microglobulin (>3/<3/missing; %)	61/37/5	67/34/3
Bone pain (none/mild/requires narcotic/missing; %)	31/37/30/2	37/23/40/0

Source: D_DEMOBL.xpt

Reviewer's Comments:

1. This dataset corroborates information presented in the Applicant's study report.
2. Approximately 52 % of the E1A00 study population was over 70 years of age and 10 % was non-Caucasian.
3. Only two patients were receiving anticoagulation at randomization. Both had atrial fibrillation and both were in the Thal/Dex treatment arm.
4. Baseline demographics appeared well-balanced between treatment arms.

Patient Disposition during Protocol Therapy:

Two hundred and three of the 207 randomized patients comprised the *safety population*, defined as those patients who received at least one dose of study medication. The Applicant excluded three patients from the safety population because they were randomized but did not receive study treatment (10016 and 10075) or because no study data was submitted (10532).

Two hundred patients comprised the *efficacy population*, defined as those who were randomized and met all eligibility criteria. The Applicant excluded five patients from the efficacy population

because baseline laboratory values did not show measurable disease or M-protein levels (10041, 10047, 10085, 10108, and 10113), and two were excluded because they lacked sufficient data to confirm eligibility (10116 and 10532).

Reviewer's Table 10: E1A00 patient disposition for first 4 cycles

Population	Number of Patients (%)		
	Thal/Dex	Dex alone	Total
All randomized (ITT)	103 (100 %)	104 (100 %)	207 (100 %)
Safety ^a	102 (99.0 %)	102 (98.1 %)	204 (98.6 %)
Efficacy ^b	99 (96.1 %)	101 (97.1 %)	200 (96.6 %)

Source: ^a D_DEMOBL where SAFC = yes, by RXARMC

^b D_DEMOBL where EEC = yes, by RXARMC

Reviewer's Comments:

1. This datasets corroborated information presented in CRFs and the Applicant's study report.
2. Patients excluded from the safety and efficacy populations were relatively few, were excluded for appropriate reasons, and appeared well-balanced between treatment arms. These exclusions therefore unlikely biased study conclusions.

One hundred twenty-seven (62.3 %) of the 204 patients in the safety population completed four cycles of protocol treatment, and 77 (37.7 %) discontinued treatment before completing 4 cycles.

Reviewer's Table 11: Disposition of safety population (n = 204) during first four cycles

Disposition	Thal/Dex	Dex alone	Overall
Completed four cycles	65 (63.7 %)	62 (60.8 %)	127 (62.3 %)
Did not complete four cycles	37 (36.3 %)	40 (39.2 %)	77 (37.7 %)
Total	102 (100 %)	102 (100 %)	204 (100 %)

For the 77 patients who discontinued treatment before completing 4 cycles, the Applicant reported 7 possible reasons for discontinuation. These are summarized in Reviewer's Table 12.

Reviewer's Table 12: Reported reasons for discontinuing protocol treatment

Reason for discontinuation	Thal/Dex	Dex alone	Overall
Disease progression/relapse	2 (2.0 %)	10 (9.8 %)	12 (5.9 %)
Toxicity	26 (25.5 %)	13 (12.7 %)	39 (19.1 %)
Withdrawal of consent	1 (1.0 %)	5 (4.9 %)	6 (2.9 %)
Alternative therapy	1 (1.0 %)	2 (2.0 %)	3 (1.5 %)
Other complicating disease	2 (2.0 %)	1 (1.0 %)	3 (1.5 %)
Death (without progression)	3 (2.9 %)	4 (3.9 %)	7 (3.4 %)
Other	1 (1.0 %)	5 (4.9 %)	6 (2.9 %)
Missing	1 (1.0 %)	0	1 (0.5 %)
Total	37 (36.3 %)	40 (39.2 %)	77 (37.7 %)

Source D_DISP; where SAFC = yes, C4COMPC = No; by REASONC and RXARMC

Reviewer's Comments:

1. A similar proportion of patients in each treatment arm completed 4 cycles of protocol therapy.
2. More patients in the Thal/Dex treatment arm discontinued treatment because of toxicity, suggesting that combination therapy is more toxic.
3. More patients on the dexamethasone-alone treatment arm discontinued treatment because of disease progression or relapse, suggesting that thalidomide increases the antimyeloma activity of dexamethasone. Alternatively, because the trial was unblinded, patients could have preferentially withdrawn consent for dexamethasone-alone.

The Applicant listed ten patients as having discontinued treatment during the first 4 cycles because of “other”, “missing” or “alternative therapy”. These are summarized in Reviewer’s Table 13.

Reviewer’s Table 13: Selected early treatment discontinuations

Reason for early discontinuation	Thal/Dex	Dex alone
Other	Patient 10503	Patients 10047, 10125, 10163, 10517, and 10536
Missing	Patient 10054	None
Alternative therapy	Patient 10150	Patients 10148 and 10165

Source D_DISP; where SAFC = yes, C4COMPC = No; by REASONC and RXARMC

Reviewer’s Comment: It is unclear how many of these 10 patients discontinued treatment because of lack of efficacy as opposed to unacceptable toxicity. Since these patients represent < 5 % of the population, this information would probably not have significantly altered the study conclusions.

Efficacy of Protocol Therapy:

The primary efficacy variable specified in the statistical analysis plan was best ECOG response (CR, NCR or PR) during the first 4 cycles of treatment. The Applicant claimed that in the ITT population (n = 207), 62 of 103 (60.2 %) of patients in the Thal/Dex treatment arm and 40 of 104 (38.5 %) patients in the dexamethasone-alone arm met that primary endpoint (1-sided Fisher Exact $p = 0.001$). The Applicant’s reported primary efficacy data are summarized in Reviewer’s Table 14.

Reviewer’s Table 14: Applicant’s derived best response, first 4 cycles (ITT pop.)

ECOG response	Thal/Dex n (%)	Dex alone n (%)	<i>P</i> (one-sided Fisher Exact)
CR	5 (4.9)	1 (0.9)	
NCR	0	1 (0.9)	
PR	57 (55.3)	38 (36.5)	
SD	21 (20.3)	40 (38.4)	
PD	2 (1.9)	3 (2.8)	
Not evaluable	17 (16.5)	21 (20.2)	
Total	62 (60.2 %)	40 (38.5 %)	0.001

Source: D_RESP.JMP by RXARM and RESP4MC

Reviewer's comment: The Applicant claimed that primary endpoint was met by more patients in the Thal/Dex treatment arm than in the dexamethasone-alone arm. This difference was due to higher numbers of CRs and PRs, but not NCRs, in the Thal/Dex treatment arm.

At the first interim analysis, the Applicant calculated the rate of *monitored* AEs (grade ≥ 3 thrombosis/embolism, rash, neuropathy, or bradycardia or any grade 4 AE) to be 41.0 % for the Thal/Dex treatment arm and 16.0 % for the dexamethasone-alone arm. This difference was due primarily to an increased rate of thrombosis/embolism in the Thal/Dex arm. The *p*-value for this difference (0.023) exceeded the Pocock boundary of < 0.001 that would have required stopping the trial at any of the interim analyses for excessive toxicity in one treatment group. The interim response rate calculated by the Applicant was also higher than expected in the Thal/Dex treatment arm as compared to the dexamethasone-alone arm (79.0% vs. 49.0%; *p* = 0.0030), and exceeded the O'Brien-Fleming boundaries for rejecting the null hypothesis. As all patients were accrued to the trial and had completed a minimum of four cycles of therapy, the Data Monitoring Committee considered that the benefit of combination therapy outweighed the associated risks, and in collaboration with the NCI CTEP allowed the study to continue.

ECOG adjudicated and assigned patient responses using data tabulated in CSR Listing 16.2.6.2), which was in turn obtained from ECOG CRFs. The Applicant submitted these responses to the FDA as *derived datasets* (define.pdf). The Applicant stated, however, that it was not possible to "derive" these responses solely using the *raw datasets* submitted. I therefore reviewed Listing 16.2.6.2 for each patient that the Applicant claimed as having met the primary response endpoint, and adjudicated each claimed response independently, using ECOG, SWOG, and EBMT response criteria. My findings are summarized in Reviewer's Tables 15 and 16.

Reviewer's Table 15: Applicant's claimed PR or better to Thal/Dex, first 4 cycles (ITT pop.)

Patient	Applicant's Claim ^a	FDA Analysis ^b		
		ECOG	SWOG	EBMT
10004	PR	No	No	No
10007	PR	PR	OR	PR
10010	PR	No	No	No
10013	PR	No	No	No
10015	PR	No	No	No
10017	PR	PR	OR	PR
10022	PR	No	No	No
10025	PR	PR	Imp	PR
10027	PR	PR	OR	PR
10031	PR	PR	Imp	PR
10032	PR	No	No	No
10034	PR	PR	Imp	PR
10037	CR	CR	OR	CR
10038	CR	No	No	No
10042	PR	No	No	No
10046	PR	No	No	No
10048	PR	No	No	No
10050	PR	No	No	No

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10059	PR	No	No	No
10061	PR	PR	No	No
10062	PR	No	No	No
10063	PR	No	No	No
10068	PR	PR	OR	PR
10069	PR	No	No	No
10073	PR	PR	OR	PR
10076	PR	PR	OR	PR
10079	PR	PR	OR	PR
10080	PR	No	No	No
10083	PR	No	No	No
10087	PR	PR	OR	PR
10090	CR	CR	OR	CR
10094	PR	PR	OR	PR
10095	PR	No	No	No
10100	PR	No	No	No
10106	CR	CR	OR	CR
10108	PR	No	No	No
10111	PR	No	No	No
10114	PR	No	No	No
10118	PR	PR	No	No
10121	PR	No	No	No
10122	PR	No	No	No
10135	CR	NCR	OR	PR
10137	PR	No	No	No
10141	PR	No	No	No
10145	PR	No	No	No
10146	CR	NCR	OR	PR
10152	PR	No	No	No
10156	PR	No	No	No
10157	PR	PR	No	No
10159	PR	No	No	No
10164	PR	PR	Imp	PR
10166	PR	PR	OR	PR
10506	PR	No	No	No
10507	PR	No	No	No
10513	PR	PR	No	No
10516	PR	PR	OR	PR
10518	PR	PR	OR	PR
10521	PR	No	No	No
10522	PR	No	No	No
10528	PR	No	No	No
10533	PR	No	No	No
10539	PR	No	No	No
Total	62 (60.2 %)	25 (24.3 %)	21 (20.4 %)	21 (20.4 %)

Source: ^aD_RESP where RXARMC = Thal/Dex and RESP4M <3

^b Patient listing 16.2.6.2 in CSR and KLDSAS.jmp

Reviewer's Comment: I agreed with the 23 of the 62 patients which the Applicant claimed as having met the primary endpoint in the Thal/Dex treatment arm, plus assessed two claimed CRs as an NCR, for an ECOG response rate of 25/104 (24.3 %). My calculated response rates in the Thal/Dex arm by SWOG and EBMT criteria were each 20.4 %.

Reviewer's Table 16: Applicant's claimed PR or better to Dex-alone, first 4 cycles (ITT pop.)

Patient	Applicant's Claim ^a	FDA Analysis ^b		
		ECOG	SWOG	EBMT
10005	PR	No	No	No
10018	PR	No	No	No
10020	PR	PR	OR	PR
10023	PR	PR	Imp	PR
10026	PR	No	No	No
10029	PR	PR	OR	PR
10035	PR	No	No	No
10040	PR	PR	No	No
10045	PR	No	No	No
10049	PR	PR	OR	PR
10053	PR	No	No	No
10057	PR	PR	No	PR
10064	NCR	NCR	OR	PR
10065	PR	No	No	No
10072	PR	No	No	No
10074	PR	PR	No	No
10078	PR	No	No	No
10086	PR	PR	OR	PR
10092	PR	PR	OR	PR
10096	PR	No	No	No
10097	PR	No	No	No
10099	PR	No	No	No
10101	PR	PR	OR	PR
10105	PR	No	No	No
10120	PR	No	No	No
10123	PR	PR	Imp	PR
10124	PR	No	No	No
10128	PR	No	No	No
10133	PR	PR	OR	PR
10140	PR	No	No	No
10153	PR	No	No	No
10155	PR	PR	Imp	PR
10161	PR	PR	No	No
10165	PR	No	No	No
10167	PR	No	No	No
10505	PR	PR	OR	PR

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10510	PR	No	No	No
10519	PR	PR	OR	PR
10523	PR	PR	Imp	PR
10534	PR	No	No	No
Total	40 (38.5 %)	18 (17.3 %)	14 (13.5 %)	15 (14.4 %)

Source: ^a D_RESP where RXARMC = Dex and RESP4M <3

^b CSR listing 16.2.6.2 and KLDSAS jmp

Reviewer's Comment: I agreed with the Applicant's adjudication of the primary endpoint in 18 of the 40 patients in the dexamethasone-only treatment arm, for an ECOG response rate of 17.3 %. In the other 22 patients, I disagreed with the Applicant's assessment. My calculated response rates in the dexamethasone-only arm by SWOG and EBMT criteria were 13.5 % and 14.4 %, respectively.

Differences in response rates between treatment arms by FDA adjudication were then analyzed using the Fisher Exact test. These findings are summarized in Reviewer's Table 19.

Reviewer's Table 17: Response rates by treatment arm, FDA adjudication (ITT pop.)

Response	Thal/Dex (n = 103) n (%)	Dex alone (n = 104) n (%)	P (one-sided Fisher Exact)
ECOG CR, NCR, or PR	25 (24.3 %)	18 (17.3)	0.306
SWOG OR or Improvement	21 (20.4 %)	14 (13.5)	
EBMT PR or CR	21 (20.4 %)	15 (14.4)	

Source: Reviewer's Tables 15 and 16

Reviewer's Comment: Differences in response rates between treatment arms by FDA adjudication did not meet the conventional definition of statistical significance either by ECOG or by standard response criteria.

For those 25 patients in the Thal/Dex treatment arm and 18 patients in the dexamethasone-alone arm whom I agreed met the primary endpoint ECOG CR, NCR, or PR at 4 months, I analyzed the time to first response. These findings are summarized in Reviewer's Table 18 and 19.

Reviewer's Table 18: Time to response (Thal/Dex; n = 25)

Patient	ECOG Response	Time to Response (days) ^a	Subsequent Treatment ^b
10007	PR	30	HDC/autol. Transplant
10017	PR	32	Pt assistance program
10025	PR	30	None
10027	PR	28	None
10031	PR	94	Cyclophosphamide
10034	PR	29	None
10037	CR	35	HDC/autol. Transplant
10061	PR	31	Bisphosphonate infusion
10068	PR	87	Unspec. Chemotherapy
10073	PR	114	HDC/autol. Transplant

10076	PR	58	HDC/autol. transplant
10079	PR	127	Dexamethasone
10087	PR	86	HDC/autol. Transplant
10090	CR	117	None
10094	PR	34	HDC/autol. Transplant
10106	CR	84	HDC/autol. Transplant
10118	PR	51	None
10135	NCR	92	None
10146	CR	89	RT to L1-L5
10157	PR	58	Cyclophosphamide
10164	PR	28	Thalidomide100 mg/d
10166	PR	36	HDC/autol. Transplant
10513	PR	96	None
10516	PR	119	Unspec. Hormonal
10518	PR	120	Unspec. hormonal

Source: ^a CSR listing 16.2.6.2

^b BALTFW.jsp, BANPRX.jsp, and KJFWUP.jsp

Reviewer's Table 19: Time to response (Dex-alone; n = 18)

Patient	ECOG Response	Time to Response (days) ^a	Subsequent Treatment ^b
10020	PR	61	None
10023	PR	60	Dexamethasone
10029	PR	85	Unspec Tx for anemia
10040	PR	26	Melphalan and pred.
10049	PR	29	None
10057	PR	54	Thalidomide
10064	NCR	57	HDC/autol. transplant
10074	PR	56	Thalidomide
10086	PR	32	None
10092	PR	30	HDC/autol. Transplant
10101	PR	81	HDC/autol. Transplant
10123	PR	32	None
10133	PR	118	HDC/autol. Transplant
10155	PR	106	HDC/autol. Transplant
10161	PR	113	HDC/autol. Transplant
10505	PR	63	None
10519	PR	28	None
10523	PR	51	HDC/allog. Transplant

Source: ^a CSR listing 16.2.6.2

^b BALTFW.jsp, BANPRX.jsp, and KJFWUP.jsp

Using data compiled in reviewer's tables 18 and 19, I summarized the times to response in both treatment arms. These comparisons are presented in Reviewer's table 26 terms of mean, median, and range.

Reviewer's Table 20: response from tables 18 and 19 above