

| Time to response (days) | Thal/Dex (n = 25) | Dex-alone (n = 18) |
|-------------------------|----------------------|-----------------------|
| Mean | 68 | 60 |
| Median | 78 | 56 |
| Range | 22 – 447 | 26 – 118 |

Reviewer's Comments:

1. Mean and median times to response appeared fairly similar between treatment arms.
2. Study ECOG E1A00 was not designed to assess response duration. Because these data were not systematically recorded and post-study treatment was nonrandomized, I could not draw conclusions regarding response duration within or between treatment arms.

I disagreed with the Applicant's adjudication of the primary endpoint (ECOG CR, NCR or PR at 4 months) for 41 patients in the Thal/Dex treatment arm and 22 patients in the dexamethasone-alone arm. Reasons for these disagreements are summarized case by case below (Tables 21 and 22).

Reviewer's Table 21: Applicant-FDA differences in adjudication, Thal/Dex (n = 40)

| Patient | ECOG Response at 4 months | | Reason for Disagreement | | | | |
|---------|---------------------------|-----|-------------------------|---------|-------------|-------------|------------------------|
| | Applicant | FDA | Serum M | Urine M | Bone Marrow | Skel. Surv. | Hb or Ca ⁺⁺ |
| 10004 | PR | No | NB | OK | OK | NB | OK |
| 10010 | PR | No | OK | NB, NA | OK | NB | OK |
| 10013 | PR | No | OK | OK | OK | NB | OK |
| 10015 | PR | No | OK | NA | OK | OK | OK |
| 10022 | PR | No | OK | NA | OK | OK | OK |
| 10032 | PR | No | OK | OK | NR | NB | OK |
| 10038 | CR | No | NC | NC | OK | OK | OK |
| 10042 | PR | No | Incon | Incon | OK | NB | OK |
| 10046 | PR | No | OK | NC | OK | OK | OK |
| 10048 | PR | No | OK | OK | OK | P | OK |
| 10050 | PR | No | OK | P | OK | OK | OK |
| 10059 | PR | No | OK | NA | NR | P | OK |
| 10062 | PR | No | NB, Inad | NB,NA | NR | OK | OK |
| 10063 | PR | No | OK | OK | OK | NB | OK |
| 10069 | PR | No | OK | NC | OK | OK | OK |
| 10080 | PR | No | OK | OK | NR | P | OK |
| 10083 | PR | No | Inad | OK | OK | NB | OK |
| 10095 | PR | No | OK | OK | OK | NB | OK |
| 10100 | PR | No | OK | Inad | NR | P | OK |
| 10108 | PR | No | OK | NA | NR | P | OK |
| 10111 | PR | No | OK | NC | OK | P | OK |
| 10114 | PR | No | NC | NB, NA | OK | OK | OK |
| 10121 | PR | No | OK | NA | P | NB | OK |
| 10122 | PR | No | NA | NB, NA | NR | P | OK |
| 10135 | CR | NCR | IEF | IEF | OK | OK | OK |

Clinical Review
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Thalidomide (Thalomid)

| | | | | | | | |
|--------------|----|-----------|-----------|-----------|----------|-----------|----------|
| 10137 | PR | No | OK | NB, NA | NR | P | OK |
| 10141 | PR | No | OK | NC | NR | NA | OK |
| 10145 | PR | No | OK | NB, NC | NR | NA | OK |
| 10146 | CR | NCR | OK | OK | NA | OK | OK |
| 10152 | PR | No | OK | Inad | OK | NB | OK |
| 10156 | PR | No | OK | NB, NA | NR | NB | OK |
| 10159 | PR | No | OK | NB, NA | OK | NB | OK |
| 10506 | PR | No | NC | OK | OK | P | OK |
| 10507 | PR | No | OK | OK | NR | NB | OK |
| 10521 | PR | No | OK | NC | NR | NB | OK |
| 10522 | PR | No | OK | OK | OK | NB | OK |
| 10528 | PR | No | OK | NC | NR | NB | OK |
| 10533 | PR | No | NC | Inad | NR | OK | OK |
| 10539 | PR | No | OK | NC | NR | NB | OK |
| Total | | 40 | 10 | 28 | 1 | 28 | 0 |

OK = meets ECOG criterion

NR = *not required* for claimed response category (e.g. bone marrow for NCR or PR)

NB = *no baseline* value measured

Inad = *inadequate* response (i.e. serum or urine paraprotein level decreased but not enough to meet definition of response)

Incon = data listings and datasets are *inconsistent*

NC = serum or urine paraprotein response *not confirmed* by a second sample

NA = *not assessed* at time of serum or urine paraprotein response

P = *progressed* at time of serum or urine paraprotein response

IEF = *immunoelectrophoresis* not submitted

Reviewer's Table 22: Applicant-FDA differences in adjudication, Dex-only (n = 22)

| Patient | Applicant's Claimed ECOG Response at 4 months | Reason for Disagreement | | | | | Hb or Ca ⁺⁺ |
|---------|---|-------------------------|---------|-------------|-------------|----|------------------------|
| | | Serum M | Urine M | Bone Marrow | Skel. Surv. | | |
| 10005 | PR | OK | NB, NA | NR | NA | OK | |
| 10018 | PR | NC | OK | NR | NA | OK | |
| 10026 | PR | NB, NC | NC | NR | P | NC | |
| 10035 | PR | OK | NA | OK | OK | OK | |
| 10045 | PR | NB, NC | OK | OK | P | OK | |
| 10053 | PR | OK | NC | OK | OK | OK | |
| 10065 | PR | OK | NA | NR | P | OK | |
| 10072 | PR | OK | NC | OK | P | OK | |
| 10078 | PR | OK | NA | NR | NA | OK | |
| 10096 | PR | OK | NB, NA | OK | OK | OK | |
| 10097 | PR | NB, NC | OK | OK | OK | OK | |
| 10099 | PR | OK | NB, NA | NR | NA | OK | |
| 10105 | PR | OK | OK | NR | P | OK | |
| 10120 | PR | I | I | OK | OK | OK | |
| 10124 | PR | OK | NA | OK | OK | OK | |
| 10128 | PR | OK | P | OK | P | OK | |
| 10140 | PR | OK | NB, NA | NR | NA | OK | |
| 10153 | PR | OK | NB, NA | NR | NA | NC | |

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Thalidomide (Thalomid)

| | | | | | | |
|--------------|-----------|----------|-----------|----------|-----------|----------|
| 10165 | PR | OK | NB, NA | OK | OK | OK |
| 10167 | PR | NC | NB, NA | OK | NA | OK |
| 10510 | PR | I | OK | OK | NA | OK |
| 10534 | PR | OK | NC | NR | NA | OK |
| Total | 22 | 7 | 16 | 0 | 15 | 2 |

Key: same as Reviewer's Table 28

Reviewer's Comments:

1. The most frequent reasons for Applicant-FDA disagreement on the primary endpoint (28 cases in the Thal/Dex treatment arm and 16 cases in the dexamethasone-alone arm) involved measurement of 24-hour urinary paraprotein.
2. For 5 patients in the Thal/Dex treatment arm and 6 patients in the dexamethasone-alone arm, a 24-hour urine paraprotein value was the *only* criterion preventing achievement of the primary endpoint.
3. The second most frequent reason for disagreement (28 cases in the Thal/Dex treatment arm and 15 in the dexamethasone-alone arm) was absence or progression of radiographic bone surveys.
4. The bone marrow plasma cell burden did not increase more than 25% in any patient during the first 4 cycles of treatment. Absence of repeat bone marrow assessment was not a cause for disagreement in any instance in the dexamethasone-only treatment arm because ECOG criteria for NCR and PR do not require repeat bone marrow assessments.

Data from Reviewer's Table 21 and 22 indicate that significant quantities of efficacy data were found to be either *missing* or *uninterpretable* for the ITT population. Those instances are summarized below in Reviewer's Table 23. This table does not include those patients for whom study data were *missing* but *not required*. Examples of the latter are patients who were removed from the study or whose serum or urine paraprotein values that were not repeated because they were undetectable at baseline.

Reviewer's Table 23: Missing or uninterpretable efficacy data (ITT pop.)^a

| Parameter | Thal/Dex (n = 103) | Dex alone (n = 104) | Total (n = 207) |
|--|-----------------------|------------------------|--------------------|
| Serum paraprotein | | | |
| Baseline | 6 (5.8 %) | 5 (4.8 %) | 11 (5.3 %) |
| Time of claimed response | 11 (10.7 %) | 12 (11.5 %) | 23 (11.1 %) |
| Claimed response confirmation | 18 (17.5 %) | 18 (17.3 %) | 36 (17.4 %) |
| Urine paraprotein | | | |
| Baseline | 27 (26.2 %) | 40 (38.5 %) | 67 (32.4 %) |
| Time of claimed response | 44 (42.7 %) | 55 (52.9 %) | 99 (47.8 %) |
| Claimed response confirmation | 56 (54.3 %) | 61 (58.6 %) | 117 (56.5 %) |
| Bone marrow | | | |
| Baseline | 6 (5.8 %) | 3 (2.9 %) | 9 (4.3 %) |
| Time of claimed response or confirmation | 32 (31.1 %) | 40 (38.5 %) | 72 (34.8 %) |
| Radiographic skeletal survey | | | |
| Baseline | 101 (98.1 %) | 100 (96.2 %) | 201 (97.1 %) |

| | | | |
|--|-------------|-------------|-------------|
| Time of claimed response or confirmation | 38 (36.9 %) | 36 (34.6 %) | 74 (35.7 %) |
| Hemoglobin and calcium | | | |
| Baseline | 2 (1.9 %) | 0 | 2 (1.0 %) |
| Time of claimed response | 5 (4.9 %) | 4 (3.8 %) | 9 (4.3 %) |
| Claimed response confirmation | 5 (4.9 %) | 6 (5.8 %) | 11 (5.3 %) |

^a patients may have 1 or more missing elements.

Reviewer's Comment:

1. Proportions of data missing from each treatment arm seemed comparable across categories
2. Only 2 of the 207 patients enrolled on Study E1A00 had every piece of data required to fulfill the strict criteria for a confirmed response (i.e. serum and urine paraprotein at baseline, time of response, and at response confirmation; bone marrow and radiographic skeletal survey at baseline and at time of either initial response or response confirmation; and hemoglobin and serum calcium levels at baseline, time of response, and at response confirmation)
3. Urinary paraprotein measurements, bone marrow examinations, and radiographic skeletal surveys tended to be missing relatively frequently. Hemoglobin and serum calcium levels, by contrast, were recorded on schedule for almost every patient.

Data from Reviewer's Table 21 and 22 also indicate those patients in whom efficacy data were collected and submitted but showed either an inadequate response (e.g. stable disease) or frank disease progression. Those instances are summarized below in Reviewer's Table 24.

Reviewer's Table 24: Stable disease or disease progression (ITT pop.)

| Parameter | Thal/Dex (n = 103) | Dex alone (n = 104) | Total (n = 207) |
|--|-----------------------|------------------------|--------------------|
| Serum paraprotein | | | |
| Time of claimed response | 10 (9.7 %) | 23 (22.1 %) | 33 (15.9 %) |
| Claimed response confirmation | 9 (8.7 %) | 38 (36.6 %) | 47 (22.7 %) |
| Urine paraprotein | | | |
| Time of claimed response | 7 (6.8 %) | 12 (11.5 %) | 19 (9.2 %) |
| Claimed response confirmation | 10 (9.7 %) | 11 (10.6 %) | 21 (10.1 %) |
| Bone marrow | | | |
| Time of claimed response or confirmation | 4 (3.9 %) | 4 (3.8 %) | 8 (3.9 %) |
| Radiographic skeletal survey | | | |
| Time of claimed response or confirmation | 16 (15.5 %) | 17 (16.3 %) | 33 (15.9 %) |
| Hemoglobin and calcium | | | |
| Time of claimed response | 0 | 0 | 0 |
| Claimed response confirmation | 0 | 0 | 0 |

Reviewer's comment: Fewer patients receiving Thal/Dex than dexamethasone alone had serum paraprotein values at the time their claimed response or response confirmation that failed to meet protocol-defined efficacy criteria.

As an exploratory analysis, I examined the effect on the primary study endpoint of including as ECOG responders all patients for whom one or more missing 24-hour urine paraprotein measurements (i.e. baseline, time of response, or both) were the *only* criterion preventing achievement of that endpoint. Patients in whom baseline and follow-up 24-hour urine paraprotein excretion were measured but failed to meet ECOG response criteria were not counted as responders in this exploratory analysis. These data are summarized in Reviewer's Tables 25 and 26. Patients whose response designation changed as a result of this exploratory analysis are displayed in bold type.

Reviewer's Table 25: Effect of missing urine on ECOG response, Thal/Dex arm (ITT pop.)

| Patient | Applicant's Claim | Method of Adjudication | |
|--------------|-------------------|------------------------|-----------|
| | | Requiring | Waiving |
| 10004 | PR | No | No |
| 10007 | PR | PR | PR |
| 10010 | PR | No | No |
| 10013 | PR | No | No |
| 10015 | PR | No | PR |
| 10017 | PR | PR | PR |
| 10022 | PR | No | PR |
| 10025 | PR | PR | PR |
| 10027 | PR | PR | PR |
| 10031 | PR | PR | PR |
| 10032 | PR | No | No |
| 10034 | PR | PR | PR |
| 10037 | CR | CR | CR |
| 10038 | CR | No | No |
| 10042 | PR | No | No |
| 10046 | PR | No | PR |
| 10048 | PR | No | No |
| 10050 | PR | No | No |
| 10059 | PR | No | No |
| 10061 | PR | PR | PR |
| 10062 | PR | No | No |
| 10063 | PR | No | No |
| 10068 | PR | PR | PR |
| 10069 | PR | No | PR |
| 10073 | PR | PR | PR |
| 10076 | PR | PR | PR |
| 10079 | PR | PR | PR |
| 10080 | PR | No | No |
| 10083 | PR | No | No |
| 10087 | PR | PR | PR |
| 10090 | CR | CR | CR |
| 10094 | PR | PR | PR |
| 10095 | PR | No | No |
| 10100 | PR | No | No |
| 10106 | CR | CR | CR |

Clinical Review
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Thalidomide (Thalomid)

| | | | |
|-----------------------------|--------------------|--------------------|--------------------|
| 10108 | PR | No | No |
| 10111 | PR | No | No |
| 10114 | PR | No | PR |
| 10118 | PR | PR | PR |
| 10121 | PR | No | No |
| 10122 | PR | No | No |
| 10135 | CR | NCR | NCR |
| 10137 | PR | No | No |
| 10141 | PR | No | No |
| 10145 | PR | No | No |
| 10146 | CR | NCR | NCR |
| 10152 | PR | No | No |
| 10156 | PR | No | No |
| 10157 | PR | PR | PR |
| 10159 | PR | No | No |
| 10164 | PR | PR | PR |
| 10166 | PR | PR | PR |
| 10506 | PR | No | No |
| 10507 | PR | No | No |
| 10513 | PR | PR | PR |
| 10516 | PR | PR | PR |
| 10518 | PR | PR | PR |
| 10521 | PR | No | No |
| 10522 | PR | No | No |
| 10528 | PR | No | No |
| 10533 | PR | No | No |
| 10539 | PR | No | No |
| Total Responders (%) | 62 (60.2 %) | 25 (24.3 %) | 30 (28.8 %) |

Reviewer's Table 26: Effect of missing urine on ECOG response, Dex-alone (ITT pop.)

| Patient | Applicant's Claim | Method of Adjudication | |
|--------------|-------------------|------------------------|-----------|
| | | Requiring | Waiving |
| 10005 | PR | No | No |
| 10018 | PR | No | No |
| 10020 | PR | PR | PR |
| 10023 | PR | PR | PR |
| 10026 | PR | No | No |
| 10029 | PR | PR | PR |
| 10035 | PR | No | PR |
| 10040 | PR | PR | PR |
| 10045 | PR | No | No |
| 10049 | PR | PR | PR |
| 10053 | PR | No | PR |
| 10057 | PR | PR | PR |
| 10064 | NCR | NCR | NCR |

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Thalidomide (Thalomid)

| | | | |
|-----------------------------|--------------------|--------------------|--------------------|
| 10065 | PR | No | No |
| 10072 | PR | No | No |
| 10074 | PR | PR | PR |
| 10078 | PR | No | No |
| 10086 | PR | PR | PR |
| 10092 | PR | PR | PR |
| 10096 | PR | No | PR |
| 10097 | PR | No | No |
| 10099 | PR | No | No |
| 10101 | PR | PR | PR |
| 10105 | PR | No | No |
| 10120 | PR | No | No |
| 10123 | PR | PR | PR |
| 10124 | PR | No | PR |
| 10128 | PR | No | No |
| 10133 | PR | PR | PR |
| 10140 | PR | No | No |
| 10153 | PR | No | No |
| 10155 | PR | PR | PR |
| 10161 | PR | PR | PR |
| 10165 | PR | No | PR |
| 10167 | PR | No | No |
| 10505 | PR | PR | PR |
| 10510 | PR | No | No |
| 10519 | PR | PR | PR |
| 10523 | PR | PR | PR |
| 10534 | PR | No | No |
| Total Responders (%) | 40 (38.5 %) | 18 (17.3 %) | 23 (22.1 %) |

Reviewer's Comment: In this exploratory analysis assuming that missing measurements of 24-hour urine paraprotein excretion would have been within the parameters required to achieve ECOG responses claimed by the Applicant, the ECOG response rate increased in the Thal/Dex treatment arm to 28.8 % and in the dexamethasone-alone arm to 22.1 %.

I compared response rates by treatment arm (1-sided Fisher Exact) and whether or not missing 24-hour urine paraprotein measurements were waived. These results are summarized in Reviewer's Table 27.

Reviewer's Table 27: Best response during first 4 cycles by urine paraprotein (ITT pop.)

| ECOG CR, NCR, or PR | Thal/Dex (n = 103) | Dex alone (n = 104) | P (one-sided Fisher Exact) |
|--|---------------------------|----------------------------|-----------------------------------|
| Requiring three 24-h urine paraprotein samples (at baseline, time of response, and confirmatory) | 25 (24.3 %) | 18 (17.3 %) | 0.306 |
| Waiving missing 24-h urine paraprotein samples | 30 (29.1 %) | 23 (22.1 %) | 0.134 |

Reviewer's Comment: The difference in response rates between treatment arms after inclusion of patients with missing 24-hour urine paraprotein values was not statistically significant.

As a second exploratory analysis, I examined the effect on the primary study endpoint of including as ECOG responders all patients for whom one or more missing radiographic bone surveys (i.e. baseline, time of response, or both) were the *only* criterion preventing achievement of that endpoint. Patients in whom radiographic *progression* prevented achievement of the primary endpoint were not considered as responders in this exploratory analysis. These data are summarized in Reviewer's Tables 31 and 32. Patients whose response designation in this exploratory analysis differs from my adjudication based on strict criteria (tables 15 and 16) are displayed in bold type.

Reviewer's Table 28: Impact of missing radiographs on ECOG response, Thal/Dex (ITT pop.)

| Patient | Applicant's Claim | Method of Adjudication | |
|--------------|-------------------|------------------------|-----------|
| | | Requiring | Waiving |
| 10004 | PR | No | No |
| 10007 | PR | PR | PR |
| 10010 | PR | No | No |
| 10013 | PR | No | PR |
| 10015 | PR | No | No |
| 10017 | PR | PR | PR |
| 10022 | PR | No | No |
| 10025 | PR | PR | PR |
| 10027 | PR | PR | PR |
| 10031 | PR | PR | PR |
| 10032 | PR | No | No |
| 10034 | PR | PR | PR |
| 10037 | CR | CR | CR |
| 10038 | CR | No | No |
| 10042 | PR | No | PR |
| 10046 | PR | No | No |
| 10048 | PR | No | No |
| 10050 | PR | No | No |
| 10059 | PR | No | No |
| 10061 | PR | PR | PR |
| 10062 | PR | No | No |
| 10063 | PR | No | PR |
| 10068 | PR | PR | PR |
| 10069 | PR | No | No |
| 10073 | PR | PR | PR |
| 10076 | PR | PR | PR |
| 10079 | PR | PR | PR |
| 10080 | PR | No | PR |
| 10083 | PR | No | PR |
| 10087 | PR | PR | PR |
| 10090 | CR | CR | CR |
| 10094 | PR | PR | PR |

Clinical Review
Michael Brave, M.D.
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Thalidomide (Thalomid)

| | | | |
|-----------------------------|--------------------|--------------------|--------------------|
| 10095 | PR | No | PR |
| 10100 | PR | No | No |
| 10106 | CR | CR | CR |
| 10108 | PR | No | No |
| 10111 | PR | No | No |
| 10114 | PR | No | No |
| 10118 | PR | PR | PR |
| 10121 | PR | No | No |
| 10122 | PR | No | No |
| 10135 | CR | NCR | NCR |
| 10137 | PR | No | No |
| 10141 | PR | No | No |
| 10145 | PR | No | No |
| 10146 | CR | NCR | NCR |
| 10152 | PR | No | No |
| 10156 | PR | No | No |
| 10157 | PR | PR | PR |
| 10159 | PR | No | No |
| 10164 | PR | PR | PR |
| 10166 | PR | PR | PR |
| 10506 | PR | No | No |
| 10507 | PR | No | PR |
| 10513 | PR | PR | PR |
| 10516 | PR | PR | PR |
| 10518 | PR | PR | PR |
| 10521 | PR | No | No |
| 10522 | PR | No | PR |
| 10528 | PR | No | No |
| 10533 | PR | No | No |
| 10539 | PR | No | No |
| Total Responders (%) | 62 (60.2 %) | 25 (24.3 %) | 33 (32.0 %) |

Reviewer's Table 29: Impact of missing radiographs on ECOG response, Dex-alone (ITT pop.)

| Patient | Applicant's Claim | Method of Adjudication | |
|---------|-------------------|------------------------|---------|
| | | Requiring | Waiving |
| 10005 | PR | No | No |
| 10018 | PR | No | No |
| 10020 | PR | PR | PR |
| 10023 | PR | PR | PR |
| 10026 | PR | No | No |
| 10029 | PR | PR | PR |
| 10035 | PR | No | No |
| 10040 | PR | PR | PR |
| 10045 | PR | No | No |
| 10049 | PR | PR | PR |

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

| | | | |
|-----------------------------|--------------------|--------------------|--------------------|
| 10053 | PR | No | No |
| 10057 | PR | PR | PR |
| 10064 | NCR | NCR | NCR |
| 10065 | PR | No | No |
| 10072 | PR | No | No |
| 10074 | PR | PR | PR |
| 10078 | PR | No | No |
| 10086 | PR | PR | PR |
| 10092 | PR | PR | PR |
| 10096 | PR | No | No |
| 10097 | PR | No | No |
| 10099 | PR | No | No |
| 10101 | PR | PR | PR |
| 10105 | PR | No | PR |
| 10120 | PR | No | No |
| 10123 | PR | PR | PR |
| 10124 | PR | No | No |
| 10128 | PR | No | No |
| 10133 | PR | PR | PR |
| 10140 | PR | No | No |
| 10153 | PR | No | No |
| 10155 | PR | PR | PR |
| 10161 | PR | PR | PR |
| 10165 | PR | No | No |
| 10167 | PR | No | No |
| 10505 | PR | PR | PR |
| 10510 | PR | No | No |
| 10519 | PR | PR | PR |
| 10523 | PR | PR | PR |
| 10534 | PR | No | No |
| Total Responders (%) | 40 (38.5 %) | 18 (17.3 %) | 19 (18.3 %) |

I compared response rates by treatment arm (1-sided Fisher Exact) and whether or not missing radiographic skeletal surveys were waived. These results are summarized in Reviewer's Table 30.

Reviewer's Table 30: Best response during first 4 cycles by radiographic data (ITT pop.)

| ECOG CR, NCR, or PR | Thal/Dex (n = 103) | Dex alone (n = 104) | P (one-sided Fisher Exact) |
|---|---------------------------|----------------------------|-----------------------------------|
| Requiring radiographic bone survey at baseline and time of response | 25 (24.3 %) | 18 (17.3 %) | 0.306 |
| Waiving bone survey requirement if missing | 33 (32.0 %) | 18 (18.3 %) | 0.013 |

Reviewer's Comment: The difference in response rates between treatment arms after inclusion of patients with missing radiographic data reached statistical significance.

As a third exploratory analysis, I examined the effect on the primary study endpoint of including as ECOG responders all patients for whom one or more missing serum or urine paraprotein measurements *or* radiographic bone surveys (i.e. baseline, time of response, or both) prevented achievement of that endpoint. Patients for whom paraprotein or radiographic *progression* prevented achievement of the primary endpoint could be considered responders in this exploratory analysis as long as that progression occurred after the primary endpoint would have otherwise been met. These data are summarized in Reviewer's Table 36. Patients whose response designation in this exploratory analysis differed from that which the FDA adjudicated based on strict criteria (Reviewer's Tables 31 and 32) are displayed in bold type.

Reviewer's Table 31: Impact of missing paraprotein *or* radiographic data on ECOG response, Thal/Dex (ITT pop.)

| Patient | Applicant's Claim | Method of Adjudication | |
|--------------|-------------------|------------------------|-----------|
| | | Requiring | Waiving |
| 10004 | PR | No | No |
| 10007 | PR | PR | PR |
| 10010 | PR | No | PR |
| 10013 | PR | No | PR |
| 10015 | PR | No | PR |
| 10017 | PR | PR | PR |
| 10022 | PR | No | PR |
| 10025 | PR | PR | PR |
| 10027 | PR | PR | PR |
| 10031 | PR | PR | PR |
| 10032 | PR | No | No |
| 10034 | PR | PR | PR |
| 10037 | CR | CR | CR |
| 10038 | CR | No | No |
| 10042 | PR | No | PR |
| 10046 | PR | No | PR |
| 10048 | PR | No | PR |
| 10050 | PR | No | No |
| 10059 | PR | No | PR |
| 10061 | PR | PR | PR |
| 10062 | PR | No | No |
| 10063 | PR | No | PR |
| 10068 | PR | PR | PR |
| 10069 | PR | No | PR |
| 10073 | PR | PR | PR |
| 10076 | PR | PR | PR |
| 10079 | PR | PR | PR |
| 10080 | PR | No | PR |
| 10083 | PR | No | PR |
| 10087 | PR | PR | PR |
| 10090 | CR | CR | CR |
| 10094 | PR | PR | PR |
| 10095 | PR | No | PR |

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

| | | | |
|-----------------------------|--------------------|--------------------|--------------------|
| 10100 | PR | No | PR |
| 10106 | CR | CR | CR |
| 10108 | PR | No | No |
| 10111 | PR | No | No |
| 10114 | PR | No | PR |
| 10118 | PR | PR | PR |
| 10121 | PR | No | PR |
| 10122 | PR | No | No |
| 10135 | CR | NCR | NCR |
| 10137 | PR | No | PR |
| 10141 | PR | No | PR |
| 10145 | PR | No | No |
| 10146 | CR | NCR | NCR |
| 10152 | PR | No | No |
| 10156 | PR | No | PR |
| 10157 | PR | PR | PR |
| 10159 | PR | No | PR |
| 10164 | PR | PR | PR |
| 10166 | PR | PR | PR |
| 10506 | PR | No | No |
| 10507 | PR | No | PR |
| 10513 | PR | PR | PR |
| 10516 | PR | PR | PR |
| 10518 | PR | PR | PR |
| 10521 | PR | No | No |
| 10522 | PR | No | PR |
| 10528 | PR | No | PR |
| 10533 | PR | No | No |
| 10539 | PR | No | PR |
| Total Responders (%) | 62 (60.2 %) | 25 (24.3 %) | 48 (46.6 %) |

Reviewer's Table 32: Impact of missing paraprotein *or* radiographic data on response rate, Dex-alone (ITT pop.)

| Patient | Applicant's Claim | Method of Adjudication | |
|--------------|-------------------|------------------------|-----------|
| | | Requiring | Waiving |
| 10005 | PR | No | PR |
| 10018 | PR | No | No |
| 10020 | PR | PR | PR |
| 10023 | PR | PR | PR |
| 10026 | PR | No | No |
| 10029 | PR | PR | PR |
| 10035 | PR | No | PR |
| 10040 | PR | PR | PR |
| 10045 | PR | No | No |
| 10049 | PR | PR | PR |

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

| | | | |
|-----------------------------|--------------------|--------------------|--------------------|
| 10053 | PR | No | PR |
| 10057 | PR | PR | PR |
| 10064 | NCR | NCR | NCR |
| 10065 | PR | No | PR |
| 10072 | PR | No | No |
| 10074 | PR | PR | PR |
| 10078 | PR | No | PR |
| 10086 | PR | PR | PR |
| 10092 | PR | PR | PR |
| 10096 | PR | No | PR |
| 10097 | PR | No | No |
| 10099 | PR | No | No |
| 10101 | PR | PR | PR |
| 10105 | PR | No | PR |
| 10120 | PR | No | No |
| 10123 | PR | PR | PR |
| 10124 | PR | No | PR |
| 10128 | PR | No | PR |
| 10133 | PR | PR | PR |
| 10140 | PR | No | PR |
| 10153 | PR | No | Yes |
| 10155 | PR | PR | PR |
| 10161 | PR | PR | PR |
| 10165 | PR | No | PR |
| 10167 | PR | No | No |
| 10505 | PR | PR | PR |
| 10510 | PR | No | No |
| 10519 | PR | PR | PR |
| 10523 | PR | PR | PR |
| 10534 | PR | No | PR |
| Total Responders (%) | 40 (38.5 %) | 18 (17.3 %) | 29 (27.9 %) |

I compared response rates by treatment arm (1-sided Fisher Exact) and whether or not missing urine paraprotein *or* radiographic skeletal surveys were waived. These results are summarized in Reviewer's Table 33.

Reviewer's Table 33: Best response during first 4 cycles waiving missing data (ITT pop.)

| ECOG CR, NCR, or PR | Thal/Dex (n = 103) | Dex alone (n = 104) | P (one-sided Fisher Exact) |
|---|---------------------------|----------------------------|-----------------------------------|
| Using strict protocol-defined criteria | 25 (24.3 %) | 18 (17.3 %) | 0.306 |
| Waiving missing paraprotein and radiographic data | 48 (46.6 %) | 29 (27.9 %) | 0.003 |

Reviewer's Comment:

1. When patients with missing paraprotein *and* radiographic data were counted as having responded, the difference in response rates between treatment arms during the first 4 cycles is statistically persuasive.
2. I did not apply any statistical adjustment for multiple primary analyses because these analyses were exploratory. Applying a more conservative Bonferroni adjustment for 3 different analyses, the difference would still be significant.

Post-Protocol Therapy:

Of the 207 patients initially randomized to study E1A00, the Applicant listed 4 (1 in the Thal/Dex treatment arm and 3 in the dexamethasone-alone arm) as having progressed during the first 4 treatment cycles and 76 (37 in the Thal/Dex arm and 39 in the dexamethasone-alone arm) as having dropped out during the first 4 treatment cycles for other reasons. One hundred twenty seven patients (65 in the Thal/Dex arm and 62 in the dexamethasone-alone arm) completed all 4 cycles of therapy, and 40 of those patients (27 in the Thal/Dex arm and 13 in the dexamethasone-alone arm) went on the extension phase of treatment. The reasons for which patients discontinued study treatment or enrolled in the protocol extension were summarized previously in other Reviewer’s Table 12 of this review.

Reviewer’s Table 34: Patient disposition beyond first 4 cycles

| Population | Number of Patients (%) | | |
|---|------------------------|-------------|-------------|
| | Thal/Dex | Dex | Total |
| Randomized (ITT) | 103 (100 %) | 104 (100 %) | 207 (100 %) |
| Safety ^a | 102 (99 %) | 102 (98 %) | 204 (99 %) |
| Per protocol (efficacy) ^b | 99 (96 %) | 101 (97 %) | 200 (97 %) |
| Completed 4 treatment cycles ^c | 65 (63 %) | 62 (60 %) | 127 (61%) |
| Enrolled in extension phase ^d | 27 (26 %) | 13 (12 %) | 40 (19 %) |

Source: ^a D_DEMOBL where SAFC = yes, by RXARMC
^b D_DEMOBL where EEC = yes, by RXARMC
^c D_DEMOBL where C4COMP = yes, by RXARMC
^d D_DEMOBL where CNTPRTC = yes, by RXARMC

The Applicant reported best ECOG responses during all cycles (first 4 plus extension phase) of therapy. These reported response rates are presented in Reviewer’s Table 35.

Reviewer’s Table 35: Applicant’s derived best response during all cycles (ITT pop.)

| ECOG Response | Thal/Dex n (%) | Dex alone n (%) |
|---------------|-------------------|--------------------|
| CR | 6 (5.8) | 1 (0.9) |
| NCR | 0 | 1 (0.9) |
| PR | 58 (56.3) | 38 (36.6) |
| SD | 21 (20.3) | 40 (38.5) |
| PD | 2 (1.9) | 3 (2.9) |
| Not evaluable | 16 (15.5) | 21 (20.2) |
| Total | 103 | 104 |

Source: D_RESP.JMP by RXARMC and BORESPC

The impact of the extension phase on the overall ECOG response rate is summarized in Reviewer's Table 36.

Reviewer's Table 36: Impact extension phase on OR rate (Applicant's data; ITT pop.)

| ECOG CR, NCR, or PR) | Thal/Dex n (%) | Dex alone n (%) |
|-----------------------------|---------------------------|----------------------------|
| During first 4 cycles | 62/103 (60.2 %) | 40/104 (38.5 %) |
| During all-cycles | 64/103 (62.1 %) | 40/104 (38.5 %) |

Reviewer's comment: The Applicant's reported only two additional ECOG responses during the extension phase that had not already occurred during the first 4 cycles. As a result, the OR rate increased relatively little during the extension phase of therapy.

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. The Applicant claimed that the primary objective of the study, a difference in prespecified definition of OR rate at 4 months, was met.

My independent review did not confirm the Applicant's primary efficacy claim using strict criteria. The difference between the Applicant's and my adjudication of this endpoint was largely driven by missing urine paraprotein and radiographic data. Determining the response rate by serum or urine paraprotein as opposed to requiring both to have been confirmed resulted in a statistically significant difference between treatment arms in favor of the combination. This analysis is justified by the fact that discordance between serum and urine paraprotein results is rarely if ever seen.

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

7.1 Methods and Findings

7.1.1 Deaths

The Applicant identified three treatment-related deaths – one in each treatment arm within 30 days of the last dose, and one in the dexamethasone-alone arm more than 30 days after the last dose. The Applicant assessed the 2 treatment-related deaths in the Thal/Dex arm as due to pulmonary emboli and suicide, and the single treatment-related death in the dexamethasone-alone arm as due to multiple organ failure. All deaths recorded between randomization and clinical cutoff are summarized in Reviewer’s Table 37.

Reviewer’s Table 37: Deaths by Applicant’s attribution (safety pop.)

| Time period | Thal/Dex (n = 102) | Dex alone (n = 102) |
|---|-----------------------|------------------------|
| During protocol or within 30 days of last dose^a | 11 (10.7 %) | 9 (8.9 %) |
| Assessed as protocol related | 1 (0.9 %) | 1 (0.9 %) |
| Assessed as disease related | 2 (1.9 %) | 2 (1.9 %) |
| Assessed as due to other cause | 8 (7.8 %) | 6 (5.9 %) |
| More than 30 days after last dose^b | 19 (18.6 %) | 17 (16.7 %) |
| Assessed as protocol related | 0 | 1 (0.9) |
| Assessed as disease related | 12 (11.8 %) | 8 (7.8 %) |
| Assessed as due to other cause | 7 (6.9 %) | 6 (5.9 %) |
| Data missing | 0 | 2 (2.0) |
| Total | 30 (29.4 %) | 26 (25.5 %) |

Source: ^a D_DISP; where SAFC = “yes” and DTH30DC or DTHTRT = “yes”; by RXARMC and DTHCAUSEC
^b D_DISP; where SAFC = “yes” and DTHGT30C = “yes”; by RXARMC and DTHCAUSEC

Reviewer’s Comment:

1. The Applicant attributed most deaths during the protocol or within 30 days of the last dose as due to other causes.
2. The Applicant attributed most deaths more than 30 days after the last dose as being either disease-related or due to other causes.
3. Datasets provided corroborated information presented in CFRs.

The Applicant reported a specific cause of death for each patient who died between randomization and the clinical cutoff date (dataset D_DISP; where STATUS = “dead” and SAFC = “yes”; by RXARMC and DTHSPEC). In order to better understand the causes of deaths between randomization and clinical cutoff, I grouped deaths into categories that seemed likely to reflect common processes (Reviewer’s Table 38).

Reviewer’s Table 38: Clinical reviewer’s organization of deaths (safety pop.)

| | Thal/Dex | Dex alone |
|--|----------|-----------|
| | | |

| Category | Reports grouped together | (n = 102) | (n = 102) |
|--------------------------|---|-----------|-----------|
| Unknown | <ul style="list-style-type: none"> Information missing COD unknown, had been discharged with sx improved after Rx for fungal pneumonia Patient was in hospital with multiple problems Multiple myeloma encephalitis | 8 | 8 |
| Primary disease | <ul style="list-style-type: none"> Multiple myeloma Infection, progressive myeloma Multiple myeloma – ESRD Plasmacytoma obstructed function of kidney Progressive myeloma with organ failure Severe anemia 2^o multiple myeloma | 6 | 4 |
| Pulmonary | <ul style="list-style-type: none"> Pneumonia Aspiration pneumonia Respiratory arrest Respiratory arrest – pneumonia Respiratory distress | 2 | 4 |
| Cardiovascular | <ul style="list-style-type: none"> Calcific atherosclerosis with 50% luminal narrowing Cardiac arrest error Cardiac ischemia infarction Myocardial infarction Progressive cardiac cachexia and heart failure | 5 | 0 |
| Stroke | <ul style="list-style-type: none"> CNS bleed Massive stroke Multiple chronic brain infarctions – sepsis | 1 | 2 |
| Thrombotic | <ul style="list-style-type: none"> Extensive pulmonary thromboemboli with severe coronary atherosclerosis Hypotension, pulmonary emboli-cardiopulmonary arrest | 2 | 0 |
| Transplant complications | <ul style="list-style-type: none"> Graft vs. heart disease (suspect misprint) Transplant complications Complications from BMT | 2 | 1 |
| Other malignancy | <ul style="list-style-type: none"> Lung cancer | 0 | 1 |
| Hemorrhagic | <ul style="list-style-type: none"> Massive hemothorax Upper GI bleed 2^o ulcer 2^o dexamethasone, anemia 2^o myeloma | 0 | 2 |
| Sepsis | <ul style="list-style-type: none"> Multiorgan failure Sepsis Septic shock, acute gangrenous cholecystitis Urosepsis | 3 | 3 |
| Renal failure | <ul style="list-style-type: none"> Renal failure | 0 | 1 |
| Suicide | <ul style="list-style-type: none"> Suicide | 1 | |
| Total | | 30 | 26 |

Reviewer's Comments:

1. Discriminating a single "cause" of death is difficult when a patient has several morbid conditions present simultaneously. Each one presumably contributed to the demise or initiated a process that may have led to the next event. The method I used to group causes of death in Reviewer's Table 38 was somewhat arbitrary, creating categories based on my best assumption, given the available information. This analysis is therefore exploratory.
2. Despite this limitation, a trend toward more deaths due to cardiovascular and thrombotic problems seems apparent in the Thal/Dex treatment arm (7 versus 0). This association is discussed in the context of published medical literature in Section 7.2.2.3 of this review.
3. No consistent patterns were apparent for the other causes of death.

The Applicant reported 9 deaths as *possibly*, *probably*, or *definitely* protocol-related. The causes of death for those 9 patients are summarized in Reviewer's Table 39.

Reviewer's Table 39: Protocol-related deaths

| Treatment Arm/Patient | Study Day of Death | Cause of Death |
|-----------------------|--------------------|-------------------------------|
| Thal/Dex | | |
| 10066 | 203 | Cardiac ischemia |
| 10070 | 317 | Infection without neutropenia |
| 10116 | 40 | Infection with unknown ANC |
| 10151 | 88 | Infection with unknown ANC |
| 10503 | 21 | Depression |
| Dex | | |
| 10033 | 120 | Infection/febrile neutropenia |
| 10077 | 71 | Infection without neutropenia |
| 10147 | 118 | Cerebrovascular ischemia |
| 10531 | 80 | Melena/GI bleeding |

Source: D_AE where AESEV = 5 and AEREL ≥ 3; by CASE, AECODEC, and RXARMC

Reviewer's Comment: No single protocol-related cause of death appeared to cluster in the Thal/Dex treatment arm.

7.1.2 Other Serious Adverse Events

Because of the characteristics of the drug, disease, and population, and the overlap of some AEs and outcome measures, all patients in the Thal/Dex treatment arm and all but two patients in the dexamethasone-alone arm experienced at least one AE which the Applicant assessed as possibly, probably, or definitely related to the study medication. These events are tabulated and discussed in detail below in section 7.1.5.

The dose of thalidomide was reduced or interrupted at least once for 34/102 (33.0 %) patients in the Thal/Dex treatment arm during the first four treatment cycles. The median time to first dose reduction or interruption was 49.5 days. Study drug dose-modification is detailed in Reviewer's Table 40.

Reviewer's Table 40: Study drug dose-modification (safety pop.)

| | Thal/Dex (n = 102) | | Dex alone (n = 102) |
|--|--------------------|--------------|------------------------|
| | Thal | Dex | |
| First 4 cycles | | | |
| Thalidomide Dose | | | |
| Maximum > 200 mg/d (n; %) ^a | 101 (98.1 %) | | |
| Maximum > 100 mg/d (n; %) ^b | 1 (1.0 %) | | |
| Mean (mg) ^c | 172.5 | | |
| At least one dose reduction ^d | 34 (33.0 %) | 28 (27.2 %) | 18 (17.3 %) |
| Time to first dose reduction (weeks) | | | |
| Mean ^e | 51.7 | 59.3 | 57.6 |
| Range | 6.0 - 134.0 | 17.0 - 114.0 | 21.0 - 106.0 |
| Overall | | | |
| Thalidomide Dose | | | |
| >200 mg/d ^f | 101 (98.1 %) | | |
| >100 mg/d ^g | 1 (1.0 %) | | |
| Mean ^h | 169.7 | | |
| At least one dose reduction ⁱ | 38 (36.9 %) | 32 (31.1 %) | 20 (19.2 %) |
| Time to first dose reduction (weeks) | | | |
| Mean ^j | 65.6 | 71.7 | 65.6 |
| Range | 6.0 - 366.0 | 17.0 - 198.0 | 21.0 - 142.0 |

^{a,b} D_SDSUM; where SAFC = yes, RXARM = Thal/Dex; by THALMAX4

^c D_SDSUM; where SAFC = yes, RXARMC = Thal/Dex; analyze AVGDOST4 mean

^d D_SDSUM; where SAFC = yes and RXARMC = Thal/Dex or Dex; by REUCT4C or REUCD4C

^e D_SDSUM; where SAFC = yes, RXARMC = Thal/Dex or Dex, and REDUCT4C or REDUCD4C = yes; analyze TTREDT4 mean

^{f,g} D_SDSUM; where SAFC = yes, RXARM = Thal/Dex; by THALMAX4

^h D_SDSUM; where SAFC = yes, RXARMC = Thal/Dex; analyze AVGDOST mean

ⁱ D_SDSUM; where SAFC = yes and RXARMC = Thal/Dex or Dex; by REUCTC or REUCDC

^j D_SDSUM; where SAFC = yes, RXARMC = Thal/Dex or Dex, and REDUCTC = yes; analyze TTREDD or TTREDD mean

Reviewer's Comments:

1. The dataset corroborates information presented in the CSR.
2. Almost every patient in the Thal/Dex treatment arm initially received the protocol-specified 200 mg daily dose.
3. One third thalidomide-treated patients required at least one dose reduction during the first 4 cycles of treatment.
4. More patients in the Thal/Dex treatment arm than in the dexamethasone-alone arm required at least one dose reduction. The reported time to first dose reduction was similar in both treatment arms.

The datasets submitted contain insufficient information to discern which patients required more than one dose reduction or to calculate the frequency of dose delays or interruptions. We queried the Applicant about this point. In response, the Applicant stated that of the 103 patients randomized to the Thal/Dex treatment arm, 5 (4.9 %) required 2 or more dose reductions during the first 4 treatment cycles.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

As previously summarized in Reviewer's Table 11, 77 patients in Study E1A00 – 37 in the Thal/Dex treatment arm and 40 in the dexamethasone-alone arm – failed to complete 4 scheduled treatment cycles. The characteristics of those 77 who dropped out of Study E1A00 before completing 4 treatment cycles are compared with those of the 127 who completed 4 cycles in Reviewer's Table 41.

Reviewer's Table 41: Characteristics of patients who dropped out of study ECOG E1A00

| Characteristic | <u>Dropped out before 4 Cycles^a</u> | | <u>Completed 4 Cycles^b</u> | |
|----------------------------|--|-----------------|---------------------------------------|-----------------|
| | Thal/Dex (n = 37) | Dex (n = 40) | Thal/Dex (n = 65) | Dex (n = 62) |
| Demographic | | | | |
| Gender | | | | |
| Male/ | 18 (49 %) | 25 (62 %) | 34 (52 %) | 34 (55 %) |
| Female | 19 (51 %) | 15 (38 %) | 31 (48 %) | 27 (44 %) |
| Missing (%) | 0 | 0 | 0 | 1 (1 %) |
| Age (years) | | | | |
| Median | 65 | 68 | 64 | 62 |
| Range | (39-83) | (38-83) | (37-82) | (38-78) |
| Caucasian (%) | 30 (81 %) | 36 (90 %) | 59 (91 %) | 52 (84 %) |
| General health | | | | |
| ECOG score | | | | |
| 0 | 14 (38 %) | 14 (35 %) | 29 (45 %) | 25 (40 %) |
| 1 | 20 (54 %) | 18 (45 %) | 30 (46 %) | 28 (45 %) |
| 2 | 3 (8 %) | 8 (20 %) | 6 (9 %) | 9 (15 %) |
| Concurrent chronic disease | | | | |
| Yes | 23 (62 %) | 24 (60 %) | 42 (65 %) | 39 (63 %) |
| No | 14 (38 %) | 15 (38 %) | 22 (34 %) | 23 (37 %) |
| Missing | 0 | 1 (2 %) | 1 (1 %) | 0 |
| History of DVT | | | | |
| Yes | 0 | 0 | 0 | 0 |
| No | 37 (100 %) | 40 (100 %) | 65 (100 %) | 62 (100 %) |
| Multiple myeloma | | | | |
| Stage | | | | |
| I | 4 (11 %) | 7 (18 %) | 10 (15 %) | 10 (16 %) |
| II | 17 (46 %) | 11 (27 %) | 30 (46 %) | 33 (53 %) |
| III | 16 (43 %) | 22 (55 %) | 25 (39 %) | 19 (31 %) |
| Lytic lesions | | | | |
| 0 | 0 | 5 (12 %) | 19 (29 %) | 9 (15 %) |
| 1-3 | 7 (19 %) | 9 (23 %) | 17 (26 %) | 10 (16 %) |
| >3 | 13 (35 %) | 15 (38 %) | 21 (33 %) | 25 (40 %) |
| Missing | 8 (22 %) | 11 (27 %) | 8 (12 %) | 18 (29 %) |
| Serum M-component | | | | |

| | | | | |
|-------------------------------|-----------|------------|-----------|-----------|
| Present | 34 (92 %) | 40 (100 %) | 61 (94 %) | 59 (95 %) |
| Absent | 3 (8 %) | 0 | 4 (6 %) | 2 (3 %) |
| Missing | 0 | 0 | 0 | 1 (2 %) |
| Urine M-component | | | | |
| Present | 30 (81 %) | 34 (85 %) | 52 (80 %) | 50 (81 %) |
| Absent | 5 (14 %) | 6 (15 %) | 11 (17 %) | 10 (16 %) |
| Missing | 2 (5 %) | 0 | 2 (3 %) | 2 (3 %) |
| Heavy chain | | | | |
| IgG | 24 (65 %) | 23 (58 %) | 39 (60 %) | 37 (60 %) |
| IgM | 0 | 0 | 0 | 1 (2 %) |
| IgA | 6 (16 %) | 12 (30 %) | 15 (23 %) | 9 (14 %) |
| Biclonal | 0 | 0 | 0 | 1 (2 %) |
| Missing (%) | 7 (19 %) | 5 (12 %) | 11 (17 %) | 14 (22 %) |
| Light chain | | | | |
| κ | 22 (59 %) | 21 (52 %) | 32 (49 %) | 32 (52 %) |
| λ | 8 (22 %) | 16 (40 %) | 18 (28 %) | 22 (35 %) |
| Missing | 7 (19 %) | 3 (8 %) | 15 (23 %) | 8 (13 %) |
| β ₂ -microglobulin | | | | |
| >3 | 24 (65 %) | 27 (68 %) | 37 (57 %) | 38 (61 %) |
| ≤3 | 11 (30 %) | 13 (32 %) | 26 (40 %) | 21 (34 %) |
| Missing | 2 (5 %) | 0 | 2 (3 %) | 3 (5 %) |
| Bone pain | | | | |
| None | 10 (27 %) | 13 (32 %) | 22 (34 %) | 24 (39 %) |
| Mild | 13 (35 %) | 9 (23 %) | 25 (38 %) | 15 (24 %) |
| Requires narcotic | 13 (35 %) | 18 (45 %) | 18 (28 %) | 23 (37 %) |
| Missing | 1 (3 %) | 0 | 0 | 0 |

Source: ^a D_DISP where COMP4C = No by RXARMC and variable of D_DEMOG

^b D_DISP where COMP4C = Yes by RXARMC and variable of D_DEMOG

Reviewer's Comment: No single pretreatment factor emerged as strongly predictive of the ability to complete 4 cycles of protocol treatment.

7.1.3.2 Adverse events associated with dropouts

The Applicant did not submit in the form of a table or dataset information regarding which AEs led treatment discontinuation. I therefore obtained this information in the following manner:

1. I queried dataset D_DISP for those patients that the Applicant assessed as having terminated treatment because of "Toxicity/side effects/complications (physician directed or patient choice)" or "Death". This query identified a subset of 56 patients (29 in the Thal/Dex treatment arm and 17 in the dexamethasone-alone arm).
2. The Applicant submitted 57 CRFs – 20 in a folder titled *deaths* plus 37 in a folder titled *discontinued*. Those 57 CRFs included 40 of the 56 patients, (27 in the Thal/Dex treatment arm and 13 in the dexamethasone-alone arm) for which dataset D_DISP

indicated toxicity or death led to treatment discontinuation. CRFs appeared to be missing for 7 patients (3 in the dexamethasone-alone treatment arm and 4 in the Thal/Dex arm).

- I examined the 40 available CRFs for whom the Applicant claimed discontinued study treatment because of toxicity or death and in each case tried to identify the AE most responsible for discontinuation. My findings are summarized in Reviewer's Table 42.

Reviewer's Table 42: AEs associated with dropouts

| Patient | Toxicity |
|--|------------------------|
| Thal/Dex Treatment Arm | |
| 10008 | Gastritis |
| 10017 | No CRF submitted |
| 10019 | Infection |
| 10022 | Anxiety |
| 10129 | Myocardial infarction |
| 10131 | No CRF submitted |
| 10137 | Rash |
| 10038 | No CRF submitted |
| 10039 | Rash |
| 10042 | Pneumonia |
| 10052 | Syncope |
| 10061 | Dehydration |
| 10068 | Pancreatitis |
| 10179 | No CRF submitted |
| 10080 | PE and stroke |
| 10081 | Not stated |
| 10088 | Sepsis |
| 10102 | Psychosis |
| 10103 | Malaise |
| 10104 | Pneumonia/PE |
| 10116 | Sepsis |
| 10129 | Myocardial infarction |
| 10137 | Rash |
| 10142 | Weakness |
| 10145 | Sudden death |
| 10146 | No CRF submitted |
| 10156 | Neuropathy |
| 10166 | Pulmonary embolus |
| 10507 | Neuropathy/fatigue |
| 10511 | Pneumonia |
| 10521 | Neuropathy |
| 10535 | Confusion |
| 10539 | Deep venous thrombosis |
| Dexamethasone-alone Treatment Arm | |
| 10012 | Rash (shingles) |
| 10014 | Not stated |

| | |
|-------|--|
| 10020 | Myopathy |
| 10040 | Motor neuropathy, atrial fibrillation, CHF, pneumonia, LV thrombus |
| 10056 | Not stated |
| 10072 | Not stated |
| 10096 | Not stated |
| 10098 | No CRF submitted |
| 10099 | Pneumonia, weakness |
| 10123 | No CRF submitted |
| 10140 | No CRF submitted |
| 10158 | Ocular herpes simplex |
| 10167 | Myopathy |
| 10526 | Not stated |
| 10531 | Bleeding gastric ulcer |
| 10537 | Confusion |

Reviewer's Comments:

1. I discovered specific reasons why treatment was discontinued in varying locations among the 40 CRFs examined. In some, I found the information in Medwatch forms, whereas in others I found it in "off-study forms", progress notes, or hand-written statements in margins of AE forms.
2. In 7 patients for whom no CRFs were submitted, I could not discern a specific reason why the study was terminated.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Primary prespecified safety endpoints in study E1A00 were the severity and timing of AEs and their relationship to study drug. The investigator graded all AEs using National Cancer Institute Cancer Therapy Evaluation Program (NCI/CTEP) Common Toxicity Criteria (v2.0) and assessed their relationship to the protocol therapy.

Because thalidomide is a marketed product but investigational for MM, AEs requiring expedited reporting in patients randomized to study Arm A were reported using the NCI Adverse Expedited Reporting System (AdEERS). AEs requiring expedited reporting that occurred in patients randomized to dexamethasone-alone were reported using the MedWatch system.

Reviewer's Comment: The investigators did not record dates when AEs decreased in severity or resolved, nor did they collect information on what actions, if any (e.g. dose-modification,

symptomatic therapy) were taken in response to individual AEs. It was therefore not possible to calculate AE durations or consequences from the datasets provided.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Applicant used the MedDRA dictionary for classifying AEs and applied it throughout the program. All study centers were in the United States so all AEs were initially recorded in English. Preferred terms were examined for this review and spot-checked against CRFs, particularly for patients who died. The Applicant appears to have classified reports equitably among the treatment groups.

7.1.5.3 Incidence of common adverse events

The Applicant examined and presented the AEs reported for Study E1A00 separately, which is appropriate.

7.1.5.4 Common adverse event tables

Numbers of patients in Study E1A00 experiencing at least 1 treatment-emergent AE are summarized in Reviewer's Table 43.

Reviewer's Table 43: Treatment-emergent AEs in Study E1A00 (safety pop.)

| AE Category | Thal/Dex (n = 102) | Dex alone (n = 102) |
|-------------------------|--------------------|---------------------|
| First 4 cycles | | |
| All grades ^a | 102 (100 %) | 102 (100 %) |
| Grade 3/4 ^b | 84 (82.4 %) | 71 (69.6 %) |
| Grade 3 ^b | 76 (74.5 %) | 65 (63.7 %) |
| Grade 4 ^b | 40 (39.2 %) | 31 (30.4 %) |
| All cycles | | |
| All grades ^c | 102 (100 %) | 102 (100 %) |
| Grade 3/4 ^d | 86 (84.3 %) | 75 (75.3 %) |
| Grade 3 ^g | 78 (76.5 %) | 69 (67.7 %) |
| Grade 4 ^h | 40 (39.2 %) | 31 (30.4 %) |

Source: ^aD_AE where CYCLE <= 4 by CASE and RXARMC; by RXARMC

^bD_AE where CYCLE <= 4, AESEV >=3, 3, or 4, and RXARMC = Thal/Dex or Dex; by CASE

^cD_AE by CASE and RXARMC; by RXARMC

^dD_AE where AESEV >= 3, 3, or 4 and RXARMC = Thal/Dex or Dex; by CASE

Reviewer's Comments:

1. Datasets provided corroborated information presented in the CSR.
2. Total numbers of patients experiencing grade 3 and grade 4 AEs was higher in the Thal/Dex treatment arm than the dexamethasone-alone arm during both the first 4 cycles of treatment and during all cycles.

The Applicant submitted AEs by NCI CTC grade and by MedDRA Organ System Class and Preferred Term. Frequently reported (incidence $\geq 5\%$ overall or $\geq 2\%$ grade 3/4) treatment-emergent AEs are summarized by Organ System Class and Preferred Term below in tables 44 and 45, respectively.

Reviewer's Table 44: Reported treatment-emergent AEs $\geq 5\%$ (all cycles; safety pop.)

| MedDRA Preferred Term | Thal/Dex (n = 102) | | Dex-alone (n = 102) | |
|---------------------------|-------------------------|------------------------|-------------------------|------------------------|
| | All grades ^a | Grade 3/4 ^b | All grades ^c | Grade 3/4 ^d |
| Fatigue | 81 (79.4 %) | 17 (16.7 %) | 72 (70.6 %) | 13 (12.7 %) |
| Hemoglobin | 79 (77.5 %) | 14 (13.7 %) | 88 (86.3 %) | 6 (5.9 %) |
| Hyperglycemia | 74 (72.5 %) | 15 (14.7 %) | 81 (79.9 %) | 18 (17.6 %) |
| Hypocalcemia | 73 (71.3 %) | 11 (10.8 %) | 60 (58.8 %) | 5 (4.9 %) |
| Edema | 58 (56.9 %) | 6 (5.9 %) | 47 (46.1 %) | 4 (3.9 %) |
| Constipation | 56 (54.9 %) | 8 (7.8 %) | 29 (28.4 %) | 1 (1.0 %) |
| Neuropathy-sensory | 55 (53.9 %) | 4 (3.9 %) | 28 (27.5 %) | 1 (1.0 %) |
| Hyponatremia | 44 (43.1 %) | 11 (10.8 %) | 49 (48.0 %) | 13 (12.7 %) |
| Dyspnea | 43 (42.2 %) | 13 (12.7 %) | 32 (31.4 %) | 15 (14.7 %) |
| Muscle weakness | 41 (40.2 %) | 6 (5.9 %) | 38 (37.3 %) | 13 (12.7 %) |
| Creatinine | 36 (35.5 %) | 1 (1.0 %) | 43 (42.2 %) | 4 (3.9 %) |
| Leukocytes | 36 (36.5 %) | 6 (5.9 %) | 30 (29.4 %) | 3 (2.9 %) |
| Neutrophils | 32 (31.4 %) | 10 (9.8 %) | 24 (23.5 %) | 10 (9.8 %) |
| Bone pain | 31 (30.4 %) | 5 (5.9 %) | 37 (36.3 %) | 11 (10.8 %) |
| Rash/desquamation | 31 (30.4 %) | 4 (3.9 %) | 18 (17.6 %) | 2 (2.0 %) |
| Anorexia | 29 (28.4 %) | 4 (3.9 %) | 25 (24.5 %) | 2 (2.0 %) |
| Confusion | 29 (28.4 %) | 9 (8.8 %) | 12 (11.8 %) | 3 (2.9 %) |
| Nausea | 29 (28.4 %) | 5 (5.9 %) | 23 (22.5 %) | 1 (1.0 %) |
| Alkaline phosphatase | 27 (26.5 %) | 0 | 29 (28.4 %) | 1 (1.0 %) |
| Anxiety/agitation | 26 (25.5 %) | 1 (1.0 %) | 14 (13.7 %) | 3 (2.9 %) |
| Tremor | 26 (25.5 %) | 1 (1.0 %) | 6 (5.9 %) | 0 |
| Pain-other | 25 (24.5 %) | 4 (3.9 %) | 26 (25.5 %) | 3 (2.9 %) |
| SGOT | 25 (24.5 %) | 2 (2.0 %) | 24 (23.5 %) | 2 (2.0 %) |
| Fever | 24 (23.5 %) | 1 (1.0 %) | 20 (19.6 %) | 3 (2.9 %) |
| Platelets | 24 (23.5 %) | 3 (2.9 %) | 34 (33.3 %) | 3 (2.9 %) |
| Hypokalemia | 23 (22.5 %) | 4 (3.9 %) | 23 (22.5 %) | 1 (1.0 %) |
| Insomnia | 23 (22.5 %) | 0 | 48 (47.1 %) | 5 (4.9 %) |
| Thrombosis/embolism | 23 (22.5 %) | 21 (20.6 %) | 5 (4.9 %) | 5 (4.9 %) |
| Weight loss | 23 (22.5 %) | 1 (1.0 %) | 21 (20.6 %) | 2 (2.0 %) |
| Depression | 22 (21.6 %) | 3 (2.9 %) | 24 (23.5 %) | 1 (1.0 %) |
| Neuropathy-motor | 22 (21.6 %) | 8 (7.8 %) | 16 (16.7 %) | 5 (4.9 %) |
| Weight gain | 22 (21.6 %) | 1 (1.0 %) | 13 (12.7 %) | 0 |
| Dry skin | 21 (20.6 %) | 0 | 11 (10.8 %) | 0 |
| Dizziness/lightheadedness | 20 (19.6 %) | 1 (1.0 %) | 14 (13.7 %) | 0 |
| Headache | 20 (19.6 %) | 3 (2.9 %) | 23 (22.5 %) | 0 |
| Hyperkalemia | 19 (18.6 %) | 3 (2.9 %) | 20 (19.6 %) | 2 (2.0 %) |
| Infection w/o neutropenia | 18 (17.6 %) | 6 (5.9 %) | 18 (17.6 %) | 7 (6.9 %) |
| Myalgia | 17 (16.7 %) | 0 | 14 (13.7 %) | 1 (1.0 %) |

| | | | | |
|-----------------------------------|-------------|-----------|-------------|-----------|
| Depressed level of consciousness | 16 (16.7 %) | 3 (2.9 %) | 3 (2.9 %) | 3 (2.9 %) |
| Hypotension | 16 (16.7 %) | 8 (7.8 %) | 15 (14.7 %) | 5 (4.9 %) |
| Cough | 15 (14.7 %) | 0 | 19 (18.6 %) | 0 |
| Bilirubin | 14 (13.7 %) | 2 (2.0 %) | 2 (2.0 %) | 2 (2.0 %) |
| Arthralgia | 13 (12.7 %) | 0 | 10 (9.8 %) | 2 (2.0 %) |
| Diarrhea w/o prior colostomy | 12 (11.8 %) | 1 (1.0 %) | 17 (16.7 %) | 3 (2.9 %) |
| Mouth dryness | 12 (11.8 %) | 1 (1.0 %) | 6 (5.9 %) | 0 |
| Vomiting | 12 (11.8 %) | 2 (2.0 %) | 12 (11.8 %) | 1 (1.0 %) |
| Blurred vision | 11 (10.8 %) | 1 (1.0 %) | 9 (8.8 %) | 1 (1.0 %) |
| Hypertension | 11 (10.8 %) | 0 | 12 (11.8 %) | 9 (8.8 %) |
| Hypoglycemia | 10 (9.8 %) | 2 (2.0 %) | 7 (6.9 %) | 0 |
| Rigors/chills | 10 (9.8 %) | 0 | 2 (2.0 %) | 0 |
| Ataxia | 9 (8.8 %) | 0 | 6 (5.9 %) | 1 (1.0 %) |
| Dehydration | 9 (8.8 %) | 5 (4.9 %) | 7 (6.9 %) | 2 (2.0 %) |
| Hypernatremia | 9 (8.8 %) | 0 | 5 (4.9 %) | 0 |
| Supraventricular arrhythmias | 9 (8.8 %) | 7 (6.9 %) | 4 (3.9 %) | 4 (3.9 %) |
| Taste disturbance | 9 (8.8 %) | 0 | 4 (3.9 %) | 0 |
| Dyspepsia | 8 (7.8 %) | 1 (1.0 %) | 19 (18.6 %) | 1 (1.0 %) |
| Pneumonitis/pulmonary infiltrates | 8 (7.8 %) | 6 (5.9 %) | 8 (7.8 %) | 8 (6.9 %) |
| Sweating | 8 (7.8 %) | 0 | 9 (8.8 %) | 0 |
| Syncope | 8 (7.8 %) | 8 (6.9 %) | 0 | 0 |
| Transfusion: pRBCs | 8 (7.8 %) | 8 (7.8 %) | 1 (1.0 %) | 1 (1.0 %) |
| Dysphagia | 7 (6.9 %) | 3 (2.9 %) | 6 (5.9 %) | 1 (1.0 %) |
| Hypercalcemia | 7 (6.9 %) | 1 (1.0 %) | 11 (10.8 %) | 1 (1.0 %) |
| PT | 7 (6.9 %) | 2 (2.0 %) | 0 | 0 |
| Urinary frequency/urgency | 7 (6.9 %) | 0 | 0 | 0 |
| Cardiac-ischemia | 6 (5.9 %) | 5 (4.9 %) | 2 (2.0 %) | 2 (2.0 %) |
| Hypoalbuminemia | 6 (5.9 %) | 1 (1.0 %) | 1 (1.0 %) | 0 |
| Infection w/ unknown ANC | 6 (5.9 %) | 4 (3.9 %) | 5 (4.9 %) | 2 (2.0 %) |
| Joint, muscle, bone-other | 6 (5.9 %) | 3 (2.9 %) | 7 (6.9 %) | 2 (2.0 %) |
| Sinus bradycardia | 6 (5.9 %) | 0 | 1 (1.0 %) | 0 |

Source: ^a D_AE where RXARM = Thal/Dex; by AECODEC and CASE; by AECODEC

^b D_AE where RXARM = Thal/Dex and AESEV >= 3; by AECODEC and CASE; by AECODEC

^c D_AE where RXARM = Dex; by AECODEC and CASE; by AECODEC

^d D_AE where RXARM = Dex and AESEV >= 3; by AECODEC and CASE; by AECODEC

Reviewer's Table 45: Reported treatment-emergent AEs ≥ 5 % (all cycles; safety pop.)

| MedDRASystem Organ Class | Thal + Dex (n = 102) | | Dex alone (n = 102) | |
|---|----------------------|-------------|---------------------|-------------|
| | All Grades | Grade 3-4 | All Grades | Grade 3-4 |
| Metabolic/Laboratory (hyperglycemia, hypocalcemia, hyponatremia, hyperkalemia, hypercalcemia, acidosis) | 97 (95.1 %) | 33 (32.4 %) | 96 (94.1 %) | 30 (29.4 %) |
| Neurology (neuropathy – sensory, insomnia, depression, confusion, anxiety/agitation, neuropathy – motor, dizziness/lightheaded-ness, | 92 (90.2 %) | 30 (29.4 %) | 76 (74.5 %) | 18 (17.6 %) |

| | | | | |
|---|-------------|-------------|-------------|-------------|
| tremor, seizure, neurologic – other) | | | | |
| Constitutional Symptoms (fatigue, fever, weight loss, weight gain) | 91 (89.2 %) | 19 (18.6 %) | 84 (82.4 %) | 16 (15.7 %) |
| Blood/Bone Marrow (hemoglobin, leukocytes, neutrophils, platelets) | 88 (86.3) | 29 (28.4 %) | 96 (94.1 %) | 19 (18.6 %) |
| Gastrointestinal (constipation, anorexia, nausea, diarrhea, vomiting, mouth dryness, dyspepsia, stomatitis, dehydration, pancreatitis) | 83 (81.4 %) | 19 (18.6 %) | 70 (68.6 %) | 16 (15.7 %) |
| Cardiovascular (edema, thrombosis/embolism, hypotension, hypertension, cardiac ischemia) | 70 (68.6 %) | 37 (36.3 %) | 60 (58.8 %) | 21 (20.6 %) |
| Pain (bone pain, pain-other, headache, myalgia, arthralgia) | 64 (62.7 %) | 10 (9.8 %) | 66 (64.7 %) | 15 (14.7 %) |
| Pulmonary (dyspnea, cough, pneumonia/pulmonary infiltrate, hypoxia, acute resp. distress syndrome) | 52 (51.0 %) | 19 (18.6 %) | 51 (50.0 %) | 20 (19.6 %) |
| Dermatology/Skin (rash/desquamation, dry skin) | 48 (47.1 %) | 5 (4.9 %) | 35 (34.3 %) | 2 (2.0 %) |
| Hepatic (alkaline phosphatase, SGOT, bilirubin, hypoalbuminemia) | 47 (46.1 %) | 7 (6.9 %) | 45 (44.1 %) | 4 (3.9 %) |
| Renal/genitourinary (creatinine, renal failure) | 43 (42.2 %) | 5 (4.9 %) | 49 (48.0 %) | 8 (7.8 %) |
| Musculoskeletal (muscle weakness, joint/muscle/bone-other) | 42 (41.2 %) | 9 (8.8 %) | 41 (40.2 %) | 14 (13.7 %) |
| Infection/febrile neutropenia (infection without neutropenia, Infection with unknown ANC, infection – other) | 23 (22.5 %) | 10 (9.8 %) | 28 (27.5 %) | 13 (12.7 %) |
| Ocular/visual (blurred vision) | 17 (16.7 %) | 0 | 15 (14.7 %) | 0 |
| Cardiovascular arrhythmia (supraventricular arrhythmias, conduction abnormality) | 0 | 11 (10.8 %) | 0 | 5 (4.9 %) |
| Coagulation (DIC, PT) | 0 | 4 (3.9 %) | 0 | 0 |
| Hemorrhage (Melena, GI bleeding) | 0 | 4 (3.9 %) | 0 | 1 (1.0 %) |

Source: ^a D_AE where RXARM = Thal/Dex; by AECODEC and CASE; by AECODEC

^b D_AE where RXARM = Thal/Dex and AESEV \geq 3; by AECODEC and CASE; by AECODEC

^c D_AE where RXARM = Dex; by AECODEC and CASE; by AECODEC

^d D_AE where RXARM = Dex and AESEV \geq 3; by AECODEC and CASE; by AECODEC

Reviewer's Comments:

1. The dataset corroborates information presented in the CSR.
2. Rates of all-grade and grade 3/4 AEs were higher in the Thal/Dex treatment arm than with dexamethasone alone.
3. Sensory and motor neuropathy, tremor, fatigue, constipation, VTE, and rash were more frequent in the Thal/Dex treatment arm than with dexamethasone alone. This toxicity profile is consistent with previously published literature on thalidomide in MM.

7.1.5.4.5 Identifying common and drug-related adverse events

The Applicant submitted AE data using MedDRA Preferred Terms and MedDRA Organ System Class. The latter incompletely captures the most frequent thalidomide-associated AEs described in published literature – sedation, constipation, neuropathy, rash, and VTE. For example, sedation may be categorized as either Neurology (e.g. depression, confusion) or Constitutional (e.g. fatigue), neuropathy as either Neurology (e.g. neuropathy – sensory, tremor, neurologic – other) or Musculoskeletal (muscle weakness), and VTE as either Cardiovascular or Cardiovascular Arrhythmia. Acknowledging these limitations, my analysis of Special Populations (section 8.3) relied on AEs reported under MedDRA Organ System Classes of Constitutional Symptoms, Gastrointestinal, Neurology, Dermatology/Skin, and Cardiovascular as rough approximations of the incidences of sedation, constipation, neuropathy, rash and VTE, respectively.

7.1.5.5 Additional analyses and explorations

Please see section 8.3 (Special Populations).

7.1.6 Less Common Adverse Events

Infrequently reported (incidence < 5 % overall or < 2 % grade 3/4) treatment-emergent AEs are summarized by MedDRA Preferred Term below in Reviewer’s Table 46.

Reviewer’s Table 46: Reported treatment-emergent AEs < 5 % (all cycles; safety pop.)

| MedDRA Preferred Term | Thal/Dex (n = 102) | | Dex-alone (n = 102) | |
|-------------------------|-------------------------|------------------------|-------------------------|------------------------|
| | All grades ^a | Grade 3/4 ^b | All grades ^c | Grade 3/4 ^d |
| Abdominal pain | 5 (4.9 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Cushingoid appearance | 5 (4.9 %) | 0 | 8 (7.8 %) | 0 |
| Hypoxia | 5 (4.9 %) | 5 (4.9 %) | 5 (4.9 %) | 4 (3.9 %) |
| Melena/GI bleeding | 5 (4.9 %) | 3 (2.9 %) | 1 (1.0 %) | 1 (1.0 %) |
| Chest pain | 4 (3.9 %) | 0 | 1 (1.0 %) | 0 |
| Extrapyramidal movement | 4 (3.9 %) | 0 | 2 (2.0 %) | 1 (1.0 %) |
| Hot flashes | 4 (3.9 %) | 0 | 2 (2.0 %) | 0 |
| Neurologic-other | 4 (3.9 %) | 2 (2.0 %) | 2 (2.0 %) | 0 |
| Palpitations | 4 (3.9 %) | 0 | 2 (2.0 %) | 0 |
| Pleural effusion | 4 (3.9 %) | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) |
| Pulmonary-other | 4 (3.9 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Renal failure | 4 (3.9 %) | 2 (2.0 %) | 2 (2.0 %) | 2 (2.0 %) |
| Skin-other | 4 (3.9 %) | 0 | 6 (5.9 %) | 0 |
| Stomatitis | 4 (3.9 %) | 1 (1.0 %) | 14 (13.7 %) | 0 |
| Vertigo | 4 (3.9 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Allergic rhinitis | 3 (2.9 %) | 0 | 6 (5.9 %) | 1 (1.0 %) |

| | | | | |
|------------------------|-----------|-----------|-----------|-----------|
| Arrhythmia-other | 3 (2.9 %) | 0 | 1 (1.0 %) | 0 |
| Conduction abnormality | 3 (2.9 %) | 3 (2.9 %) | 0 | 0 |
| Dry eye | 3 (2.9 %) | 0 | 1 (1.0 %) | 0 |
| Flushing | 3 (2.9 %) | 0 | 5 (4.9 %) | 0 |
| Infection-other | 3 (2.9 %) | 0 | 8 (7.8 %) | 4 (3.9 %) |
| Metabolic-other | 3 (2.9 %) | 0 | 0 | 1 (1.0 %) |
| Neuropathic pain | 0 | 0 | 3 (2.9 %) | 1 (1.0 %) |
| Ocular-other | 3 (2.9 %) | 0 | 2 (2.0 %) | 0 |
| PTT | 3 (2.9 %) | 1 (1.0 %) | 0 | 0 |
| Pruritus | 3 (2.9 %) | 0 | 3 (2.9 %) | 0 |
| SGPT | 3 (2.9 %) | 0 | 0 | 0 |
| Seizure | 3 (2.9 %) | 3 (2.9 %) | 0 | 0 |
| Tearing | 0 | 0 | 3 (2.9 %) | 0 |
| Wound - infectious | 3 (2.9 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| (ARDS) | 2 (2.0 %) | 2 (2.0 %) | 2 (2.0 %) | 2 (2.0 %) |
| Acidosis | 2 (2.0 %) | 2 (2.0 %) | 0 | 0 |
| Arthritis | 2 (2.0 %) | 0 | 1 (1.0 %) | 0 |
| Bruising | 2 (2.0 %) | 0 | 2 (2.0 %) | 0 |
| Constitutional | 2 (2.0 %) | 0 | 1 (1.0 %) | 0 |
| DIC | 2 (2.0 %) | 2 | 0 | 0 |
| Endocrine – other | 0 | 0 | 2 (2.0 %) | 1 (1.0 %) |
| Erythema | 2 (2.0 %) | 1 (1.0 %) | 0 | 0 |
| Flatulence | 2 (2.0 %) | 0 | 2 (2.0 %) | 0 |
| GI-other | 2 (2.0 %) | 0 | 3 (2.9 %) | 0 |
| Gastric ulcer | 0 | 0 | 2 (2.0 %) | 1 (1.0 %) |
| Gastritis | 2 (2.0 %) | 1 (1.0 %) | 0 | 0 |
| Hearing-other | 2 (2.0 %) | 0 | 1 (1.0 %) | 0 |
| Hemoptysis | 0 | 0 | 2 (2.0 %) | 0 |
| Hiccoughs | 2 (2.0 %) | | 5 (4.9 %) | 0 |
| Hyperuricemia | 0 | 0 | 2 (2.0 %) | 0 |
| Hypophosphatemia | 2 (2.0 %) | 1 (1.0 %) | 0 | 0 |
| Incontinence | 2 (2.0 %) | 0 | 2 (2.0 %) | 1 (1.0 %) |
| Memory loss | 2 (2.0 %) | 0 | 3 (2.9 %) | 0 |
| Pancreatitis | 2 (2.0 %) | 2 (2.0 %) | 0 | 0 |
| Personality | 2 (2.0 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Photophobia | 0 | 0 | 2 (2.0 %) | 0 |
| Renal/GU-other | 2 (2.0 %) | 1 (1.0 %) | 0 | 0 |
| Sense of smell | 2 (2.0 %) | 0 | 0 | 0 |
| Ventricular arrhythmia | 2 (2.0 %) | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) |
| Voice changes/stridor | 2 (2.0 %) | 0 | 2 (2.0 %) | 0 |
| Wound - non-infectious | 2 (2.0 %) | 1 (1.0 %) | 0 | 0 |
| Allergic reaction | 1 (1.0 %) | 0 | 1 (1.0 %) | 0 |
| Alopecia | 1 (1.0 %) | 0 | 2 (2.0 %) | 0 |
| Ascites | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) | 0 |
| Bicarbonate | 0 | 0 | 1 (1.0 %) | 0 |
| CPK | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Cardiac troponin I | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |

| | | | | |
|------------------------------------|-----------|-----------|-------------|-----------|
| Cardiac-left ventricular function | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Cardiac-other | 1 (1.0 %) | 0 | 0 | 0 |
| Cerebrovascular ischemia | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) |
| CNS hemorrhage | 0 | 0 | 0 | 1 (1.0 %) |
| Cognitive disturbance | 1 (1.0 %) | 0 | 0 | 0 |
| Colitis | 1 (1.0 %) | 0 | 0 | 0 |
| Conjunctivitis | 1 (1.0 %) | 0 | 1 (1.0 %) | 0 |
| Diarrhea w/ prior colostomy | 1 (1.0 %) | 0 | 0 | 0 |
| Double vision | 1 (1.0 %) | 0 | 1 (1.0 %) | 0 |
| Duodenal ulcer | 1 (1.0 %) | 0 | 0 | 0 |
| Dysuria | 1 (1.0 %) | 0 | 19 (18.6 %) | 0 |
| Earache | 1 (1.0 %) | 0 | 10 (9.8 %) | 0 |
| Epistaxis | 1 (1.0 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Erectile impotence | 0 | 0 | 1 (1.0 %) | 1 (1.0 %) |
| Euphoria | 1 (1.0 %) | 0 | 0 | 0 |
| Febrile neutropenia | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) |
| Fistula | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Glaucoma | 0 | 0 | 1 (1.0 %) | 0 |
| Gynecomastia | 0 | 0 | 1 (1.0 %) | 0 |
| Hallucinations | 0 | 0 | 1 (1.0 %) | 1 (1.0 %) |
| Hand-foot reaction | 1 (1.0 %) | 0 | 0 | 0 |
| Hematuria | 1 (1.0 %) | 0 | 0 | 0 |
| Hemorrhage assoc. with surgery | 1 (1.0 %) | 0 | 5 (4.9 %) | 1 (1.0 %) |
| Hemorrhage-other | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) | 0 |
| Hemorrhage w/o gr 3 or 4 platelet | | | 0 | 0 |
| Hepatic-other | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Hypermagnesemia | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Hypomagnesemia | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Infection w/ gr 3 or 4 neutropenia | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) |
| Injection site reaction | 0 | 0 | 1 (1.0 %) | 0 |
| Inner ear/hearing | 1 (1.0 %) | 0 | 2 (2.0 %) | 0 |
| Libido | 1 (1.0 %) | 0 | 0 | 0 |
| Lipase | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Lymphopenia | 0 | 0 | 0 | 1 (1.0 %) |
| Male infertility | 0 | 0 | 1 (1.0 %) | 1 (1.0 %) |
| Osteonecrosis | 0 | 0 | 1 (1.0 %) | 0 |
| Petechiae | 1 (1.0 %) | 0 | 0 | 0 |
| Photosensitivity | 0 | 0 | 1 (1.0 %) | 0 |
| Pleuritic pain | 1 (1.0 %) | 0 | 0 | 0 |
| Proctitis | 1 (1.0 %) | 0 | 2 (2.0 %) | 1 (1.0 %) |
| Proteinuria | 1 (1.0 %) | 0 | 0 | 0 |
| Pulmonary fibrosis | 0 | 0 | 1 (1.0 %) | 0 |
| Rectal bleeding | 1 (1.0 %) | 1 (1.0 %) | 4 (3.9 %) | 0 |
| Rectal or perirectal pain | 0 | 0 | 1 (1.0 %) | 0 |
| Sinus tachycardia | 1 (1.0 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Speech impairment | 1 (1.0 %) | 0 | 1 (1.0 %) | 0 |
| Transfusion: platelets | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |

| | | | | |
|---------------------------|-----------|-----------|-----------|-----------|
| Urinary frequency/urgency | 1 (1.0 %) | 1 (1.0 %) | 8 (7.8 %) | 0 |
| Urinary retention | 1 (1.0 %) | 0 | 4 (3.9 %) | 1 (1.0 %) |
| Vaginal bleeding | 0 | 0 | 1 (1.0 %) | 0 |
| Vasovagal episode | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |

Source: ^a D_AE where RXARM = Thal/Dex; by AECODEC and CASE; by AECODEC

^b D_AE where RXARM = Thal/Dex and AESEV >= 3; by AECODEC and CASE; by AECODEC

^c D_AE where RXARM = Dex; by AECODEC and CASE; by AECODEC

^d D_AE where RXARM = Dex and AESEV >= 3; by AECODEC and CASE; by AECODEC

As noted above, AEs were reported for every patient in Study E1A00. Uncommon AEs were also reported frequently. Three hundred and fifty nine AEs were reported at the < 5 % frequency among the 204 patients in the safety population – 155 in the Thal/Dex treatment arm and 204 in the dexamethasone-alone arm. I summarized the uncommon events that were reported at least 1 % more in thalidomide-treated patients (Reviewer’s Table 47).

Reviewer’s Table 47: Uncommon AEs reported ≥ 1 % more in Thal/Dex treatment arm

| MedDRA Preferred Term | Thal/Dex (n = 102) | | Dex-alone (n = 102) | |
|------------------------|--------------------|-----------|---------------------|-----------|
| | All grades | Grade 3/4 | All grades | Grade 3/4 |
| Abdominal pain | 5 (4.9 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Melena/GI bleeding | 5 (4.9 %) | 3 (2.9 %) | 1 (1.0 %) | 1 (1.0 %) |
| Chest pain | 4 (3.9 %) | 0 | 1 (1.0 %) | 0 |
| Hot flashes | 4 (3.9 %) | 0 | 2 (2.0 %) | 0 |
| Neurologic-other | 4 (3.9 %) | 2 (2.0 %) | 2 (2.0 %) | 0 |
| Palpitations | 4 (3.9 %) | 0 | 2 (2.0 %) | 0 |
| Pleural effusion | 4 (3.9 %) | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) |
| Pulmonary-other | 4 (3.9 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Renal failure | 4 (3.9 %) | 2 (2.0 %) | 2 (2.0 %) | 2 (2.0 %) |
| Vertigo | 4 (3.9 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Arrhythmia-other | 3 (2.9 %) | 0 | 1 (1.0 %) | 0 |
| Conduction abnormality | 3 (2.9 %) | 3 (2.9 %) | 0 | 0 |
| Dry eye | 3 (2.9 %) | 0 | 1 (1.0 %) | 0 |
| PTT | 3 (2.9 %) | 1 (1.0 %) | 0 | 0 |
| SGPT | 3 (2.9 %) | 0 | 0 | 0 |
| Seizure | 3 (2.9 %) | 3 (2.9 %) | 0 | 0 |
| Wound - infectious | 3 (2.9 %) | 1 (1.0 %) | 2 (2.0 %) | 0 |
| Acidosis | 2 (2.0 %) | 2 (2.0 %) | 0 | 0 |
| Arthritis | 2 (2.0 %) | 0 | 1 (1.0 %) | 0 |
| Constitutional | 2 (2.0 %) | 0 | 1 (1.0 %) | 0 |
| DIC | 2 (2.0 %) | 2 | 0 | 0 |
| Erythema | 2 (2.0 %) | 1 (1.0 %) | 0 | 0 |
| Gastritis | 2 (2.0 %) | 1 (1.0 %) | 0 | 0 |
| Hearing-other | 2 (2.0 %) | 0 | 1 (1.0 %) | 0 |
| Hypophosphatemia | 2 (2.0 %) | 1 (1.0 %) | 0 | 0 |
| Pancreatitis | 2 (2.0 %) | 2 (2.0 %) | 0 | 0 |
| Renal/GU-other | 2 (2.0 %) | 1 (1.0 %) | 0 | 0 |
| Sense of smell | 2 (2.0 %) | 0 | 0 | 0 |
| Ventricular arrhythmia | 2 (2.0 %) | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) |

| | | | | |
|-----------------------------------|-----------|-----------|-----------|---|
| Ascites | 1 (1.0 %) | 1 (1.0 %) | 1 (1.0 %) | 0 |
| CPK | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Cardiac troponin I | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Cardiac-left ventricular function | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Cardiac-other | 1 (1.0 %) | 0 | 0 | 0 |
| Cognitive disturbance | 1 (1.0 %) | 0 | 0 | 0 |
| Colitis | 1 (1.0 %) | 0 | 0 | 0 |
| Diarrhea w/ prior colostomy | 1 (1.0 %) | 0 | 0 | 0 |
| Duodenal ulcer | 1 (1.0 %) | 0 | 0 | 0 |
| Euphoria | 1 (1.0 %) | 0 | 0 | 0 |
| Fistula | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Hand-foot reaction | 1 (1.0 %) | 0 | 0 | 0 |
| Hematuria | 1 (1.0 %) | 0 | 0 | 0 |
| Hepatic-other | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Hypermagnesemia | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Hypomagnesemia | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Libido | 1 (1.0 %) | 0 | 0 | 0 |
| Lipase | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Petechiae | 1 (1.0 %) | 0 | 0 | 0 |
| Pleuritic pain | 1 (1.0 %) | 0 | 0 | 0 |
| Proteinuria | 1 (1.0 %) | 0 | 0 | 0 |
| Transfusion: platelets | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |
| Vasovagal episode | 1 (1.0 %) | 1 (1.0 %) | 0 | 0 |

Source: ^a D_AE where RXARM = Thal/Dex; by AECODEC and CASE; by AECODEC

^b D_AE where RXARM = Thal/Dex and AESEV >= 3; by AECODEC and CASE; by AECODEC

^c D_AE where RXARM = Dex; by AECODEC and CASE; by AECODEC

^d D_AE where RXARM = Dex and AESEV >= 3; by AECODEC and CASE; by AECODEC

7.1.7 Laboratory Findings

These were explored in the previous NDA and reflected in the thalidomide label.

7.1.8 Vital Signs

Vital sign data were not specifically analyzed for any of the 3 registration trials. Within this limitation, no obvious aberrations in vital signs were apparent.

7.1.9 Electrocardiograms (ECGs)

Electrocardiography was not routinely obtained for any of the 3 registration trials.

7.1.10 Immunogenicity

Not applicable to this efficacy supplement.

7.1.11 Human Carcinogenicity

Not applicable to this efficacy supplement.

7.1.12 Special Safety Studies

Not applicable to this efficacy supplement.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Thalidomide has no known withdrawal phenomena or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

Not applicable to this efficacy supplement.

7.1.15 Assessment of Effect on Growth

Not applicable to this efficacy supplement.

7.1.16 Overdose Experience

No cases of thalidomide overdose have to my knowledge been reported.

7.1.17 Postmarketing Experience

Thalidomide is currently approved in the United States only for the treatment of cutaneous manifestation of ENL. It is also distributed by Pharmion in Australia, New Zealand, and Turkey, where it is approved for both ENL and for the treatment of patients with relapsed and refractory MM.

In order to minimize fetal exposure, thalidomide must be prescribed in the United States through the restricted distribution of S.T.E.P.S.[®] Under this program, only registered prescribers and pharmacists can dispense thalidomide. All patients must complete the program's informed consent and comply with its requirements. Patients may also voluntarily participate in a

confidential surveillance registry conducted by an outside organization designed to monitor patient understanding and compliance with S.T.E.P.S.[®] In the United States that organization in Boston University's Slone Epidemiology Center.

The current Annual Report to NDA 20-785, covering the period from July 17, 2003 through July 16, 2004, contains prescribing information and AEs reported from July 1, 2003 through June 30, 2004. During this time, the S.T.E.P.S. Program enrolled 26,577 new patients, of which 1,247 were females of childbearing potential. The most frequent indications for use are summarized in Applicant's Table 48.

Applicant's Table 48: Most frequent indications for thalidomide reported by S.T.E.P.S.

| Indication | Total Patients |
|---|----------------|
| Multiple myeloma and immunoproliferative neoplasms | 11,477 |
| Neoplasm not otherwise specified | 2,401 |
| Malignant neoplasm of kidney and other urinary organs | 1,574 |
| Melanoma | 1,338 |
| Unknown | 1,297 |
| Malignant neoplasm of prostate | 943 |
| Malignant neoplasm of brain | 746 |
| Other diseases of blood and blood forming organs | 474 |
| Malignant neoplasm of liver and intrahepatic bile ducts | 320 |

Source: NDA 20-785 Annual Report

Reviewer's Comments:

1. Thalidomide is used in general practice most commonly for MM, followed by other malignancies.
2. The current Thalomid Annual Report indicates that thalidomide is used uncommonly in the United States for ENL.

During this reporting period, Celgene submitted a total of 7,091 15-Day Alert Postmarketing reports, of which 6309 were initial reports and 782 were follow-up. An additional 3704 reports were received from the Slone Epidemiology Center and 29 were received from Canada. Of the 7,091 total 15-Day Alerts during this reporting period, 129 (69 initial reports and 40 follow-up reports) pertained to Serious, Unlabeled Events.

Reviewer's Comments:

1. A relatively small percentage of all submitted 15-Day Alerts pertained to serious, unlabeled events.
2. No single category of event or group of events appeared to be responsible for an unexpected number of deaths due to serious, unlabeled AEs.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Please see section 4 of this review.

7.2.1.2 Demographics

Please see section 6 of this review.

7.2.1.3 Extent of exposure (dose/duration)

7.2.1.3.1 Study E1A00

The Applicant reported the doses of study drugs and duration of treatment for each patient. These data are summarized in Reviewer's Table 49.

Reviewer's Table 49: Drug exposure in Study E1A00

| Exposure | Thal/Dex (n = 102) | | Dex alone (n = 102) |
|------------------------------------|--------------------|------|---------------------|
| | Thal | Dex | |
| First 4 cycles | | | |
| Mean dose (mg/d) ^a | 172.5 | 18.6 | 18.6 |
| Mean duration (weeks) ^b | 13.7 | | 12.7 |
| Overall | | | |
| Mean dose (mg/d) ^c | 169.7 | 18.4 | 18.5 |
| Mean duration (weeks) ^d | 18.4 | | 14.0 |

^a D_SDSUM; where SAFC = yes and RXARM = Thal/Dex or Dex; by AVGDOSD4 or AVGDOST4

^b D_SDSUM; where SAFC = yes and RXARM = Thal/Dex or Dex; by TRTDUR4W

^c D_SDSUM; where SAFC = yes and RXARM = Thal/Dex or Dex; by AVGDOST or AVGDOST

^d D_SDSUM; where SAFC = yes and RXARM = Thal/Dex or Dex; by TRTDUR

Mean durations of treatment during the first four cycles of study ECOG E1A00 were 13.7 weeks (range 1.9 to 22.0) in the Thal/Dex treatment arm and 12.7 weeks (range 1.7 to 16.0) for dexamethasone-alone arm. When all cycles of treatment were considered the difference was greater, with a mean of 18.4 weeks (range 1.9 to 79.1) in the Thal/Dex group compared to 14.0 weeks (range 1.7 to 61.6) for the dexamethasone-alone group.

Reviewer's Comments: Average daily thalidomide doses were approximately 86 % of intended during the first 4 cycles. Average daily dexamethasone doses were similar between treatment groups.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The Applicant referred to primary data Studies Mayo 98-80-13 and Thal MM-99-002 submitted with the original sNDA December 22, 2003. Published literature was reviewed to gather perspective on the Applicant's findings. Where those other sources were used, they were referenced in the review.

7.2.2.2 Postmarketing experience

Please see section 7.1.1.7 of this review.

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

The three registration studies used prospectively defined hypotheses and objectives and appropriate methods for assessing response variables. Patients in Study E1A00 were randomized to ensure comparability of treatment groups and to minimize bias.

The study designs were adequate to reach a conclusion about the primary endpoint, and doses and durations of exposure were adequate to assess safety for the intended use.

Blood concentrations were not measured, as none of the registration studies were designed to directly assess dose-response relationships. The Applicant used a starting doses and dose adjustment schedules identified as reasonably safe and effective by prior clinical studies.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This sNDA was based on clinical safety testing. Preclinical models of MM were not applicable.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing for adverse effects was generally appropriate and satisfactory. The negative reactions to dose administration were appropriately monitored and collected.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

These assessments have not been done with this drug, as explained in Sections 1 and 2 of this review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant's efforts to detect AEs that are potentially problematic and might be expected with any drug (e.g., renal insufficiency, hepatitis) or that were previously reported with thalidomide (e.g. rash, neuropathy) were adequate.

7.2.8 Assessment of Quality and Completeness of Data

Data quality and completeness was adequate.

7.2.9 Additional Submissions, Including Safety Update

The Applicant provided two additional submissions to the sNDA. The first was an ECOG manuscript for Study E1A00 submitted September 16, 2005. The second consisted of financial disclosure statements (FDA form 3454) regarding the conduct organization of Studies ECOG E1A00, Mayo 98-80-13, and Thal MM-99-002, submitted September 30, 2005.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The population studied for this sNDA is one in which multiple clinical problems often overlap. Because nearly every patient experiences AEs, many of which are serious, the relationships among drug, event, and disease are difficult to isolate. Despite these limitations, primary data submitted supported previously published information and highlight sedation, constipation, neuropathy, VTE and rash as the chief complications of thalidomide therapy in MM.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The three clinical studies for which primary data were submitted to support this sNDA differed significantly in terms of patient population and dosing schedule. I therefore analyzed efficacy for each of the studies separately. Please see my previous review for the 2 studies in relapsed/refractory MM patients.

7.4.2 Explorations for Predictive Factors

Please see section 7.1 of this review.

7.4.3 Causality Determination

The difficulties and challenges of this drug, disease, and intended population have been described in this review. These factors converge when attempting to sort out drug-event relationships.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

8.2 Drug-Drug Interactions

Study ECOG E1A00 was not designed to assess drug-drug interactions.

8.3 Special Populations

The proportion of patients experiencing at least 1 treatment-emergent AE of any grade and of grade 3/4 are summarized by age, gender, and baseline creatinine clearance in Reviewer's Table 60. Patients with mild hepatic impairment (serum bilirubin > 1.5 mg/dL or serum aminotransferases > 2.5 times the upper limit of normal) were excluded from Study E1A00.

Reviewer's Table 50: Patients experiencing at least 1 treatment-emergent AEs (safety pop.)

| Parameter | Thal/Dex (n = 102) | | Dex-alone (n = 102) | |
|-----------|--------------------|-----------|---------------------|-----------|
| | All grades | Grade 3/4 | All grades | Grade 3/4 |

| | | | | |
|------------------|---------------|--------------|---------------|--------------|
| Age | | | | |
| < 65 years | 51/51 (100 %) | 40/51 (78 %) | 49/49 (100%) | 35/49 (71 %) |
| ≥ 65 years | 51/51 (100 %) | 46/51 (90 %) | 53/53 (100 %) | 40/53 (75 %) |
| Gender | | | | |
| Female | 50/50 (100 %) | 42/50 (84 %) | 42/42 (100 %) | 31/42 (74 %) |
| Male | 52/52 (100 %) | 43/52 (83 %) | 59/59 (100 %) | 43/59 (73 %) |
| Unknown | 0 | | 1/1 (100 %) | 1/1 (100 %) |
| Serum Creatinine | | | | |
| < 1.5 mg/dL | 90/90 (100 %) | 75/90 (83 %) | 79/79 (100 %) | 59/79 (75 %) |
| > 1.5 mg/dL | 12/12 (100 %) | 11/12 (92 %) | 23/23 (100 %) | 16/23 (70 %) |

Reviewer's Comment: Most patients in each population analyzed experienced at least 1 grade 3/4 AE. In the Thal/Dex treatment arm, patients over age 65 and those with baseline serum creatinine > 1.5 mg/dL appeared to be at slightly higher risk of grade 3/4 toxicity.

As discussed in section 7.1.5.5 of this review, it was not possible from the information provided to accurately quantify the incidences of thalidomide-induced fatigue, peripheral neuropathy, constipation, VTE, and rash. Using the Applicant's AE data submitted by MedDRA Organ System Class, I analyzed the incidences of grade 3/4 *Constitutional, Neurology, Gastrointestinal, Cardiovascular, and Dermatology/Skin* AEs in special populations (age, gender and renal function) as rough approximations of the events of interest, respectively. These findings are summarized in Reviewer's Tables 51, 52 and 53.

Reviewer's Table 51: Treatment-related grade 3/4 toxicity by age (safety pop.)

| Organ System Class | Thal/Dex (n = 102) | | Dex-alone (n = 102) | |
|--------------------|--------------------|--------------|---------------------|--------------|
| | Age < 65 | Age ≥ 65 | Age < 65 | Age ≥ 65 |
| Constitutional | 3/51 (6 %) | 16/51 (31 %) | 7/49 (14 %) | 9/53 (17 %) |
| Neurology | 14/51 (27 %) | 17/51 (33 %) | 3/49 (6 %) | 15/53 (28 %) |
| Gastrointestinal | 8/51 (16 %) | 14/51 (27 %) | 3/49 (6 %) | 5/53 (9 %) |
| Cardiovascular | 27/51 (53 %) | 22/51 (43 %) | 11/49 (22 %) | 10/53 (19 %) |
| Dermatology/Skin | 2/51 (4 %) | 3/51 (6 %) | 0 | 2/53 (4 %) |

Reviewer's Comment: On the Thal/Dex treatment arm, a higher proportion of patients age ≥ 65 experienced grade 3/4 constitutional, neurological, and gastrointestinal toxicity than those under age 65. Older patients did not appear at greater risk of grade 3/4 thalidomide-induced cardiovascular or dermatologic toxicity.

Reviewer's Table 52: Treatment-related grade 3/4 toxicity by gender (safety pop.)

| Organ System Class | Thal/Dex (n = 102) | | Dex-alone (n = 101*) | |
|--------------------|--------------------|--------------|----------------------|--------------|
| | Female | Male | Female | Male |
| Constitutional | 9/50 (18 %) | 10/52 (19 %) | 6/42 (14 %) | 10/59 (17 %) |
| Neurology | 14/50 (28 %) | 16/52 (31 %) | 7/42 (17 %) | 11/59 (19 %) |
| Gastrointestinal | 11/50 (22 %) | 11/52 (21 %) | 3/42 (7 %) | 5/59 (8 %) |
| Cardiovascular | 19/50 (38 %) | 18/52 (35 %) | 8/42 (19 %) | 13/59 (22 %) |
| Dermatology/Skin | 1/50 (2 %) | 4/52 (8%) | 2/42 (5 %) | 0 |

* data omitted for one patient whose gender was not reported