

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761035Orig1s000

MEDICAL / STATISTICAL REVIEW(S)

CLINICAL and STATISTICAL REVIEW

Application Type Original BLA
Application Number 761035
Priority or Standard Priority
Submitted June 29, 2015
Received June 29, 2015
PDUFA Goal February 29, 2016
Division/Office Division of Hematology Products
Office of Hematology and Oncology Drug Products
Reviewer Nicole Gormley, MD
Division/Office Division of Biometrics V
Office of Biostatistics
Reviewer Chia-Wen Ko, PhD
Review Completion Date November 13, 2015
Established Name Elotuzumab
Proposed Trade Name Empliciti
Applicant Bristol-Myers Squibb
Formulations Injection: 300 mg and 400 mg lyophilized powder in a single-(b) (4) vial
Proposed Dosing Regimen

- With lenalidomide and dexamethasone: 10 mg/kg administered intravenously every week for the first two cycles and every 2 weeks thereafter until disease progression or unacceptable toxicity.

(b) (4)

Applicant Proposed Indications/Population Indicated for the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone (b) (4)

Recommended Regulatory Action Regular Approval
Recommended Indication/Population Elotuzumab is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

Table of Contents

Glossary.....	7
1 Executive Summary	9
1.1. Product Introduction.....	9
1.2. Conclusions on the Substantial Evidence of Effectiveness	9
1.3. Benefit-Risk Assessment	10
2 Therapeutic Context	15
2.1. Analysis of Condition.....	15
2.2. Analysis of Current Treatment Options	15
3 Regulatory Background	17
3.1. U.S. Regulatory Actions and Marketing History.....	17
3.2. Summary of Pre-submission/Submission Regulatory Activity.....	17
3.3. Foreign Regulatory Actions and Marketing History.....	18
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	19
4.1. Office of Scientific Investigations (OSI)	19
4.2. Product Quality	19
4.3. Clinical Microbiology	19
4.4. Nonclinical Pharmacology/Toxicology	19
4.5. Clinical Pharmacology	20
4.5.1. Mechanism of Action	20
4.5.2. Pharmacodynamics.....	20
4.5.3. Pharmacokinetics.....	20
4.6. Devices and Companion Diagnostic Issues	20
4.7. Consumer Study Reviews.....	21
5 Sources of Clinical Data and Review Strategy	21
5.1. Table of Clinical Studies.....	21
5.2. Review Strategy.....	25
6 Review of Relevant Individual Trials Used to Support Efficacy	25

6.1.	Study CA204004	25
6.1.1.	Study Design.....	25
6.1.2.	Study Results.....	47
6.2.	Study CA204009	59
6.2.1.	Study Design.....	60
6.2.2.	Study Results.....	65
7	Integrated Review of Effectiveness	73
7.1.	Assessment of Efficacy Across Trials	73
7.1.1.	Primary Endpoints.....	73
7.2.	Additional Efficacy Considerations.....	76
7.2.1.	Considerations on Benefit in the Postmarket Setting	76
7.3.	Integrated Assessment of Effectiveness	76
8	Review of Safety	77
8.1.	Safety Review Approach	77
8.2.	Review of the Safety Database	77
8.2.1.	Overall Exposure	77
8.2.2.	Relevant characteristics of the safety population	81
8.2.3.	Adequacy of the safety database	81
8.3.	Adequacy of Applicant’s Clinical Safety Assessments.....	81
8.3.1.	Issues Regarding Data Integrity and Submission Quality	81
8.3.2.	Categorization of Adverse Events.....	81
8.3.3.	Routine Clinical Tests	81
8.4.	Safety Results	82
8.4.1.	Deaths	83
8.4.2.	Nonfatal Serious Adverse Events.....	84
8.4.3.	Dropouts and/or Discontinuations Due to Adverse Effects	85
8.4.4.	Significant Adverse Events Study.....	85
8.4.5.	Treatment Emergent Adverse Events and Adverse Reactions	85
8.4.6.	Laboratory Findings	88
8.4.7.	Vital Signs	90
8.4.8.	Electrocardiograms (ECGs).....	97

8.4.9. QT	97
8.4.10. Immunogenicity.....	97
8.5. Analysis of Submission-Specific Safety Issues	97
8.5.1. Second Primary Malignancies.....	97
8.5.2. Hepatotoxicity.....	100
8.5.3. Infusion Reactions.....	105
8.5.4. Infections	108
8.5.5. Elotuzumab Interference in SPEP and IFE.....	110
8.6. Specific Safety Studies/Clinical Trials.....	111
8.6.1. Pooled Safety Analyses	111
8.6.2. Safety Update	114
8.7. Additional Safety Explorations	118
8.7.1. Human Carcinogenicity or Tumor Development	118
8.7.2. Human Reproduction and Pregnancy.....	118
8.7.3. Pediatrics and Assessment of Effects on Growth	118
8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound	118
8.8. Safety in the Postmarket Setting.....	118
8.8.1. Safety Concerns Identified Through Postmarket Experience.....	118
8.8.2. Expectations on Safety in the Postmarket Setting	118
8.9. Additional Safety Issues From Other Disciplines.....	119
8.10. Integrated Assessment of Safety.....	119
9 Advisory Committee Meeting and Other External Consultations.....	120
10 Labeling Recommendations	121
10.1. Prescribing Information.....	121
10.2. Patient Labeling	121
11 Risk Evaluation and Mitigation Strategies (REMS)	122
12 Post-marketing Requirements and Commitments.....	122
13 Appendices	122
13.1. References	122
13.2. Financial Disclosure	123

Table of Tables

Table 1. Currently Available Therapies for Multiple Myeloma.....	16
Table 2. Regulatory History.....	17
Table 3. Listing of Clinical Trials Relevant to BLA 761035.....	22
Table 4. Protocol Amendments Study CA204004.....	45
Table 5. Subject Disposition Study CA204004.....	48
Table 6. Relevant Protocol Deviations Study CA204004.....	49
Table 7. Demographic characteristics Study CA204004.....	50
Table 8. Baseline Disease Characteristics Study CA204004.....	51
Table 9. Primary Efficacy Results Study CA204004.....	54
Table 10. Sensitivity Analyses to the Primary IRC-assessed PFS analysis.....	54
Table 11. Preliminary Overall Survival Result Study CA204004.....	55
Table 12. IRC-assessed PFS vs. Investigator-determined PFS Study CA204004.....	59
Table 13. Potential IRC-PFS results with subsequent anti-myeloma therapy as an event.....	59
Table 14. Subject Disposition Study CA204009.....	66
Table 15. Demographic Characteristics Study CA204009.....	66
Table 16. Baseline Disease Characteristics Study CA204009.....	67
Table 17. Primary Efficacy Results Study CA204009.....	69
Table 18. Secondary Efficacy Results Study CA204009.....	70
Table 19. Updated PFS and OS Results for Study CA204009.....	72
Table 20. Response Rate Study HuLuc63-1703.....	74
Table 21. Median Duration of Response Study HuLuc63-1703.....	74
Table 22. Progression Free Survival Study HuLuc63-1703.....	75
Table 23. Safety Population, Size and Denominators.....	78
Table 24. Exposure in Study CA204004.....	78
Table 25. Safety Overview Study CA204004.....	82
Table 26. Nonfatal Serious Adverse Events Study CA204004.....	84
Table 27. Treatment-emergent adverse events.....	85
Table 28. Laboratory Test Abnormalities Study CA204004.....	89
Table 29. Outlier Vital Signs Study CA204004.....	90
Table 30. Second primary malignancy listing.....	98
Table 31. Second primary malignancy categorization.....	99
Table 32. Incidence of Infusion Reactions.....	107
Table 33. Opportunistic Infection Incidence.....	109
Table 34. Treatment Emergent Adverse Events Pooled Trials.....	112
Table 35. Safety Update Treatment-emergent AE Summary.....	115
Table 36. Safety Update- Listing of SPMs.....	116

Table of Figures

Figure 1. Design Schema Study CA204004	26
Figure 2. Elotuzumab Infusion Rate Study CA204004	29
Figure 3. Treatment Schedule Study CA204004	31
Figure 4. Dexamethasone Dose Modifications Study CA204004	32
Figure 5. Dexamethasone Dose Levels Study CA204004.....	33
Figure 6. Lenalidomide Dose Modifications Study CA204004.....	34
Figure 7. Screening Phase Schedule of Events Study CA204004.....	35
Figure 8. Cycles 1 & 2 Schedule of Events Study CA204004.....	36
Figure 9. Cycles 3 & beyond Schedule of Events Study CA204004.....	38
Figure 10. IRC-PFS Subgroup Hazard Ratios Study CA204004.....	57
Figure 11. Design Schema Study CA204009	60
Figure 12. Treatment Schedule Study CA204009	63
Figure 13. Study CA204004 and CA204009 comparison of Investigator-assessed PFS.....	71
Figure 14. Progression Free Survival Study HuLuc63-1703	75
Figure 15. Distribution of Exposure (number of subjects) to Elotuzumab in months.....	79
Figure 16. Distribution of Elotuzumab Dose Intensity (number of subjects) in Cycles 1 & 2 in mg/kg/week	80
Figure 17. Distribution of Elotuzumab Dose intensity (number of subjects) in Cycles 3 & beyond in mg/kg/week	80
Figure 18. Increasing Systolic Blood Pressure Change from baseline Study CA204004.....	91
Figure 19. Decreasing Systolic Blood Pressure Change from Baseline Study CA204004	92
Figure 20. Increasing Diastolic Blood Pressure Change from Baseline Study CA204004	93
Figure 21. Decreasing Diastolic Blood Pressure Change from Baseline Study CA204004.....	94
Figure 22. Increasing Heart Rate Change from Baseline Study CA204004.....	95
Figure 23. Decreasing Heart Rate Change from Baseline Study CA204004	96
Figure 24. Potential Hy's law plot- Total bilirubin vs. ALT	105
Figure 25. Elotuzumab Interference with SPEP and IFE	111

Glossary

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
BLA	Biologics License Application
bpm	Beats per minute
CHF	Congestive heart failure
CI	Confidence interval
CR	Complete Response
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract Research Organization
CSR	Clinical study report
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
EBMT	European Group for Blood and Bone Marrow Transplant
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOP1	End of phase 1
ESRD	End stage renal disease
G-CSF	Granulocyte colony stimulating factor
IFE	Immunofixation
IHC	Immunohistochemistry
IMiD	Immunomodulatory drugs
IMWG	International Myeloma Working Group
IRC	Independent review committee
ITT	Intent to treat
IV	Intravenously
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minimal Response
MTD	Maximum tolerated dose
NAbs	Neutralizing antibodies
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NE	Not evaluable
NK	Natural killer
NRF	Normal renal function
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall Survival

PD	Progressive Disease
PFS	Progression-free survival
PO	Per os (by mouth)
PR	Partial Response
RI	Renal impairment
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SLAMF7	Signaling Lymphocyte Activation Molecule F7
SPEP	Serum Protein Electrophoresis
SPM	Second Primary Malignancies
TRAIL	Tumor necrosis factor apoptosis-inducing ligand
ULN	Upper limit of normal
UPEP	Urine Protein Electrophoresis
US	United States
VGPR	Very Good Partial Response
WOCBP	Women of childbearing potential

1 Executive Summary

1.1. Product Introduction

Elotuzumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody directed to Signaling Lymphocyte Activation Molecule F7 (SLAMF7) protein. SLAMF7 is present on myeloma cells and also expressed on natural killer (NK) cells. It is thought that elotuzumab binds to SLAMF7 on the surface of myeloma cells and recruits NK cells to the vicinity of the myeloma cells. It is also thought that elotuzumab causes NK cell activation, resulting in killing of the multiple myeloma cells via an antibody-dependent cellular cytotoxicity (ADCC) mechanism.

The proposed dose is 10 mg/kg administered intravenously every week for the first two cycles then every 2 weeks thereafter until disease progression or unacceptable toxicity.

The Applicant's proposed indication for elotuzumab is for the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone (b) (4).

Elotuzumab is a new therapeutic biological product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness for elotuzumab in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received 1 to 3 prior therapies.

This conclusion is based on the results of the phase 3, pivotal trial CA204004, which evaluated elotuzumab in combination with lenalidomide and dexamethasone (E-Ld) compared with lenalidomide and dexamethasone alone (Ld). The co-primary endpoints of this trial were progression-free survival and overall response rate (both as assessed by the independent review committee (IRC)). In study CA204004, a total of 646 patients were enrolled (321 in the E-Ld arm and 325 in the Ld arm). The results showed an estimated hazard ratio for PFS of 0.70 for E-Ld over Ld (95% CI: 0.57, 0.85; p=0.0004). The median PFS was 19.4 months (95% CI: 16.6, 22.2) in the E-Ld arm vs. 14.9 months (95% CI: 12.1, 17.2) in the Ld arm. The ORR was 78.5% (95% CI: 73.6, 82.9) in the E-Ld arm vs. 65.5% (95% CI: 60.1, 70.7) in the Ld arm. The overall survival data at the time of the clinical database cutoff was not mature with occurrence of only 49% of the total required events for the final analysis. The preliminary OS data suggests a hazard ratio of 0.71 (95% CI: 0.54, 0.93) for E-Ld over Ld. The median OS was not evaluable (NE) (95%CI: 36.2, NE) in the E-Ld arm and 34.6 (95% CI: 29.0, NE) in the Ld arm.

(b) (4)

Study CA204009 enrolled a total of 152 patients (77 in the E-Bd arm and 75 in the Bd arm). The primary endpoint of this trial was investigator-assessed PFS. The trial was designed to be a proof-of-concept trial (b) (4)

As such, the comparison was to be evaluated at the one-sided, (b) (4) significance level. The efficacy results demonstrated an estimated hazard ratio for PFS was (b) (4) for E-Bd over Bd (b) (4). The median PFS was 9.7 months (b) (4) in the E-Bd arm vs. 6.9 months (b) (4), (b) (4), (b) (4) in the Bd arm. The ORR was (b) (4)% ((b) (4) (b) (4)) in the E-Bd arm vs. (b) (4)% (b) (4) in the Bd arm. The overall survival data was only descriptive with occurrence of only 40 events at the time of the analysis. The hazard ratio was (b) (4) (b) (4) (b) (4)). The median OS was NE (b) (4) (b) (4) (b) (4) in the E-Bd arm vs. (b) (4) (b) (4) in the Bd arm.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Multiple myeloma is a neoplastic proliferation of clonal plasma cells that produce a monoclonal immunoglobulin. The clinical features of multiple myeloma are a consequence of the proliferation and accumulation of clonal plasma cells or damage from excess light chains. Patients may present with signs and symptoms of anemia, bone pain or pathologic fractures, renal insufficiency, fatigue, hypercalcemia, or weight loss. Multiple Myeloma is primarily a disease of the elderly, with a median age at diagnosis of 66. Treatment options for multiple myeloma have significantly improved over recent decades with the introduction of alkylating agents, the use of high-dose therapy in combination with autologous stem cell rescue, and the introduction of new classes of agents such as immunomodulatory agents and proteasome inhibitors. With these new therapeutic options, median overall survival estimates for newly diagnosed patients are more than 6 years (1). Despite these advances, patients with multiple myeloma often relapse or develop refractory disease.

Elotuzumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against SLAMF7 protein, which is present on myeloma cells. The proposed indication is for the treatment of patients with multiple myeloma who have received one or more prior therapies in combination with lenalidomide and dexamethasone. As a new therapeutic biological product, elotuzumab provides a novel mechanism of action.

The efficacy of elotuzumab in combination with lenalidomide and dexamethasone was based on the results of a phase 3, pivotal trial, which evaluated elotuzumab in combination with lenalidomide and dexamethasone (E-Ld) compared with lenalidomide and dexamethasone alone (Ld). Elotuzumab was administered as a 10 mg/kg dose intravenously every week for the first two cycles then every 2 weeks thereafter until disease progression or unacceptable toxicity. Lenalidomide was to be taken orally once daily for the first 3 weeks of a 4-week cycle. Dexamethasone was to be administered at a weekly dose of 40 mg. The co-primary endpoints of this trial were progression-free survival and overall response rate. The results showed an estimated hazard ratio for PFS of 0.70 for E-Ld over Ld (95% CI: 0.57, 0.85; $p=0.0004$). The median PFS was 19.4 months (95% CI: 16.6, 22.2) in the E-Ld arm vs. 14.9 months (95% CI: 12.1, 17.2) in the Ld arm. The ORR was 78.5% (95% CI: 73.6, 82.9) in the E-Ld arm vs. 65.5% (95% CI: 60.1, 70.7) in the Ld arm. The overall survival data at the time of the clinical database cutoff was not mature with occurrence of only 49% of the total required events for the final analysis. The preliminary OS data suggests a hazard ratio of 0.71 (95% CI: 0.54, 0.93) for E-Ld over Ld. The median OS was not evaluable (NE) (95%CI: 36.2, NE) in the E-Ld arm and 34.6 (95% CI: 29.0, NE) in the Ld arm. Treatment with elotuzumab in combination with lenalidomide and dexamethasone resulted in a clinically meaningful and statistically significant improvement in both progression-free survival and overall response rate.

The safety dataset was primarily based on the results of the phase 3 trial, but were also supported by pooled data from phase 2 trials evaluating elotuzumab in combination with lenalidomide and dexamethasone. Nonfatal serious adverse events occurred in 64.1% of patients in the E-Ld arm compared with 55.2% in the Ld arm. The most frequent SAEs were in the E-Ld arm vs. the Ld arm respectively were: Pneumonia (15.4% vs. 11.4%), pyrexia (6.3% vs. 4.4%), respiratory tract infection (4.7% vs. 2.5%), anemia (2.5% vs. 1.9%), pulmonary embolism (2.5% vs. 2.2%), and acute renal failure (2.5% vs. 1.6%). TEAEs that occurred at an incidence $\geq 10\%$ in either arm and had a $\geq 5\%$ higher rate in the E-Ld arm compared with the Ld arm respectively were: diarrhea (46.9% vs. 35.5%), constipation (34.9% vs. 26.8%), vomiting (14.5% vs. 8.8%), fatigue (61 vs. 51.1%), pyrexia (36.8% vs. 24.3%), peripheral edema (25.8% vs. 21.8%), nasopharyngitis (24.2% vs. 19.2%), upper respiratory tract infection (22.6% vs. 17.4%), weight decreased (13.8% vs. 6%), creatinine increased (12.6% vs. 7.6%), decreased appetite (20.4% vs. 12.6%), pain in extremity (16.4% vs. 9.8%), musculoskeletal pain (12.6% vs. 8.5%), headache (15.4% vs. 7.6%), peripheral neuropathy (13.8% vs. 8.2%), cough (31.3% vs. 18%), and oropharyngeal pain (10.1% vs. 4.4%).

Additional safety issues identified with the use of elotuzumab in combination with lenalidomide and dexamethasone include: infusion reactions, second primary malignancies, hepatotoxicity, infections, and elotuzumab interference with response assessment. Infusion reactions occurred in 10% of patients. Second primary malignancies occurred in 8.2% of subjects in the E-Ld arm compared with 4.7% of subjects in the Ld arm. Hepatotoxicity was also noted in the trial and there was one case that met Hy's law criteria and had biopsy findings consistent with drug-induced liver injury. The safety profile observed with elotuzumab in combination with lenalidomide and dexamethasone is acceptable given that it is designed to treat a life-threatening illness.

Elotuzumab when combined with lenalidomide and dexamethasone resulted in a statistically significant and clinically meaningful improvement in progression free survival and response rate. The adverse reactions seem with elotuzumab were significant, but are not outside the scope of that typically seen with cancer therapeutics. As such the risk-benefit assessment supports regular approval for the proposed indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Multiple myeloma is a neoplastic proliferation of clonal plasma cells that produce a monoclonal immunoglobulin. The median overall survival for patients diagnosed with multiple myeloma between the years 2006-2010 was 6.1 years (1). 	Multiple Myeloma is often a symptomatic disease, and is associated with significant morbidity and mortality.
Current Treatment Options	<ul style="list-style-type: none"> Current treatment regimens for multiple myeloma often consist of two to three drug regimens. High dose chemotherapy followed by autologous stem cell transplant is pursued for those patients deemed fit enough. Despite advances in therapy, patients with multiple myeloma often relapse or develop refractory disease. 	Given that multiple myeloma is a disease frequently associated with relapse and development of refractory disease, new therapies are needed.
Benefit	<ul style="list-style-type: none"> In the phase 3, randomized, controlled trial of lenalidomide and dexamethasone with or without Elotuzumab, there was an improvement in progression-free survival (PFS) with a hazard ratio of 0.70 (95%CI:0.57,0.85; p=0.0004), with a median PFS of 19.4 months in the E-Ld arm compared with 14.9 months in the Ld arm. The overall response rate was also improved: 78.5% in the E-Ld arm compared with 65.5% in the Ld arm. 	Treatment with elotuzumab in combination with lenalidomide and dexamethasone resulted in a clinically meaningful and statistically significant improvement in both progression-free survival and overall response rate.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	<ul style="list-style-type: none"> • Serious adverse reactions occurred in 64.1% of patients in the E-Ld arm compared with 55.2% in the Ld arm. The most frequent SAEs were: pneumonia, pyrexia, and respiratory tract infection. • The most common adverse reactions were: fatigue, diarrhea, pyrexia, constipation, cough, peripheral edema, nasopharyngitis, upper respiratory tract infection, and decreased appetite. • Infusion reactions occurred in 10% of patients. • Second primary malignancies occurred in 8.2% of subjects in the E-Ld arm compared with 4.7% of subjects in the Ld arm. • Hepatotoxicity occurred in the trial and there was one case that met Hy’s law criteria and had biopsy findings consistent with drug-induced liver injury. 	<p>The safety profile observed with elotuzumab in combination with lenalidomide and dexamethasone is acceptable given that it is designed to treat a life-threatening illness.</p>
Risk Management	<ul style="list-style-type: none"> • Infusion reactions were mitigated by protocol-required pre-medication schedule and frequent vital sign measurements during infusion. • Elotuzumab may interfere with the serum electrophoresis (SPEP) and immunofixation (IFE) assays used for assessment of response to treatment. 	<p>The Prescribing Information will include information about pre-medications for infusion reactions and management of infusion reactions should they occur. It will also include, in the Warnings and Precautions section, information about the risk of second primary malignancies, hepatotoxicity, infections, and interference with the SPEP and IFE so that prescribers will be aware.</p>

2 Therapeutic Context

2.1. Analysis of Condition

Multiple myeloma is a neoplastic proliferation of clonal plasma cells that produce a monoclonal immunoglobulin.

The clinical features of multiple myeloma are a consequence of the proliferation and accumulation of clonal plasma cells or damage from excess light chains. Patients may present with signs and symptoms of anemia, bone pain or pathologic fractures, renal insufficiency, fatigue, hypercalcemia, or weight loss. The International Myeloma Working Group (IMWG) has developed standardized diagnostic criteria for multiple myeloma.

It is estimated that there will be 26,850 new cases and 11,240 deaths from multiple myeloma in the United States in the year 2015 (2). Multiple myeloma is primarily a disease of the elderly, with a median age at diagnosis of 66. Myeloma is more common in men than women (7.9 vs. 5.1 per 100,000 persons per year). African Americans or Blacks are the most affected race and account for twice as many new cases of myeloma than Whites: 12.8 vs. 5.8 per 100,000 persons per year (3).

Treatment options for multiple myeloma have significantly improved over recent decades with the introduction of alkylating agents, the use of high-dose therapy in combination with autologous stem cell rescue, and the introduction of new classes of agents such as immunomodulatory agents and proteasome inhibitors. The median overall survival for a cohort diagnosed between the years 2006-2010 was 6.1 years, compared with 4.6 years for the cohort diagnosed between the years 2001-2005 (1).

Despite these advances, patients with multiple myeloma often relapse or develop refractory disease, underscoring the need for new therapies.

2.2. Analysis of Current Treatment Options

The table below lists the currently approved FDA agents for the treatment of multiple myeloma. Current treatment regimens tend to consist of two to three drug combinations. High dose chemotherapy followed by autologous stem cell transplant is pursued in those patients deemed fit enough to be eligible for high dose therapy and autologous transplant.

Table 1. Currently Available Therapies for Multiple Myeloma

Drug	Year/ Approval Type	Indication	Endpoint	Trial Design and Results	Survival Benefit
Cytosan (cyclophosphamide)	1959 Regular Approval	MM	-	Case series	NE
Alkeran tablet (melphalan)	1964 Regular Approval	MM Palliative treatment	-	Case series	NE
BiCNU (carmustine)	1977 Regular Approval	MM	-	Case series	NE
Alkeran injection (melphalan)	1992 Regular Approval	MM Palliative treatment	Response Rate	Randomized trial: Alkeran injection + prednisone vs. oral melphalan + pred; ORR at 22 weeks : 38% (iv) vs. 44% (oral)	NE
Velcade (bortezomib)	2003 Accelerated Approval	3 rd Line MM	Response Rate	Single-arm trial: ORR -27%	NE
	2005 Regular Approval	2 nd Line MM	TTP/OS	Randomized, open-label trial: VD vs. D TTP: 6.2 mos (VD) vs. 3.5 mos (D)	Yes HR: 0.57 (p<0.05)
	2008	Untreated MM	PFS	Randomized Trial: VMP vs. MP PFS: 18.3 mos (VMP) vs. 14 mos (MP)	Yes HR: 0.61 (p=0.0078)
Thalomid (thalidomide)	2006 Accelerated Approval	Newly Diagnosed MM	ORR/TTP	Two RCT: Study 1: T+Dex vs Dex alone; ORR: 52% vs. 36% Study 2: T+Dex vs. placebo; TTP:22.5 mos vs. 6.5 mos	Difference not statistically significant
Doxil (doxorubicin HCL liposome)	2007 Regular Approval	2 nd Line MM (no prior Velcade)	TTP	RCT: Doxil + BTZ vs. BTZ alone; TTP: 9.3 mos vs. 6.5 mos	No
Revlimid (lenalidomide)	2005 Regular Approval	2 nd Line MM combination with dexamethasone	TTP	Two RCT: RD vs D Study 1: 13.9 mos vs 4.7 mos Study 2: 12.1 mos vs 4.7 mos	No
	2015	MM in combination with dexamethasone	PFS	Randomized, open-label trial: Rd vs. Rd18 vs. MPT PFS: 25.5 mos vs. 20.7 mos vs. 21.2 mos	Yes Interim HR: 0.75

Drug	Year/ Approval Type	Indication	Endpoint	Trial Design and Results	Survival Benefit
Kyprolis (carfilzomib)	2012 Accelerated Approval	3 rd Line MM	Response Rate	Single-arm trial: ORR-23%	NE
(in combination with lenalidomide and dexamethasone)	2015 Regular Approval	1-3 prior lines	PFS	Randomized, open-label trial: KRd vs. Rd, 26.3 mos vs. 17.6 mos , HR= 0.69	Interim Analysis, OS pending
Pomalyst (pomalidomide)	2013 Accelerated Approval	3 rd Line MM	Response Rate	Phase 2 Randomized, open-label trial: POM vs POM-d ORR- 7% vs. 29%	NE
	2015 Regular Approval	3 rd Line MM	PFS/OS	Phase 3, Randomized, Open- label: POM-d vs. D PFS: 3.6 mos vs. 1.8 mos; OS: 12.4 mos vs. 8.0 mos	Yes HR: 0.70 (p=0.009)
Farydak (Panobinostat)	2015 Accelerated Approval	3 rd Line MM	PFS	RCT: PBD vs BD PFS: 10.6 mos vs 5.8 mos	Difference not statistically significant

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Elotuzumab is a new therapeutic biological product and is not currently marketed.

3.2. Summary of Pre-submission/Submission Regulatory Activity

The key U.S. pre-submission regulatory activities are included in the table below.

Table 2. Regulatory History

Date	Meeting or Event
Feb 2006	Pre-IND meeting requested
Apr 2006	Meeting Request Withdrawn
Jul 2006	Submission of protocol HuLuc63-1703
Dec 2008	Change in sponsor (PDL BioPharma to Facet Biotech)
Jul 2010	Change in sponsor (Facet Biotech to BMS)

Date	Meeting or Event
Jul 2010	Type B EOP1/ pre Phase 3 meeting to discuss phase 3 trial CA204004 (relapsed/refractory MM in combination with lenalidomide and dexamethasone)
Jan 2011	Type B EOP2 CMC meeting to discuss manufacturing program for elotuzumab
Feb 2011	Type B EOP2 meeting to discuss Phase 3 trial CA204006 (first line treatment of MM in combination with lenalidomide and dexamethasone)
Mar 2011	Submission of study CA204004
May 2011	Submission of study CA204006
Jun 2011	Submission of study CA 204007
Sep 2011	Orphan Drug Designation granted
Dec 2011	Submission of phase 2 trial CA204009 (relapsed/refractory MM in combination with bortezomib and dexamethasone)
Oct 2012	Type B Pre-Phase 3 meeting to discuss phase 3 trial CA204024 (relapsed/refractory MM in combination with bortezomib and dexamethasone)
Mar 2013	Type C CMC meeting to discuss process change
Jan 2014	Type C to obtain Agency feedback on introduction of interim analysis into trial CA204004
May 2014	Breakthrough Therapy Designation granted
Jul 2014	Type B pre-BLA meeting preliminary comments sent to sponsor for meeting to discuss indication of elotuzumab in combination with lenalidomide and dexamethasone in patients with MM who have received one or more prior therapies. Meeting request was withdrawn after receipt of preliminary comments.
Sep 2014	Type B CMC only preliminary comments sent to the sponsor. Meeting request was withdrawn after receipt of preliminary comments.
Mar 2015	Type B Pre-BLA meeting to discuss elements of the planned BLA based on two trials CA204004 and CA204009.
May 2015	Rolling review granted for BLA 761035
May 2015	Pre-submission of Quality modules for BLA 761035
June 2015	Submission of remaining portions of the BLA

3.3. Foreign Regulatory Actions and Marketing History

Elotuzumab is not currently marketed in any country. The Applicant's clinical development program has included consultation and interaction with European regulatory authorities.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted inspections for study CA204004 at the following clinical sites: Athens, Greece (Site 4600); Halifax, Nova Scotia (Site 2407); and Boston, MA (site 1414). For study CA204009, the following clinical site was inspected: Torino, Italy (Site 4934). The sponsor was also inspected for both protocols in Wallingford, CT. At the time of this review, the inspection for site 4600 was still pending. Sites 4934 and 2407 had voluntary action indicated. Sites 1414 and the sponsor had no action indicated. At the time of this review, there were no significant findings that would affect the analyses or quality of the data submitted in the application.

4.2. Product Quality

At the time of completion of this review, the CMC reviews were ongoing. At the time of the mid-cycle meeting, there were outstanding information requests, but there were no major issues identified that would prevent the approval of elotuzumab.

4.3. Clinical Microbiology

At the time of completion of this review, the Clinical Microbiology reviews were ongoing. At the time of the mid-cycle meeting, there were outstanding information requests, but there were no major issues identified that would prevent the approval of elotuzumab.

4.4. Nonclinical Pharmacology/Toxicology

Due to the lack of a pharmacologically-relevant animal species to conduct the toxicology studies, the scope of the toxicological evaluation was limited to a tissue cross-reactivity study and in vivo studies that assessed the potential for off-target toxicity and local tolerance. In the human tissues examined, elotuzumab stained the membrane and/or cytoplasm of plasma cells and/or immunoblasts in the bone marrow, breast, cervix, esophagus, Fallopian tube, gastrointestinal tract, liver, lymph node, pancreas, salivary gland, small intestine, spleen, stomach, thymus, thyroid, tonsil, ureter, and uterus. A single dose of intravenously infused elotuzumab (0, 30, or 100mg/kg) was well tolerated in rhesus monkeys with no clinical signs at any dose. There was also no local adverse reaction when 5mg of elotuzumab was intravenously injected into the ears of New Zealand white rabbits. The nonclinical pharmacology/toxicology review team recommended approval.

4.5. Clinical Pharmacology

The Clinical Pharmacology review was based on the data in the BLA including data from multiple-dose studies evaluating elotuzumab as a single agent or in combination with other anti-myeloma therapies. The submission also included population PK and exposure-response analyses. The reviewers recommend approval.

4.5.1. Mechanism of Action

Elotuzumab is a humanized monoclonal immunoglobulin (IgG1) that binds to human Signaling Lymphocyte Activation Molecule F7 (SLAMF7) on the surface of myeloma cells and recruits natural killer (NK) cells to the area of the myeloma cell. It is thought that elotuzumab causes NK-cell activation, which kills the myeloma cell via an antibody-dependent cellular cytotoxicity (ADCC) mechanism.

4.5.2. Pharmacodynamics

The population PK model showed a relationship between elotuzumab clearance and baseline M-protein. Those with higher M-protein had a higher elotuzumab clearance. Among patients in the lowest exposure quartile, unlike the remaining groups, there was no difference in PFS between the E-Ld arm and the Ld arm. Clinical Pharmacology may require a post-marketing commitment to evaluate the need to optimize dose in patients with multiple myeloma who have lower exposure to elotuzumab at the approved dose of 10 mg/kg. Please see the Clinical Pharmacology review for more details.

4.5.3. Pharmacokinetics

Elotuzumab exhibits nonlinear pharmacokinetics resulting in greater than proportional increases in area under the concentration-time curve (AUC) indicative of target-mediated clearance. Using the population PK model, for patients given elotuzumab with lenalidomide/dexamethasone, AUC accumulation ratio was estimated to be 7.42, with the corresponding effective half-life of 33.5 days.

4.6. Devices and Companion Diagnostic Issues

No companion devices or diagnostics are included in the application. However, to address the issue of elotuzumab interference with serum protein electrophoresis (SPEP) and immunofixation assays, the sponsor is developing a "detection assay". The sponsor identified issues with their "detection assay", specifically that (b) (4)

(b) (4)
developing (b) (4)
(b) (4)
. Therefore, the sponsor is now (b) (4)

(b) (4)

Consumer Study Reviews

The Division of Medication Error Prevention and Analysis reviewed the proposed Prescribing Information and the proposed carton and vial labels. The recommendations of DMEPA were incorporated in the relevant documents.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3. Listing of Clinical Trials Relevant to BLA 761035

Trial	Design	Regimen	Population	Number of Subjects	Primary Endpoint
<i>Controlled Studies to Support Efficacy and Safety</i>					
CA204004	Phase 3, Randomized, Open-label trial comparing E-Ld vs. Ld	Elotuzumab 10mg/kg weekly in C1 and C2, and q2W in C3 and beyond + lenalidomide and dexamethasone or lenalidomide and dexamethasone alone	Relapsed and/or refractory MM after 1-3 prior therapies	N= 646 randomized (E-Ld:321, Ld:325)	Co-primary: ORR and PFS (IRC-assessed; EBMT criteria)
CA204009	Phase 2, Randomized, Open-label trial comparing E-Bd vs. Bd	Elotuzumab 10 mg/kg on Days 1, 8, 15 of C1 & C2; Days 1 and 11 of C3-C8; and Days 1 and 15 of C9 and beyond + bortezomib and dexamethasone or bortezomib and dexamethasone alone	Relapsed and/or refractory MM after 1-3 prior therapies	N= 152 randomized (E-Bd: 77, Bd: 75)	PFS (Investigator-assessed; IMWG criteria)

Trial	Design	Regimen	Population	Number of Subjects	Primary Endpoint
<i>Other Studies pertinent to the review of efficacy or safety</i>					
HuLuc63-1703	Phase Ib/II, Open-label, dose-escalation trial	Phase Ib: Elotuzumab 5, 10, or 20 mg/kg weekly in C1 & C2, q2W in C3 and beyond + lenalidomide and dexamethasone Phase II: Elotuzumab 10 or 20 mg/kg weekly in C1 & C2, q2W in C3 and beyond + lenalidomide and dexamethasone	Relapsed or refractory MM after 1-3 prior therapies	Phase Ib: N= 29 enrolled 5 mg/kg- 4 10 mg/kg- 3 20 mg/kg- 22 Phase II: N=73 enrolled 10 mg/kg- 36 20 mg/kg- 37	Phase Ib: Identify the MTD Phase II: ORR (Investigator-assessed; IMWG criteria)
HuLuc63-1702	Phase I, Open-label, dose-escalation trial	Elotuzumab 2.5, 5, 10, or 20 mg/kg twice per 21-day cycle + bortezomib and dexamethasone	Relapsed or refractory MM after 1-3 prior therapies	N= 28 enrolled 2.5 mg/kg- 3 5 mg/kg- 3 10 mg/kg- 3 20 mg/kg- 19	Identify the MTD
HuLuc63-1701	Phase I, Open-label, dose-escalation trial	Elotuzumab 0.5, 1, 2.5, 5, 10, or 20 mg/kg q2W	Relapsed or refractory MM after ≥ 2 prior therapies	N= 35 enrolled 0.5 mg/kg- 3 1 mg/kg- 4 2.5 mg/kg- 6 5 mg/kg- 4 10 mg/kg- 4 20 mg/kg- 14	Identify the MTD

Trial	Design	Regimen	Population	Number of Subjects	Primary Endpoint
CA204005	Phase I, Open-label, dose-escalation trial	Elotuzumab 10 or 20 mg/kg weekly in C1 & C2 and q2W in C3 and beyond + lenalidomide and dexamethasone	Relapsed or refractory MM (Japanese subjects)	N= 6 enrolled	Safety and tolerability
CA204007	Phase Ib, Open-label trial	Elotuzumab 10 mg/kg once in C1, weekly in C2 and C3, and q2W in C4 and beyond + lenalidomide and dexamethasone	Relapsed/refractory MM with or without severe RI or ESRD	N= 35 enrolled NRF- 8 RI- 9 ESRD- 9	Evaluating PK parameters of elotuzumab by renal function

E-Bd= Elotuzumab + bortezomib + low-dose dexamethasone; Bd= bortezomib + low-dose dexamethasone; E-Ld= elotuzumab + lenalidomide + low-dose dexamethasone; Ld= lenalidomide + low-dose dexamethasone; C1 = cycle 1; C2= cycle 2; C3= cycle 3; C8= cycle 8; C9= cycle 9; MM= multiple myeloma; ORR= overall response rate; PFS= progression-free survival; IRC= Independent review committee; IMWG= International Myeloma Working Group; EBMT= European Group for Blood and Bone Marrow Transplant; q2W= every 2 weeks; RI= Renal Impairment; ESRD= End stage renal disease; NRF= normal renal function

5.2. Review Strategy

The review was primarily based on the efficacy and safety data from Study CA204004 and CA204009. The key review materials included the following:

- NDA datasets (raw and derived), clinical study reports, and responses to the review team's information requests
- Relevant published literature
- Relevant prior regulatory history
- Sponsor presentations to the FDA

Clinical data was provided in the Clinical Data Interchange Standards Consortium (CDISC) Foundational Standards SDTM and ADaM with the exception of studies HuLuc-1701 and HuLuc-1702, which were submitted in a proprietary, non-CDISC dataset format.

The other trials listed in Table 3 were supportive trials and were used in the integrated analysis of effectiveness and safety analyses.

Sections 6 and 7 of this Review were performed jointly by Dr. Gormley and Dr. Ko. Analyses by Dr. Ko were performed using SAS 9.4 (SAS Institute, Inc.) Analyses by Dr. Gormley were performed largely using JMP 11.0 (SAS Institute, Inc.). MedDRA-Based Adverse Events Diagnostic (MAED; FDA CDER Office of Computational Science) and JReview (Integrated Clinical Systems) were used to assess for safety signals. Unless specifically referenced, all analyses and presentation of findings are the work of FDA reviewers.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study CA204004

A Phase 3, Randomized, Open-Label Trial of Lenalidomide/Dexamethasone with or without Elotuzumab in Relapsed or Refractory Multiple Myeloma (Revised Protocol Number 4)

6.1.1. Study Design

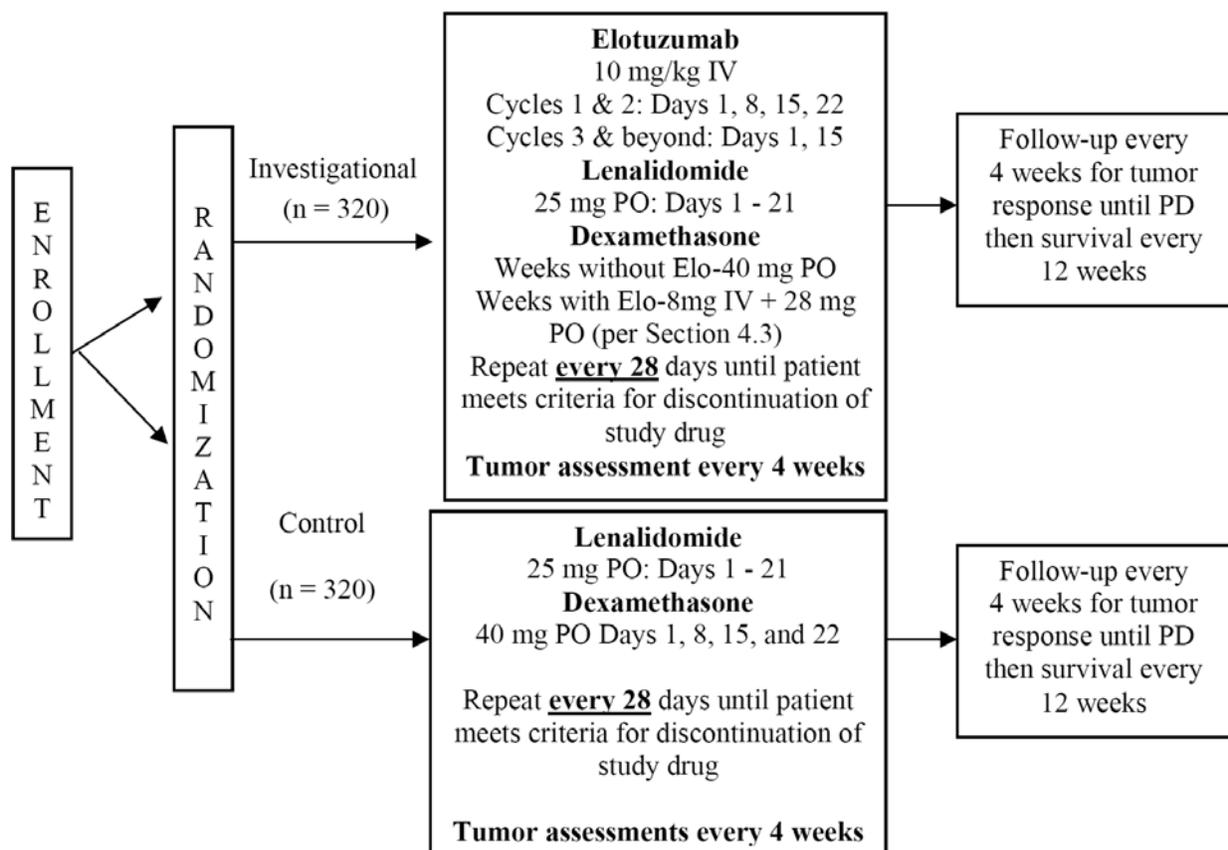
Overview and Objective

Study CA204004 was a phase 3, randomized, open-label, multicenter trial of lenalidomide/dexamethasone with or without elotuzumab in patients with previously treated, relapsed or refractory multiple myeloma. The primary objective of the trial was to compare PFS and ORR of E-LD versus Ld based on IRC tumor assessments using EBMT criteria.

Trial Design

In study CA204004, patients were randomized to the two study arms in a 1:1 ratio. There were 3 stratification factors: β 2 microglobulin (<3.5 mg/L vs. \geq 3.5 mg/L), number of prior lines of therapy (1 vs. 2 or 3), and prior immunomodulatory drugs (no vs. prior thalidomide vs. other). Subjects received E-Ld or Ld in 28-day cycles until disease progression, unacceptable toxicity, or the subject met other criteria for discontinuation, whichever occurred earliest. The study design for CA204004 is included below.

Figure 1. Design Schema Study CA204004



Source: Applicant’s Final Clinical Study Report, Appendix 1.1, Clinical Protocol, pg. 2480

Trial Population:

Eligible subjects included those with multiple myeloma who had documented disease progression from the most recent line of therapy, had received 1 to 3 prior lines of therapy, had measurable disease, and met other eligibility criteria. Given that patients might be randomized to the control arm of lenalidomide/dexamethasone, prior lenalidomide exposure was limited to those patients that had achieved at least a PR to prior lenalidomide, had not received more than 9 cycles of lenalidomide, were not refractory to lenalidomide, and did not

discontinue lenalidomide due to toxicity. The trial allowed no more than 10% of subjects who had prior lenalidomide exposure. The trial also allowed inclusion of patients with mild to moderate renal impairment as elotuzumab is a monoclonal antibody and its clearance is not thought to be affected by renal clearance and the preliminary data from the phase 1 study suggested no clinically significant renal adverse effects.

Refractory myeloma was defined as disease that progresses while on last therapy or within 60 days of last therapy. Relapsed myeloma was defined as previously treated myeloma which after a period of being off therapy required the initiation of salvage therapy for progressive disease but did not meet criteria for refractory myeloma.

Inclusion criteria (summarized):

- Willing and able to provide informed consent and comply with protocol requirements
- Age \geq 18 years
- ECOG performance status \leq 2
- Life expectancy $>$ 3 months
- Documented evidence of MM and
 - Received between 1 to 3 prior lines of therapy with documented progression by EBMT criteria after the most recent therapy and
 - Measurable disease (subject must meet one of the following 5 criteria):
 - Serum IgG M-protein \geq 0.5 g/dL
 - Serum IgA M-protein \geq 0.5 g/dL
 - Serum IgM M-protein \geq 0.5 g/dL
 - Serum IgD M-protein \geq 0.5 g/dL
 - Urine M-protein \geq 200 mg/ 24 hour
- Prior lenalidomide is permitted only if all the following are fulfilled:
 - Best response achieved was \geq PR
 - Not refractory to prior lenalidomide defined as no progression while receiving lenalidomide or within 9 months of last dose of lenalidomide
 - Did not discontinue lenalidomide due to grade \geq 3 related AE
 - Did not receive more than 9 cycles of lenalidomide and had at least 9 months between the last dose of lenalidomide and progression
- Men and women of childbearing potential (WOCBP) must use 2 acceptable methods of contraception
- WOCBP must have 2 negative pregnancy tests
- Women must not be breastfeeding
- Subjects must be willing to refrain from blood donations

Exclusion Criteria (summarized):

- Subjects with non-secretory or oligo-secretory or serum free light-chain only myeloma
- Active plasma cell leukemia (defined as either 20% of peripheral WBC comprised of

- plasma/CD138+ cells or an absolute count of $2 \times 10^9/L$)
- All adverse events of any prior chemotherapy, surgery, or radiotherapy not resolved to NCI CTCAE (v.3.0) Grade ≤ 2
 - POEMS Syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
 - Significant cardiac disease defined as:
 - Known or suspected cardiac amyloidosis
 - CHF of NYHA Class III or IV
 - Uncontrolled angina, hypertension, or arrhythmia
 - Myocardial infarction in the past 6 months
 - Any uncontrolled or severe cardiovascular disease
 - Prior cerebrovascular event with persistent neurologic deficit
 - Known HIV infection or active hepatitis A, B, or C
 - Any medical conditions that, in the investigator's opinion, would impose excessive risk to the subject
 - Prior or concurrent malignancy, except for the following:
 - Adequately treated basal cell or squamous cell skin cancer
 - Any other cancer from which the subject has been disease-free for > 5 years
 - Uncontrolled diabetes
 - Unable to tolerate thromboembolic prophylaxis including, as clinically indicated, aspirin, Coumadin or low-molecular weight heparin
 - Corrected serum calcium ≥ 11.5 mg/dL
 - ANC < 1000 cells/ mm^3
 - Platelets $< 75,000$ cells/ mm^3
 - Hemoglobin < 8 g/dL
 - Total bilirubin $\geq 2 \times$ ULN or direct bilirubin ≥ 2.0 mg/dL
 - AST or ALT $\geq 3 \times$ ULN
 - Creatine Clearance (CrCl) < 30 ml/min
 - Major surgery within 4 weeks
 - Administration of chemotherapy, biological, immunotherapy, or any investigational agent within 3 weeks
 - If prior allogeneic stem cell transplant, history of moderate or severe chronic graft versus host disease
 - Treatment with plasmapheresis within 4 weeks
 - Prior therapy with elotuzumab or any IMiD (including pomalidomide), except for prior thalidomide or lenalidomide
 - Refractory to prior lenalidomide
 - Steroids within 3 weeks
 - Known hypersensitivity to lenalidomide, dexamethasone, or any excipients in the elotuzumab formulation
 - History of grade 4 rash associated with thalidomide

- Prisoners or subjects who are involuntarily incarcerated

Study Treatment:

Eligible subjects received either elotuzumab in combination with lenalidomide and dexamethasone or lenalidomide and dexamethasone.

Elotuzumab was administered intravenously at a dose of 10 mg/kg weekly (Days 1, 8, 15, and 22 of a 4-week cycle) of the first 2 cycles and every 2 weeks (Day 1 and Day 15) thereafter. A window of -1 to +3 days was permitted in Cycles 1 and 2. Elotuzumab was provided as a lyophilized powder containing 440 mg of elotuzumab in a 20-mL vial. Elotuzumab should be reconstituted with 17 ml of sterile water for injection. After calculation of the appropriate drug volume, the appropriate dose of elotuzumab was to be further diluted into an infusion bag containing 230 mL of normal saline. Elotuzumab was administered as an IV infusion using an automated infusion pump. The infusion rates are included in the table below.

Figure 2. Elotuzumab Infusion Rate Study CA204004

Infusion Rate	Duration of infusion	Volume delivered	Volume remaining
Cycle 1 Dose 1	Total Duration: 2hrs 50min		262 mL*
0.5 mL/min	30 min	15 mL	247 mL
1 mL/min	30 min	30 mL	217 mL
2 mL/min	110 min	217 mL	0 mL
Cycle 1 Dose 2	Total Duration: 1hrs 13min		262 mL
3 mL/min	30 min	90 mL	172 mL
4 mL/min	43 min	172 mL	0 mL
Cycle 1 Dose 3 and 4	Total Duration: 53min		262 mL
5 mL/min	53 min	262 mL	0 mL
Cycle 2 +	Total Duration: 53min		262 mL
5 mL/min	53 min	262 mL	0 mL

* Volume for 80 kg subject. Total volume varies according to the subject weight.

Please note that infusion rate increase to the next higher level only if no infusion reactions encountered.

Source: Applicant’s Final Clinical Study Report, Appendix 1.1, Clinical Protocol, pg. 2585

If no infusion reactions were noted in the first 4 doses of elotuzumab, all following doses were required to start at the maximum rate of 5 ml per minute. For subjects that did not escalate elotuzumab infusion beyond 2 ml per minute, despite administration of more than 4 doses of elotuzumab and had not experienced any infusion reaction were required to undergo rate escalation using the above paradigm.

It should be noted that the infusion rate shown above was added to the protocol with the last

amendment, Amendment 12. Prior to this change, the maximum infusion rate was 2 ml/min. For the first dose of elotuzumab, the infusion was started at an initial rate of 0.5 ml/min. If the subject did not have an infusion reaction within 30 minutes, the infusion rate was to be escalated by 0.5 ml/min. If the subject still did not have an infusion reaction within 30 minutes, the infusion rate was to be escalated to the maximum of 2 ml/min. The second dose of elotuzumab was to be initiated at a rate of 1 ml/min and if the subject did not have an infusion reaction in the first 30 minutes, the rate was to be escalated to 2ml/min.

The following pre-medications were required 30-90 minutes prior to administration of elotuzumab:

- H1 blocker: diphenhydramine (25-50 mg PO or IV) or equivalent
- H2 blocker: Ranitidine (50 mg IV) or equivalent
- Acetaminophen (650-1000 mg PO)

Lenalidomide was taken orally once daily for the first 3 weeks of a 4-week cycle. On the days of elotuzumab administration, the dose of lenalidomide was to be administered at least 2 hours after completion of elotuzumab dosing.

Dexamethasone (including the control arm) was to be administered at a weekly dose of 40 mg orally on Day 1, 8, 15, and 22 (-1 to +3 days) on weeks without elotuzumab dosing. On weeks with elotuzumab dosing, the weekly dose of 40 mg dexamethasone was to be administered as a split dose of:

- 28 mg PO (between 3- 24 hours prior to the start of elotuzumab infusion) AND
- 8 mg IV (on the day of elotuzumab infusion at least 45 min prior to the start of infusion)
- At the discretion of the investigator, the oral dexamethasone component may be given as a split dose 12-24 and 3 hours prior to elotuzumab

The protocol allowed increases in the IV dexamethasone dose (with concurrent decrease in PO dexamethasone) in patients that had infusion reactions with elotuzumab.

The treatment schedule is depicted in the diagram below.

Figure 3. Treatment Schedule Study CA204004

Table 4.3.1-1: Treatment Schedule												
Lenalidomide	Day 1 - Day 21				Day 1 - Day 21				Day 1 - Day 21			
Elotuzumab ^a	↓	↓	↓	↓	↓	↓	↓	↓	↓		↓	
Dexamethasone	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
Day	1	8	15	22	1	8	15	22	1	8	15	22
Cycle	Cycle 1				Cycle 2				Cycle 3 & Beyond			

^a Experimental arm only

Source: Applicant’s Final Clinical Study Report, Appendix 1.1, Clinical Protocol, pg.2522

If the dose of one drug in the regimen (i.e., lenalidomide, dexamethasone, or elotuzumab) was delayed, interrupted, or discontinued, the treatment with the other drugs was allowed to continue as scheduled. For example, if a subject on the investigational arm had to discontinue elotuzumab due to an adverse event or other reason, the subject could continue on study therapy. Even if the subject continued solely on lenalidomide, subjects were still considered on study therapy.

General guidelines for dose reductions were provided in the protocol. Elotuzumab dose reductions were not permitted. Dexamethasone dose reduction recommendations for specific adverse events and the dexamethasone dose levels are included in the tables below. Dose reductions for persistent grade 2 or grade ≥ 3 AEs not listed in the table below were also permitted.

Figure 4. Dexamethasone Dose Modifications Study CA204004

CTCAE CATEGORY	ADVERSE EVENT	TREATMENT ADJUSTMENT*
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1 - 2 (requiring medical management)	Treat with a proton pump inhibitor. If symptoms persist despite above measures, decrease by one dose level.
	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Reduce by one dose level and resume along with concurrent therapy with a proton pump inhibitor. If symptoms persist despite above measures, reduce to dose level -3
	Acute pancreatitis	Reduce to dose level -3
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Use diuretics as needed, and decrease dexamethasone by one dose level. If edema persists despite above measures, decrease by another dose level.
Neurology	Confusion or Mood alteration ≥ Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Decrease by one dose level and resume. If symptoms persist despite above measures, decrease by another dose level.
Musculoskeletal	Muscle weakness ≥ Grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	Hold dose until muscle weakness is ≤ Grade 1. Decrease dexamethasone by 1 dose level and resume. If weakness persists despite above measures, decrease by another dose level.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treat with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease by one dose level until levels are satisfactory
Constitutional	Insomnia ≥ Grade 2	Decrease by one dose level and resume.

Source: Applicant's Final Clinical Study Report, Appendix 1.1, Clinical Protocol, pg. 2527

Figure 5. Dexamethasone Dose Levels Study CA204004

Dose Level	Weeks with Elotuzumab		Weeks without Elotuzumab	
	PO	IV	PO	IV
0	28 mg	8 mg	40 mg	0 mg
-1	12 mg	8 mg	20 mg	0 mg
-2	0 mg	8 mg	12 mg	0 mg
-3	0 mg	contact Medical Monitor	0 mg	0 mg

Source: Applicant's Final Clinical Study Report, Appendix 1.1, Clinical Protocol, pg. 2528

Dose adjustments for lenalidomide based on hematologic toxicity and renal impairment were provided. Dose reduction recommendations are included in the table below. In addition to the adverse events in the tables below, dose reductions for other grade 3 or 4 toxicities were permitted. Investigators were instructed to hold treatment and restart lenalidomide at the next lower dose level when toxicity resolved to \leq grade 2.

Figure 6. Lenalidomide Dose Modifications Study CA204004

When Platelet Counts:	Recommended Course
Fall to < 30,000/mm ³	Interrupt lenalidomide treatment; follow complete blood counts weekly.
Return to ≥ 30,000/ mm ³	Resume lenalidomide at 15 mg, Days 1 - 21, once daily.
For each subsequent drop < 30,000/ mm ³	Interrupt lenalidomide treatment.
Return to ≥ 30,000/ mm ³	Resume lenalidomide at 5 mg less than previous dose, Days 1 - 21, once daily. Do not dose below 5 mg.
When Neutrophil Counts:	Recommended Course
Fall to < 1000/ mm ³	Interrupt lenalidomide treatment, add G-CSF; ^a follow complete blood counts weekly.
Return to ≥ 1000/ mm ³ and neutropenia is the only toxicity	Resume lenalidomide at 25 mg, Days 1 - 21, once daily.
Return to ≥ 1000/mm ³ and if other toxicity	Resume lenalidomide at 15 mg, Days 1 - 21, once daily.
For each subsequent drop < 1000/ mm ³	Interrupt lenalidomide treatment.
Return to ≥ 1000/ mm ³	Resume lenalidomide at 5 mg less than previous dose, Days 1 - 21, once daily. Do not dose below 5 mg.
In case of neutropenia, consider the use of growth factors in subject management.	
Creatinine Clearance (CRCL):	Recommended Course
Moderate renal impairment (CRCL 30 - 60 mL/min)	10 mg every 24 hours
Severe renal impairment (CRCL < 30 mL/min, not requiring dialysis)	15 mg every 48 hours
End Stage Renal Disease (CRCL < 30 mL/min, requiring dialysis)	5 mg once daily. On dialysis days, dose should be administered following dialysis

Source: Applicant's Final Clinical Study Report, Appendix 1.1, Clinical Protocol, pg. 2528-9

Concomitant Medications:

Subjects were required to receive thromboembolic prophylaxis. Accepted thromboembolic prophylaxis medications included aspirin, low molecular weight heparin, and vitamin K antagonists.

IV corticosteroids, diphenhydramine, hydroxyzine, acetaminophen, H2 blockers, and leukotriene inhibitors were permitted for the management of infusion reactions.

It was recommended that bisphosphonate therapy be administered for a period of 2 years in accordance with ASCO 2007 Clinical Practice Guidelines. Use of erythropoietin or darbopoetin, red blood cell or platelet transfusions, and prophylactic administration of G-CSF were permitted.

Schedule of Events:

The following assessments were performed as part of the screening, treatment and post-

treatment periods of Study CA204004.

Figure 7. Screening Phase Schedule of Events Study CA204004

Procedure	Screening Visit	Notes
Pregnancy Test	X	For WOCBP only, 2 pregnancy tests, one 10 - 14 days prior to start of study drug and one within 24 hours prior to start of study drug. Urine tests must have a sensitivity of at least 25 IU/L.
Efficacy Assessments		All efficacy assessments must be performed within 28 days prior to randomization
Myeloma Urine and Serum Lab tests	X	Within 28 days of randomization (central laboratory analysis; Section 5.4.3). Results must be available prior to randomization.
Bone Marrow Aspiration/Biopsy	X	Within 28 days of randomization. Bone marrow aspirate is mandatory. Bone marrow biopsy is optional. (Section 5.4.3).
Cytogenetic analysis and FISH	X	Section 5.4.3 and 5.7. Central laboratory analysis.
Skeletal Survey	X	Within 28 days of randomization
CT/MRI assessment for extramedullary soft tissue plasmacytoma	X	Within 28 days of randomization, if clinically indicated.
Clinical Drug Supplies		
Randomize	X	First dose of study drug must occur within 3 days of randomization
QOL assessments		
EORTC QLQ-C30	X	
EORTC QLQ-MY20	X	
Brief Pain Inventory- Short Form (BPI-SF)	X	
Healthcare Resource Utilization	X	
Informed Consent	X	Prior to any screening procedures
Inclusion/Exclusion Criteria	X	Within 14 days of randomization
Medical History	X	Includes date of diagnosis MM (Within 28 days of randomization)
Safety Assessments		
Physical Examination	X	Includes height and weight within 14 days of randomization (Section 5.3.1)
Vital Signs	X	Temperature, BP, HR, RR within 14 days of randomization (Section 5.3.1)
Performance Status (ECOG)	X	Within 14 days of randomization
Serious Adverse Events Assessment	X	Collected from the time of informed consent
Second Primary Malignancy	X	Collected from the time of informed consent (Section 6.7)
Concomitant Medications	X	Within 14 days of randomization
2-D Echocardiogram or MUGA	X	Within 28 days of randomization (Section 5.3.3)
ECG	X	Within 28 days of randomization (Section 5.3.3)
Laboratory Assessments for Safety		
CBC, differential, platelets	X	Within 14 days of randomization (Section 5.3.4)
Serum Chemistry	X	Within 14 days of randomization (Section 5.3.4)
Coagulation Tests	X	Within 14 days of randomization (Section 5.3.4)
Serum β 2-microglobulin	X	Within 28 days of randomization. Central lab analysis for stratification.
Urinalysis	X	Within 14 days of randomization (Section 5.3.4)

Source: Applicant's Final Clinical Study Report, Appendix 1.1, Clinical Protocol, pg. 2531-2

Figure 8. Cycles 1 & 2 Schedule of Events Study CA204004

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	Notes
Efficacy Assessments						
Myeloma Urine and Serum Lab tests	Every 4 weeks from date of first dose of study drug until disease progression.					<p>Section 5.4.3. Day 1 of each cycle (except Cycle 1 - refer to Screening visit for defined window) until disease progression, even if subject is on subsequent therapy;</p> <p>24 - hour urine sample can be collected within ± 7 days of visit, and must be obtained in all subjects have measurable UPEP M protein (≥ 200 mg / 24 hours) at baseline with each cycle</p> <p>Subjects without measurable urine M protein at baseline and at two subsequent cycles do not have to submit q4 week urine samples with each cycle until SPEP M protein becomes undetectable. In order to fulfill CR/sCR criteria, both serum and urine immunofixation must be performed and be negative for a minimum of 6 weeks. Therefore, at the time SPEP becomes undetectable, UPEP collection should begin for these subjects</p>
Corrected Calcium	Every 4 weeks from date of first dose of study therapy, regardless of whether subject is on study therapy or subsequent therapy until disease progression.					<p>Serum calcium and albumin from peripheral blood at D1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as criteria for disease progression, must be confirmed by second value</p>
Bone Marrow Aspiration/Biopsy	For confirmation of CR/sCR if applicable or, if clinically indicated at time of suspected disease progression					<p>Section 5.4.3. Bone marrow aspirate is mandatory. Bone marrow biopsy is optional. However, if a patient has a CR and flow cytometry is unavailable then a bone marrow biopsy is required for immunohistochemistry. Plasma cell percentage and light chain restriction assessments must be performed.</p>
Flow Cytometry	To assess for sCR, if applicable. Performed locally per institution standard practice.					<p>Section 5.4.3 Performed locally per institution standard practice; Plasma cell percentage and light chain restriction assessments are required. If not available, IHC can be performed on bone marrow core biopsy.</p>
Serum Free Light Chain	To assess for sCR at the time of CR assessments					<p>Section 5.4.3 Normal values require confirmatory values at least 6 weeks apart to fulfill criteria of sCR.</p>
Skeletal Survey	If clinically indicated					<p>Section 5.4.4.1</p>
Safety Assessments						
Targeted Physical Examination	X					<p>Perform up to 3 days prior to dosing, include weight (Section 5.3.1)</p>
Vital Signs	X	X	X	X		<p>Measure vital signs prior to administration of pre-medication, pre-clotuzumab infusion, 30 minutes after the start of clotuzumab infusion, at the end of infusion, and 30 and 120 minutes after the completion of infusion</p> <p>Control arm measure vital signs once at each visit</p>
Performance Status (ECOG)	X					<p>Evaluate prior to dosing</p>
Serious Adverse Event Assessment	X	X	X	X		<p>Evaluate prior to dosing</p>
Adverse Events Assessment	X	X	X	X		<p>Evaluate prior to dosing</p>
Second Primary Malignancy	X	X	X	X		<p>Section 6.7</p>
Concomitant Medications	X	X	X	X		<p>Evaluate prior to dosing</p>
Laboratory Tests for Safety						
CBC, differential, platelets	X	X	X	X		<p>Can be drawn up to 3 days prior to study visit (Section 5.3.4)</p>
Serum Chemistry	X	X	X	X		<p>Can be drawn up to 3 days prior to study visit (Section 5.3.4)</p>
Coagulation Tests	X	X	X	X		<p>For subjects treated with warfarin thromboembolic prophylaxis only</p>
Pregnancy Test	X	X	X	X		<p>For WOCBP only. Urine tests must have a sensitivity of at least 25 IU/L.</p> <p>Cycle 1: Weekly test within 24 hours of study medication.</p> <p>Cycle 2: Test must be completed within 24 hours of study medication.</p> <p>If patient has irregular menstrual cycles the pregnancy test should occur on Day 1 and Day 15 of Cycle 2.</p>

Clinical & Statistical Review
 Nicole Gormley, MD & Chia-Wen Ko, PhD
 BLA 761035
 EMPLICITI (elotuzumab)

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	Notes
CT/MRI assessment for extramedullary soft tissue plasmacytoma	As clinically indicated and at the time of CR/sCR assessments					Section 5.4.4.2
Response per EBMT based criteria	Every 4 weeks from date of first dose of study drug until disease progression, regardless of whether patient is still on study therapy					Section 5.4.6 Response assessments require repeat values over 6 weeks minimum. Progression assessments require repeat values over any time interval.
Serum PK Elotuzumab arm only	<----->					Refer to Table 5.5.1-1 for specific time points
Human Anti-Human Antibody (HAHA) Elotuzumab arm only	<----->					Refer to Table 5.5.1-1 for specific time points
Dosing						
Premedication for Elotuzumab (Arm A only)	X	X	X	X		See Section 4.3.1.
Elotuzumab Infusion (Arm A only)	X	X	X	X		In Cycle 1 and 2, an elotuzumab dose that falls outside of the pre-specified window (-1 to +3 days) must be skipped. See Section 4.3.1.
Lenalidomide Administration	Days 1 - 21 of each cycle					
Dexamethasone Administration	X	X	X	X		
Dispense Lenalidomide	X					Dispense lenalidomide on Day 1 of cycle per the Revlimid Risk Management Plan
QOL assessments						
EORTC QLQ-C30	X					Complete prior to any study-related procedures, treatment or clinician assessment
EORTC QLQ-MY20	X					
Brief Pain Inventory- Short Form (BPI-SF)	X					
Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	Notes
Healthcare Resource Utilization	X					

Source: Applicant's Final Clinical Study Report, Appendix 1.1, Clinical Protocol, pg. 2533-6

Figure 9. Cycles 3 & beyond Schedule of Events Study CA204004

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 60 post end of treatment	Every 12 weeks after progression	Notes
Targeted Physical Examination	X					X			Perform up to 3 days prior to dosing, includes weight (Section 5.3.1)
Vital Signs	X		X			X			Measure vital signs prior to administration of pre-medication, pre-elotuzumab infusion, 30 minutes after the start of elotuzumab infusion, at the end of infusion, and 30 minutes after the completion of elotuzumab infusion. Control arm measure vital signs once at each visit.
Performance Status (ECOG)	X					X			Evaluate prior to dosing
Serious Adverse Event Assessment	X		X			X	X		Evaluate prior to dosing
Adverse Events Assessment	X		X			X	X		Evaluate prior to dosing
Second Primary Malignancy	X		X			X	X	X	Section 6.7 Performed at 30 and 60 day \pm 1 week EOT follow up visits. After 30 and 60 day EOT visits, second primary malignancy should be assessed every 12 weeks (\pm 2 weeks)
Concomitant Medications	X		X			X	X		Evaluate prior to dosing
Subsequent Myeloma Therapy						X	X	X	30 and 60 day visits may be performed \pm 1 week. After 30 and 60 day EOT visits subsequent myeloma should be assessed every 12 weeks (\pm 2 weeks)
Laboratory Tests for Safety									
CBC, differential, platelets	X		X			X			Can be drawn up to 3 days prior to visit (Section 5.3.4)
Serum Chemistry	X		X			X			Can be drawn up to 3 days prior to visit (Section 5.3.4)
Coagulation Tests	X		X			X			For subjects treated with warfarin thromboembolic prophylaxis only
Pregnancy Test	X		X			X	X		For WOCBP only. Tests must occur within 24 hours prior to dosing. If the subject has irregular menstrual cycles, the pregnancy test should occur on Days 1 and 15 of each cycle. Urine tests must have a sensitivity of at least 25 IU/L. (Section 5.3.4).
Efficacy Assessments									
Myeloma Urine and Serum Lab tests	<p>Every 4 weeks from date of the first dose of study drug therapy until disease progression, regardless of whether subject is on study therapy or subsequent therapy.</p>								<p>Section 5.4.3. Day 1 of each cycle until disease progression, even if subject is on subsequent therapy; 24 - hour urine sample can be collected within \pm 7 days of visit, and must be obtained in all subjects who have measurable UPEP M protein (\geq 200 mg / 24 hours) at baseline with each cycle Subjects without measurable urine M protein at baseline and at two subsequent cycles do not have to submit q4 week urine samples with each cycle until SPEP M protein becomes undetectable. In order to fulfill CR/sCR criteria, both serum and urine immunofixation must be performed and be negative for a minimum of 6 weeks. Therefore, at the time SPEP becomes undetectable, UPEP collection should begin for these subjects.</p>

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 60 post end of treatment	Every 12 weeks after progression	Notes
Corrected Calcium	Every 4 weeks from date of first dose of study therapy until disease progression, regardless of whether subject is on study therapy or subsequent therapy.								Serum calcium and albumin from peripheral blood at D1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as criteria for disease progression, must be confirmed by second value.
Bone Marrow Aspiration/Biopsy	For confirmation of CR/sCR if applicable or, if clinically indicated at time of suspected disease progression								Section 5.4.3. Bone marrow aspirate is mandatory. Bone marrow biopsy is optional if a patient has a CR and flow cytometry is unavailable then a bone marrow biopsy is required for immunohistochemistry. Plasma cell percentage and light chain restriction assessments are required.
Flow Cytometry	To assess for sCR, if applicable. Performed locally per institution standard practice.								Section 5.4.3. Performed locally per institution standard practice; Plasma cell percentage and light chain restriction assessments are required. If not available, IHC can be performed on bone marrow core biopsy.
Serum Free Light Chain	To assess for sCR at the time of CR assessments								Section 5.4.3. Normal values require confirmatory values at least 6 weeks apart to fulfill criteria of sCR
Skeletal Survey	If clinically indicated								Section 5.4.4.1
CT/MRI assessment for extramedullary soft tissue plasmacytoma	As clinically indicated and at the time of CR/sCR assessments								Section 5.4.4.2
Response per EBMT based criteria	Every 4 weeks from date of the first dose of study drug until disease progression regardless of whether on study therapy or subsequent								Section 5.4.6 Response assessments require repeat values over 6 weeks minimum. Progression assessments require repeat values over any time interval.
Serum PK Elotuzumab arm only	←-----→								Refer to Table 5.5.1-1 for specific time points
Human Anti-Human Antibody (HAHA) Elotuzumab arm only	←-----→								Refer to Table 5.5.1-1 for specific time points
Survival Status							X	X	30 and 60 day visits may be performed ± 1 week. After 30 and 60 day EOT visits survival status should be assessed every 12 weeks ± 2 weeks.
Dosing									
Premedication for Elotuzumab (Arm A only)	X		X						See Section 4.3.1.
Elotuzumab Infusion (Arm A only)	X		X						In Cycles 3 and beyond, elotuzumab dosing may be delayed for up to 1 week. If unable to administer within 1 week, then the dose should be skipped and resumption of the elotuzumab continues per the protocol defined schedule. See Section 4.3.3.1.
Lenalidomide Administration	Days 1 - 21								
Dexamethasone Administration	X	X	X	X					
Dispense Lenalidomide	X								Dispense lenalidomide on Day 1 of cycle per the Revlimid Risk Management Plan
QOL assessments									Complete prior to any study-related procedures, treatment or clinician assessment
EORTC QLQ-C30	X						X		
EORTC QLQ-MY20	X						X		
Brief Pain Inventory- Short Form (BPI-SF)	X						X		
Healthcare Resource Utilization	X						X		

Source: Applicant's Final Clinical Study Report, Appendix 1.1, Clinical Protocol, pg. 2537-9
Discontinuation Criteria:

Subjects were required to discontinue study treatment for the following criteria:

- Withdrawal of informed consent
- Any clinical adverse event, lab abnormality, or intercurrent illness, which in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb
- Loss of ability to freely provide informed consent through imprisonment or involuntary incarceration
- Progressive Disease
- Subjects who receive any non-protocol anti-myeloma therapy prior to documented progression will be discontinued from all study treatment; however, tumor assessment must continue at 4 week intervals until documented progression
- Subjects experiencing a grade 4 infusion reaction
- Subjects experiencing angioedema, grade 4 rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis related to lenalidomide must discontinue lenalidomide. Subjects in the elotuzumab arm may continue elotuzumab and dexamethasone
- Subjects experiencing a 28 day delay in all study drugs due to an adverse event related to study treatment must discontinue study drug

Efficacy Assessments and Response Criteria:

Efficacy endpoints were based on serum and urine protein electrophoresis (SPEP and UPEP), corrected calcium, and bone marrow assessments at predefined intervals as listed on the schedule of events above. Subjects were to have SPEP/UPEP, and corrected calcium performed every 4 weeks from the date of the first dose of study drug until disease progression, regardless of whether the subject was on study therapy or on subsequent therapy. If a subject did not have documented disease progression at the time of study drug discontinuation, tumor assessments were to still be performed according to the same schedule until disease progression even if subsequent anti-myeloma therapy was initiated prior to disease progression. Response criteria based on EBMT criteria were used for the primary analysis. The response criteria are described below.

Complete Response (CR):

A CR requires that all the following criteria be achieved:

1. Negative immunofixation (IFE) on both serum and urine, maintained for a minimum of 6 weeks.
2. A bone marrow aspirate or biopsy containing < 5% plasma cells. (although not required for documentation of CR using the EBMT criteria, light chain restriction (flow or IHC for kappa and lambda light chain in the bone marrow) should also be assessed to assist in classification of stringent CR using the IMWG criteria).
3. If skeletal survey showed osteolytic bone lesions, there should be no increase in the size

or number (development of a compression fracture does not exclude response).

4. If screening scans showed extramedullary plasmacytoma, complete disappearance of any must be noted.

For assessment of stringent CR per IMWG criteria, all criteria for CR must be met. In addition, bone marrow sample must be assessed for light chain restriction (as mentioned in bullet 2 above) and serum free light chains must be normalized at two time points at least 6 weeks apart, at the time of CR assessment.

Partial Response (PR):

Subjects in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements of PR. This includes subjects in whom routine electrophoresis is negative but in whom IFE has not been performed.

1. Greater than or equal to 50% reduction in serum M-protein, maintained for a minimum of 6 weeks.
2. Reduction of $\geq 90\%$ in urinary light chain excretion or a decrease to < 200 mg/24 hours, maintained for a minimum of 6 weeks.
3. Greater than or equal to 50% reduction in the size of the extramedullary plasmacytomas present at baseline (by radiography or clinical examination using bidirectional measurements).
4. If a skeletal survey is performed, no increase in the size or number of lytic lesions (development of a compression fracture does not exclude response).

Very Good Partial Response (VGPR):

VGPR is not formally included in the EMBT criteria but is derived from the IMWG criteria. It is defined by the following:

1. Serum and urine M-protein detectable by immunofixation but not on electrophoresis and that is confirmed in a subsequent assessment or
2. 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours and is confirmed on a subsequent assessment.

Minor (Minimal) Response (MR):

Subjects who have a reduction in M-protein or plasmacytoma but do not meet the criteria for PR are classified as MR if they meet all the following definitions.

1. Between 25- 49% reduction in serum M-protein, maintained for a minimum of 6 weeks
2. Between 50-89% reduction in urinary light chain excretion which still exceeds 200 mg/ 24 hours, maintained for a minimum of 6 weeks.
3. Between 25-49% reduction in the size of extramedullary plasmacytomas.
4. If a skeletal survey is performed, no increase in the size or number of lytic lesions (development of a compression fracture does not exclude response).

Progression of Disease:

Progression describes a definite increase in disease activity relative to the nadir in 2 consecutive assessments in subjects not in CR, whereas the term “relapse from CR” applies to a recurrence of evident disease in subjects previously in CR. The date of EBMT based disease progression is the first date of two consecutive values fulfilling the criteria for disease progression. Any of the following is sufficient for PD.

1. Increase of > 25% in serum M-protein (also an absolute increase of at least 5 g/L) and confirmed by at least 1 investigation.
2. Increase of > 25% urinary light chain excretion (which must also be an absolute increase of at least 200 mg/24-hours and confirmed by at least 1 investigation.
3. Increase of > 25% plasma cell percentage in the marrow (which must also be an absolute increase of at least 10%).
4. Definite increase in the size or number of lytic bone lesions or extramedullary plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
5. Development of hypercalcemia (corrected serum calcium greater than 11.5 mg/dL; 2.8 mmol/L) not attributable to any other cause.

Relapse from CR (for subjects that attain CR):

Subjects who have documented CR and then achieve at least one of the following criteria are classified as relapse from CR. According to the EBMT criteria, relapse from CR is considered to be progression of disease. The date of EBMT based relapse from CR is the first date of two consecutive values fulfilling the criteria for relapse.

1. Reappearance of serum or urinary M-protein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal reconstitution.
2. Greater than or equal to 5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
3. Any of the definitions met for progression.

Stable Disease:

Subjects do not meet criteria for any of the categories above.

Study Endpoints

ORR and PFS, both as assessed by the IRC, were the co-primary endpoints of the trial. If either of these two analyses achieved the pre-specified level of significance, the study would be declared positive. The pre-specified level of significance for ORR was 2-sided 0.5% and was 2-sided 4.5% for PFS to preserve the overall type-I error for comparing the primary endpoints at the 5% level. The analysis of ORR was to occur at 16 months after the last patient first visit and an interim analysis of PFS was to occur after a minimum follow-up of 2 years from the last patient first visit and after 70% of PFS events (per IRC) had been observed.

PFS was defined as the time from randomization to the date of the first documented tumor progression as determined by the IRC using the EBMT criteria or death due to any cause, provided death does not occur more than 10 weeks (2 or more assessment visits) after the last tumor assessment. The following censoring rules were applied for PFS:

- Subjects who receive secondary anti-myeloma therapy prior to documented progression will be censored on the date of the last tumor assessment prior to the initiation of the new therapy.
- Subjects who have an event (documented progression or death) > 10 weeks (2 assessment visits) after the last prior tumor assessment will be censored at the last prior assessment.
- Subjects who neither receive subsequent therapy prior to progression nor have a progression event will be censored at their last tumor assessment.

A sensitivity analysis was also to be performed in which PFS (per IRC) was also assessed applying an intent-to-treat definition that used all data on each randomly assigned subject until either a progression event or the end of the study. In this analysis, PFS was defined as the time from randomization to the date of the first documented tumor progression (per IRC) or to death due to any cause. Subjects who neither progressed nor died were censored on the date of their last tumor assessment. There was no censoring for subsequent therapy prior to progression or for progression events following missing assessments.

ORR was defined as the proportion of randomized subjects who had either partial response or complete response as determined by the IRC using EBMT criteria.

The key secondary endpoint was overall survival. A hierarchical procedure was used to test OS.

Statistical Analysis Plan

Study CA204004 planned to randomize 640 subjects in a 1:1 ratio to receive elotuzumab + lenalidomide and dexamethasone (E+Ld) or lenalidomide and dexamethasone (Ld). Randomization was stratified by: β 2 microglobulin (< 3.5 mg/L vs. \geq 3.5 mg/L), number of prior lines of therapy (1 vs. 2 or 3), and prior IMiD (no vs. prior thalidomide only vs. other). With 640 subjects, the study had 88.5% power to declare statistical significance at 2-sided alpha level of 0.005 for a difference of 15% in ORR between the two treatment arms (75% ORR in the E+Ld arm vs. 60% ORR in the Ld arm). The total targeted number of PFS events was 466, which would provide 88.7% power to declare statistical significance at 2-sided alpha level of 0.045 for the E+Ld versus Ld hazard ratio of 0.74 (or correspondingly, an improvement of 3.9 months in median PFS from 11.1 months to 15.0 months by adding elotuzumab). The study was also powered at 80% for the key secondary endpoint OS, with 427 events targeted at the final OS analysis at 2-sided alpha level of 0.05 testing a hazard ratio of 0.76 for the OS benefit of elotuzumab once the study had met its primary endpoints.

The primary analysis population was the intent-to-treat population including all randomized subjects. Primary analyses of ORR and PFS were based on the IRC evaluation. The primary analysis of ORR compared the two treatment arms using the Cochran-Mantel-Haenszel test stratified by the treatment randomization factors. The primary analysis of PFS compared the two treatment arms via the log-rank test stratified by the treatment randomization factors. Estimation of the hazard ratio for PFS was based on a Cox proportional hazards model with stratifications by the same factors in the stratified log-rank test. For the primary analysis, PFS was censored at the date of the last adequate tumor assessment, if subjects had started any subsequent systematic-therapy or missed ≥ 2 assessments (> 10 weeks) prior to a documented tumor progression or death.

There was no planned interim analysis for ORR. The only ORR analysis was planned at a minimum follow-up of 16 months from the last patient first visit. For PFS, there was one planned interim efficacy analysis, at a minimum of 2 years follow-up in all subjects and after at least 70% of the total targeted PFS events had occurred. One formal interim analysis was planned for OS, to occur at one year after the interim PFS analysis if the interim PFS result was statistically significant, or otherwise to occur at the time of the final PFS analysis.

Statistical Reviewer Comments:

- *ORR was introduced into the protocol as a co-primary endpoint in 2014 following a discussion between the Applicant and the Agency. The alpha allocation for ORR was much less than the alpha allocation for PFS, so that the study was not likely to stop based solely on the ORR result. In addition, a minimum of 16 months patient follow-up was required for a better determination on the duration of response as part of efficacy evaluation.*
- *The overall study Type I error was controlled at 2-sided 0.05, by splitting the alpha between the 2 co-primary endpoints and by hierarchically testing the secondary endpoint OS after the primary endpoints.*
- *With the requirement of at least 2 years of patient follow-up, the number of PFS events reached 384 or 82.4% of total targeted events at the interim analysis. The significance level for testing PFS benefit at 82.4% of information was 2-sided 0.0239 as the efficacy boundary according to the Lan-DeMets alpha spending function for an interim analysis.*
- *The Applicant clarified previously the timing of the interim OS analysis. It is expected to take a minimum follow-up of 3 years from last patient first visit to reach two thirds of the targeted death events, and therefore the formal interim OS analysis is not planned until at least one year beyond the interim PFS analysis.*

Protocol Amendments

Amendments to the protocol are listed in the table below. Notable changes include a revision of the primary endpoint in Amendment 10. In that amendment, ORR was added to PFS as the primary endpoint. This change allowed for a positive result in either ORR or PFS to be sufficient

for a declaration of success. Although this is a somewhat liberal allowance, ultimately, both ORR and PFS were positive. Another notable change occurred in Amendment 12. This amendment changed the elotuzumab rate of infusion. In the original protocol, the maximum infusion rate was 2 ml/min. Amendment 12 changed the maximum infusion rate to 5 ml/min. This issue is discussed subsequently in the safety section.

Table 4. Protocol Amendments Study CA204004

Date	Amendments
14 Oct 2010	Original protocol
25 Jan 2011	Amendment 1: Pharmacogenetics blood sample <ul style="list-style-type: none"> Permitted the collection and storage of blood samples for future pharmacogenetic research. Blood samples and health information would be collected from the main clinical trial CA204004.
27 Jan 2011	Amendment 2: Revised Protocol 01 <ul style="list-style-type: none"> Interim analysis comparison of PFS for early stopping for efficacy or futility at 50% of events removed. A formal interim safety analysis after 120 subjects was retained. The eligibility criteria for prior therapy was updated: <ul style="list-style-type: none"> Limited prior lines of therapy to 1 - 3 (original protocol allowed 1 - 4). Require at least 9 months between last dose of prior lenalidomide and disease progression (original protocol required at least 4 months). Limit prior exposure to lenalidomide to no more than 9 months (no prior limit in original protocol). Limit prior lenalidomide to no more than 10% of randomized subjects (no prior limit in original protocol). Updated dexamethasone dose modification guidelines 24 hr-urine collection window increased to \pm 5 days Clarified efficacy lab collections requirements for central lab assessments, bone marrow aspiration is mandatory while bone marrow biopsy is optional and that bone marrow will be subject to flow cytometry for confirmation of clonality.
09 Mar 2011	Amendment 3: ECG sub-study <ul style="list-style-type: none"> Permitted the collection of ECG data at select sites from subjects randomized to the E-Ld arm in trial CA204004.
10 Mar 2011	Amendment 4: Site specific amendment <ul style="list-style-type: none"> Allowed the protocol required PK and immunogenicity assessments to be optional at MD Anderson Cancer Center.
14 Jul 2011	Amendment 5: Site specific amendment <ul style="list-style-type: none"> Permitted the collection of ECG data at select Canadian sites from subjects randomized to the E-Ld arm in trial CA204004.
24 Jun 2011	Amendment 6: Site specific amendment <ul style="list-style-type: none"> Added local regulatory requirements for Japanese sites
15 Mar 2012	Amendment 7: Revised Protocol 02 <ul style="list-style-type: none"> Clarification of subject eligibility or study procedures. Including revision to the definition of measurable disease, limited exclusion criteria to <i>active</i> hepatitis Modification of screening requirements to conform to the standard of care and to enhance overall study conduct. A revision was made to timing of when pregnancy testing must be completed. This

Date	Amendments
	<p>change is in compliance with a recently approved, company-wide SOP for women of childbearing potential participating in clinical trials conducted by the Sponsor.</p> <ul style="list-style-type: none"> • Instructions for what should be done with missed doses of lenalidomide or dexamethasone. • Clarification of the requirement to discontinue elotuzumab and lenalidomide if a subject becomes pregnant. • Timing and details surrounding when certain study assessments are Performed was changed. Timing of elotuzumab pre-medications changed from 30-60 min to 30-90 minutes prior to elotuzumab. • An update to the shelf-life of reconstituted elotuzumab.
08 Feb 2012	<p>Amendment 8: Correlative sub-study</p> <ul style="list-style-type: none"> • Allowed for the evaluation of CS1 expression patterns on myeloma and NK cells .
02 Apr 2012	<p>Amendment 9: ECG sub-study</p> <ul style="list-style-type: none"> • Permitted the collection of ECG data at select EU sites from subjects randomized to the E-Ld arm in trial CA204004.
04 Apr 2012	<p>Amendment 10: Revised Protocol 03</p> <ul style="list-style-type: none"> • Addition of formal interim PFS analyses- to be conducted when 70% of the events have been observed. • A change in the hierarchy of the statistical analysis by including objective response rate (ORR) as a co-primary endpoint with PFS • The addition of a secondary objective to compare the change from baseline of the mean score of pain severity and the change from baseline of the mean score of pain interference using the Brief Pain Inventory - Short Form (BPI-SF) of E-Ld versus Ld • The addition of an exploratory objective to estimate the PFS rates at 1, 2, 3 years and the OS rates at 3, 4, 5 and 6 years. • The removal of the assessment of the Brief Pain Inventory – Short Form (BPI-SF) as an exploratory objective. • The DMC will review the formal interim efficacy analysis of PFS and ORR and provide recommendation to the Sponsor • Required revisions to the power, endpoint definitions and efficacy analyses due to the addition of the interim analyses.
21 Apr 2014	<p>Amendment 11: Site specific amendment</p> <ul style="list-style-type: none"> • Deleted appendix 7, which contained the roles and responsibilities of study personnel from Amendment 6 for Japanese sites
07 May 2014	<p>Amendment 12: Revised Protocol 04</p> <ul style="list-style-type: none"> • Elotuzumab infusion rate escalation plan added to decrease the infusion of elotuzumab to approximately 1 hour. In the previous versions, the maximum infusion rate was 2 ml/min. This amendment changed the maximum infusion rate to 5 ml/min. • Change to the UPEP efficacy testing to reduce the requirement of 24 hour urine collection in a subset of patients • Broadening of the medications that can be used for thromboprophylaxis. • Additional Clarifications in the protocol serve to reduce any ambiguity regarding study procedures, and provide additional guidance of the EBMT efficacy requirements.

Source: FDA Reviewer’s review of protocol amendments and protocol summary of changes

Data Quality and Integrity: Sponsor's Assurance

The Sponsor incorporated a strategy to assure data quality and integrity. These included the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel prior to study initiation, periodic monitoring visits by a CRO (b) (4) and use of centralized facilities (b) (4). (b) (4) Electronic data capture and electronic case report forms (eCRFs) were used in the study. Data cleaning and quality control checks were implemented by (b) (4).

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor has provided attestation that the study was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization and in accordance with the United States Code of Federal Regulations, Title 21, part 50 (21 CFR50) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC.

Financial Disclosure

The applicant submitted financial disclosure information for the investigators for this trial. One investigator, (b) (6) reported holding Abbott stock valued at \$50,000. Abbott is in a (b) (4) relationship with BMS for the elotuzumab compound. This investigator enrolled (b) (4) subjects on the trial. It is not anticipated that this financial interest affects the integrity of the trial (see Financial Disclosure in the Appendix).

Patient Disposition

As of the clinical database lock date 04-Nov-2014, Study CA204004 had 646 randomized subjects and 635 subjects received study treatment. At the time of database lock, 113 subjects (35.4%) were still being treated with E+Ld and 66 subjects (20.9%) were still being treated with Ld. The three most common reasons for treatment discontinuation were the same for both treatment groups, including: disease progression, study drug toxicity, and adverse events. The treatment discontinuation rate was lower for the E+Ld treated subjects compared to the Ld treated subjects for all the three most common reasons leading to a treatment discontinuation.

Table 5. Subject Disposition Study CA204004

(As of 04-Nov-2014)

N (%)	E+Ld Arm	Ld Arm	Total
Randomized	321	325	646
Received study treatment ¹	319 (99.4)	316 (97.2)	635 (98.3)
Still on study treatment ²	113 (35.4)	66 (20.9)	179 (28.2)
Off study treatment ²	206 (64.6)	250 (79.1)	456 (71.8)
Reason for off treatment ² :			
Disease progression	135 (42.3)	149 (47.2)	284 (44.7)
Study drug toxicity	28 (8.8)	42 (13.3)	70 (11.0)
Adverse events unrelated to study drug	15 (4.7)	26 (8.2)	41 (6.5)
Treatment refusal	20 (6.3)	13 (4.1)	33 (5.2)
Consent withdrawal	4 (1.3)	8 (2.5)	12 (1.9)
Death	1 (0.3)	1 (0.3)	2 (0.3)
Other ³	3 (0.9)	11 (3.5)	14 (2.2)

E+Ld = elotuzumab + lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone

¹ Percentage based on randomized subjects

² Percentage based on subjects received study treatment

³ Other included selection criteria violation, lack of protocol compliance, and lost to follow-up

Protocol Violations/Deviations

Protocol deviations that could be categorized as either significant or relevant protocol deviations were included in the submission. Significant protocol deviations were defined as those deviations from the protocol likely to have an impact on the subject's rights, safety, or well-being, and/or the validity of the data from analysis. Relevant protocol deviations were significant protocol deviations that were programmable and could potentially affect the interpretability of study results. Both significant and relevant protocol deviations were predefined in the protocol and statistical analysis plan.

In the ITT population, there were 26 subjects with a relevant protocol deviation, 11 in the E-Ld arm and 15 in the Ld arm. The table below includes a categorization of the deviations.

Table 6. Relevant Protocol Deviations Study CA204004

Deviation	E-Ld (N=321) n (%)	Ld (N=325) n (%)	Total (N=646) n (%)
Eligibility Deviations			
Ineligible for this study due to failure to meet criteria for retreatment with lenalidomide	3 (0.9%)	5 (1.5%)	8 (1.2%)
Non-measurable disease	3 (0.9%)	0	3 (0.5%)
On-Treatment Deviations			
No baseline tumor measurement	4 (1.2%)	9 (2.8%)	13 (2.0%)
Received non-assigned treatment regimen throughout the study	1 (0.3%)	0	1 (0.2%)
Subjects continuing to receive study therapy after 10 weeks of documented progression per investigator	1 (0.3%)	2 (0.6%)	3 (0.5%)

More than 133 subjects had a documented significant protocol deviation. There were some significant protocol deviations that occurred to all patients treated at a given site, such as those at site 4943, in which the site did not perform compliance checks for oral dexamethasone returned by patients. Many of the significant protocol deviations pertained to failure to obtain laboratory tests that pertained to efficacy assessments, ie- failure to obtain UPEP, free light chain testing, immunofixation, or skeletal survey.

Table 7. Demographic characteristics Study CA204004

Demographic Parameters	E-Ld (N=321) n (%)	Ld (N=325) n (%)	Total (N=646) n (%)
Sex			
Male	192 (59.8)	193 (59.4)	385 (59.6)
Female	129 (40.2)	132 (40.6)	261 (40.4)
Age			
Mean years (SD)	66.2 (9.3)	65.3 (10.3)	65.7 (9.8)
Median (years)	67	66	66
Min, max (years)	37, 88	38, 91	37, 91
Age Group			
< 65 years	134 (41.7)	142 (43.7)	276 (42.7)
≥ 65 years	187 (58.3)	183 (56.3)	370 (57.3)
≥ 65 - < 75 years	119 (37.1)	122 (37.5)	241 (37.3)
≥ 75 years	68 (21.2)	61 (18.8)	129 (20.0)
Race			
White	264 (82.5)	280 (86.2)	544 (84.2)
Black or African American	13 (4.1)	10 (3.1)	23 (3.6)
Asian	33 (10.3)	31 (9.5)	64 (9.9)
American Indian or Alaska Native	-	-	-
Native Hawaiian or Other Pacific Islander	1 (0.3)	-	1 (0.2)
Other	9 (2.8)	4 (1.2)	13 (2.0)
Missing ¹	1 (0.3)	0	1 (0.2)
Ethnicity			
Hispanic or Latino	5 (1.6)	1 (0.3)	6 (0.9)
Not Hispanic or Latino	28 (8.7)	33 (10.2)	61 (9.6)
Missing ¹	288 (89.7)	291 (89.5)	579 (89.6)
Region			
United States	33 (10.3)	34 (10.5)	67 (10.4)
Rest of the World	288 (89.7)	291 (89.5)	579 (89.6)
Canada	33 (10.3)	34 (10.5)	67 (10.4)
South America	-	-	-
Europe	196 (61.1)	194 (59.7)	390 (60.4)
Asia*	46 (14.3)	48 (14.7)	94 (14.6)
Africa	-	-	-
Australia	13 (4.0)	15 (4.6)	28 (4.3)

¹ Data on race and/or ethnicity were not collected in many countries because of local regulations.

* Includes Japan, Turkey and Israel

Source: FDA Clinical Reviewer's Analysis

The demographic characteristics were balanced between the two arms. The median age at diagnosis in the United States is 66 years (4). The median age in this trial of relapsed and refractory patients was 66. The patients in this trial may be slightly younger than the population of patients with relapsed and refractory multiple myeloma in the United States, but this likely does not represent a significant difference. Ten (10) percent of the patients enrolled on the trial were from the United States. In the US, African Americans account for twice as many new cases of multiple myeloma than Caucasians (5). The trial only enrolled 3.6 percent of patients that were African American.

Other Baseline Characteristics

The table below gives a summary on baseline characteristics, other than demographics, for Study CA204004 randomized subjects. These tabulated baseline characteristics include the randomization stratification factors, and protocol-specified efficacy subgroup analysis factors. In general, subjects in the two study arms were not dramatically different with respect to baseline characteristics.

Table 8. Baseline Disease Characteristics Study CA204004

	E-Ld (N=321) n (%)	Ld (N=325) n (%)	Total (N=646) n (%)
Time from Initial MM Diagnosis			
Median (years)	3.5	3.5	3.5
Range	0.3, 17.4	0.1, 16.2	0.1, 17.4
Myeloma Subtype			
IgG	218 (67.9)	234 (72.0)	452 (70.0)
IgA	69 (21.5)	62 (19.1)	131 (20.3)
IgD	3 (0.9)	5 (1.5)	8 (1.2)
IgM	1 (0.3)	1 (0.3)	2 (0.3)
Light Chain Only Disease	27 (8.4)	20 (6.2)	47 (7.3)
Bi-clonal	2 (0.6)	3 (0.9)	5 (0.8)
Not Classified	1 (0.3)	-	1 (0.2)
Number of Prior Therapies			
Median	2	2	2
Range ¹	1,5	1,4	1,5
1	151 (47.0)	159 (48.9)	310 (48.0)
2-3	170 (53.0)	166 (51.1)	336 (52.0)
Prior Therapy²			
Bortezomib	219 (68.2)	231 (71.1)	450 (69.7)
Lenalidomide	16 (5.0)	21 (6.5)	37 (5.7)

	E-Ld (N=321) n (%)	Ld (N=325) n (%)	Total (N=646) n (%)
Prior IMiD therapy			
None	155 (48.3)	151 (46.5)	306 (47.4)
Prior thalidomide only	150 (46.7)	153 (47.1)	303 (46.9)
Other	16 (5.0)	21 (6.5)	37 (5.7)
Prior stem cell transplant			
Yes	167 (52.0)	185 (56.9)	352 (54.5)
No	154 (48.0)	140 (43.1)	294 (45.5)
Response to most recent line of therapy			
Refractory	113 (35.2)	114 (35.1)	227 (35.1)
Relapsed	207 (64.5)	211 (64.9)	418 (64.7)
Baseline ECOG performance status			
0-1	297 (92.5)	291 (89.5)	588 (91.0)
2	24 (7.5)	34 (10.5)	58 (9.0)
Baseline creatinine			
< 60 ml/min	96 (29.9)	75 (23.1)	171 (26.5)
>= 60 ml/min	225 (70.1)	250 (76.9)	475 (73.5)
Myeloma risk category			
High risk	60 (18.7)	66 (20.3)	126 (19.5)
Low risk	14 (4.4)	22 (6.8)	36 (5.6)
Standard risk	231 (72.0)	221 (68.0)	452 (70.0)
Not evaluable	16 (5.0)	16 (4.9)	32 (5.0)
Cytogenetic Abnormalities n/n tested (%) ³			
t(14;16)	11/313 (3.5)	5/ 322 (1.6)	16/635 (2.5)
t(14;20)	1/258 (0.4)	1/277 (0.4)	2/ 535 (0.4)
del(17p)	102/ 315 (32.4)	104/ 322 (32.3)	206/ 637 (32.3)
t(4;14)	30/315 (9.5)	31/ 321 (9.7)	61/ 636 (9.6)
del 13	4/256 (1.6)	6/ 277 (2.2)	10/ 533 (1.9)
hypodiploidy	13/255 (5.1)	13/ 275 (4.7)	26/ 530 (4.9)
1q21 abnormalities	147/ 316 (46.5)	163/ 322 (50.6)	310/ 638 (48.6)
Baseline β2 microglobulin			
Median (mg/dL)	0.32	0.33	0.33
< 3.5 mg/L	173 (53.9)	179 (55.1)	352 (54.5)
>= 3.5 mg/L	147 (45.8)	146 (44.9)	293 (45.4)
ISS Stage at enrollment			
I	141 (43.9)	138 (42.5)	279 (43.2)
II	102 (31.8)	105 (32.3)	107 (32.0)
III	66 (20.6)	68 (20.9)	134 (20.7)
Missing	12 (3.7)	14 (4.3)	26 (4.0)

	E-Ld (N=321) n (%)	Ld (N=325) n (%)	Total (N=646) n (%)
Baseline LDH			
< 300 IU/L	241 (75.1)	239 (73.5)	480 (74.3)
>= 300 IU/L	69 (21.5)	76 (23.4)	145 (22.4)

¹ One patient in the E-Ld arm had received 5 prior therapies; 1 patient in the Ld arm had received 4 prior therapies.

² Number of Subjects that had previously received the therapy listed.

³ Cytogenetic test results were not available for a number of subjects for each test. Percentage is based on number tested, not number in each arm.

Source: FDA Clinical Reviewer's Analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance was monitored by drug accountability as well as the subject's medical record and CRF. Elotuzumab and intravenous dexamethasone doses were administered under observation.

All subjects received concomitant medications. The most frequently used (>25% of E-Ld and Ld subjects respectively) concomitant medications were in the following therapeutic classes: analgesics (96.9% and 93.1%), anti-bacterials (88.1% and 87.1%), antivirals (55.0% and 50.5%), treatment of bone disease (bisphosphonates) (48.7% and 54.3%), antithrombotic agents (48.7% and 46.7%), laxatives (37.1% and 32.2%), psycholeptics (35.5% and 33.4%), systemic corticosteroids (29.6% and 30.3%), granulocyte stimulating agents (24.8% and 30.9%), antiemetics (28.9% and 24.0%), anti-anemics (27.7% and 25.2%), antihypertensives (27.4% and 29.3%), and diuretics (28.6% and 29.7%).

Efficacy Results – Primary Endpoint

The table below shows the results for the study co-primary endpoints PFS and ORR based on assessments by IRC. For PFS, the estimated hazard ratio was 0.70 for E+Ld over Ld, and the estimated difference between treatment groups in median PFS was 4.5 months. For ORR, 78.5% of the subjects in the E+Ld treatment compared to 65.5% of subjects in the Ld treatment group achieved a response. The estimated median duration of response was 20.7 months and 16.6 months for the E+Ld group and the Ld group, respectively.

Table 9. Primary Efficacy Results Study CA204004

All Randomized Subjects

Efficacy parameter	E+Ld N = 321	Ld N = 325
IRC-assessed PFS		
Number of events (%)	179 (55.8)	205 (63.1)
1-year PFS rate (95% CI)	68% (63%, 73%)	57% (51%, 62%)
2-year PFS rate (95% CI)	41% (35%, 47%)	27% (22%, 33%)
Median in months (95% CI)	19.4 (16.6, 22.2)	14.9 (12.1, 17.2)
Hazard ratio ¹ , E+Ld/Ld (95% CI)	0.70 (0.57, 0.85)	
p-value ²	0.0004	
IRC-assessed ORR		
Number of Responders ³	252	213
% of Responders (95% CI)	78.5 (73.6, 82.9)	65.5 (60.1, 70.7)
Odds Ratio ⁴	1.94	
95% CI	(1.36, 2.77)	
p-value	0.0002	

E+Ld = elotuzumab + lenalidomide and dexamethasone; IRC = independent review committee; PFS = progression-free survival; ORR = overall response rate; CI = confidence interval

¹ Calculated using Cox hazards model with randomization factors as stratification factors

² 2-sided p-value for stratified log-rank test

³ subjects whose best overall response was partial response or better based on IRC assessments

⁴ computed using Cochran-Mantel-Haenszel test stratified by the randomization factors

The table below shows the investigator-determined PFS result and other pre-specified sensitivity analyses for PFS. They were all supportive of the primary analysis result.

Table 10. Sensitivity Analyses to the Primary IRC-assessed PFS analysis

Difference to the primary PFS analysis	E+Ld	Ld
Based on investigator-determined PFS		
Number of events/number of subjects	167/321	201/325
Hazard ratio, E+Ld/Ld (95% CI)	0.65 (0.51, 0.83)	
p-value	<0.0001	
Not censored for subsequent anti-myeloma therapy or missing assessments		
Number of events/number of subjects	192/321	231/325
Hazard ratio, E+Ld/Ld (95% CI)	0.68 (0.56, 0.82)	
p-value	<0.0001	
Did not adjust for stratification factors		
Number of events/number of subjects	179/321	205/325
Hazard ratio, E+Ld/Ld (95% CI)	0.69 (0.57, 0.85)	
p-value	0.0003	

Difference to the primary PFS analysis	E+Ld	Ld
Used only subjects who did not have major protocol violations		
Number of events/number of subjects	188/310	227/310
Hazard ratio, E+Ld/Ld (95% CI)	0.69 (0.57, 0.84)	
p-value	0.0002	

E+Ld = elotuzumab + lenalidomide and dexamethasone; IRC = independent review committee; PFS = progression-free survival; CI = confidence interval

Data Quality and Integrity – Reviewers’ Assessment

The clinical reviewer audited a sample of case report forms for consistency with datasets and patient narratives. The overall quality and integrity of the application was acceptable.

Efficacy Results – Secondary and other relevant endpoints

The overall survival (OS) data at the time of clinical database cutoff were not mature with occurrence of only 49% of the total required events for the final analysis. The preliminary OS data estimated a hazard ratio of 0.71 (95% CI: 0.54, 0.93) for E+Ld over Ld.

Table 11. Preliminary Overall Survival Result Study CA204004

All Randomized Subjects

Efficacy parameter	E+Ld N = 321	Ld N = 325
Overall Survival		
Number of events (%)	94 (29.3)	116 (35.7)
1-year OS rate (95% CI)	91% (87%, 93%)	83% (78%, 87%)
2-year OS rate (95% CI)	74% (69%, 79%)	68% (63%, 73%)
Median in months (95% CI)	NE (36.2, NE)	34.6 (29.0, NE)
Hazard ratio ¹ , E+Ld/Ld (95% CI)	0.71 (0.54, 0.93)	

E+Ld = elotuzumab + lenalidomide and dexamethasone; OS = overall survival; CI = confidence interval

¹ Calculated using Cox hazards model with randomization factors as stratification factors

Statistical Reviewer Comment:

Per Protocol, the first formal OS analysis is not to occur until one year after the PFS analysis. The OS analysis presented was based on data available at the same data cutoff as for PFS; therefore, the OS result should be considered as descriptive only. No formal interpretation can be made at this point.

Dose/Dose Response

There were no large dose-finding trials. Dose modifications for toxicity or lack of efficacy were not studied.

Durability of Response

There were too few patients on treatment for a long duration to assess the effect of elotuzumab over time.

Persistence of Effect

No patients were retreated with elotuzumab after elotuzumab was discontinued.

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses

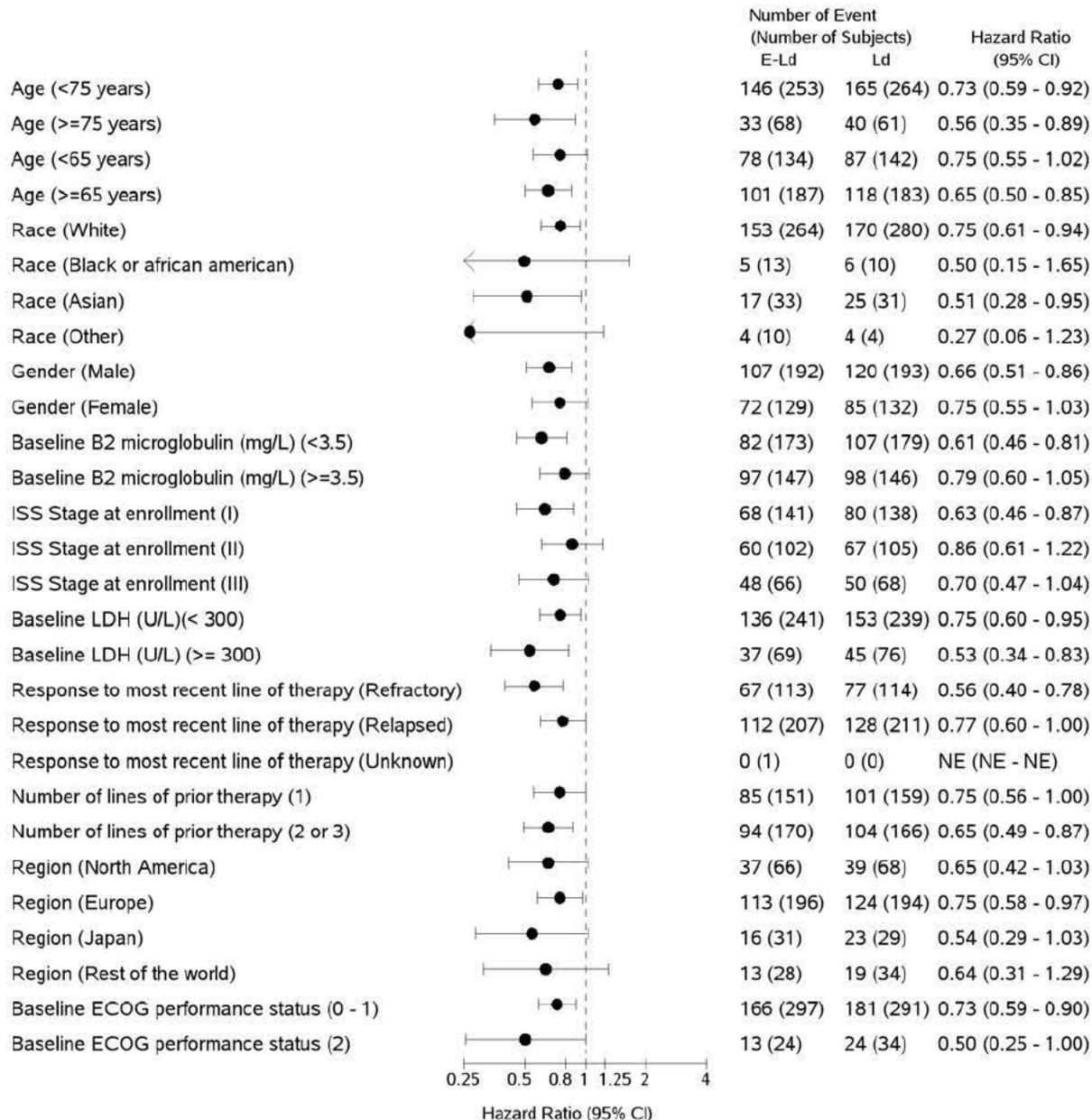
Subgroup results are displayed in Figure 10 by: age, race, gender, region, baseline β 2 microglobulin, ISS stage at enrollment, baseline LDH, baseline creatinine clearance, response to most recent line of therapy, number of prior lines of therapy, and baseline ECOG performance status, prior IMiD therapies, disease risk, and individual cytogenetic abnormalities.

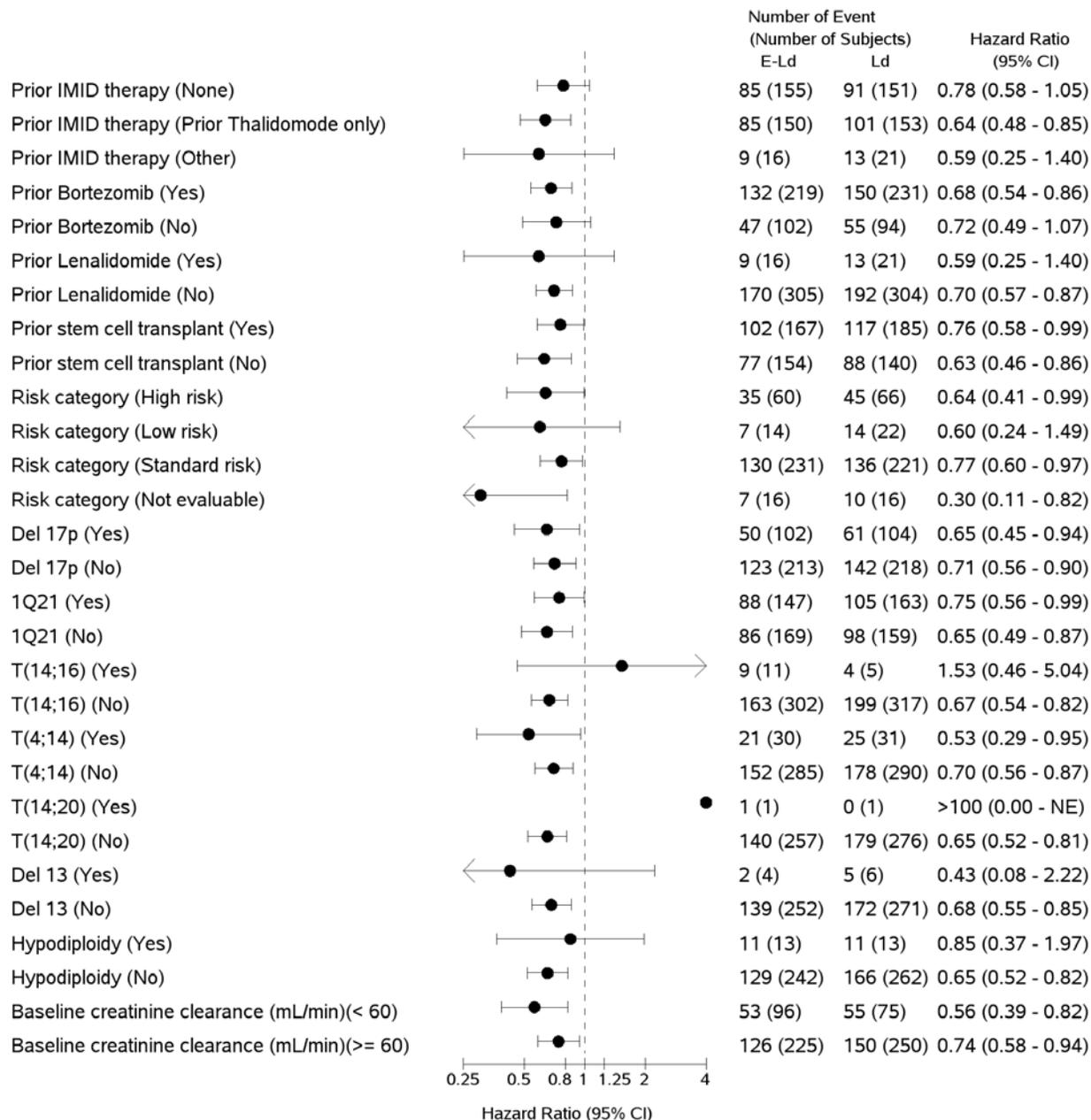
Statistical Reviewer Comment:

The subgroup analyses were not adjusted for multiplicity and therefore should be considered as exploratory. Except for extremely small subgroups, the performed subgroup analyses did not reveal any subgroups to be outliers in the comparison between treatment groups for PFS.

Figure 10. IRC-PFS Subgroup Hazard Ratios Study CA204004

All Randomized Subjects





Source: Applicant's Final Clinical Study Report, pg. 103

IRC and investigator concordance

The table below tabulates the concordance between IRC-assessed PFS and investigator-determined PFS. Disagreement rate between the IRC and the investigators in the determination of event status was 10% in the E+Ld arm and was 6.8% in the Ld arm. Almost all the subjects for whom there was a disagreement in PFS event time between the IRC and the investigators had the date of the PFS event determined earlier by the IRC, making the estimated medians based on IRC assessments shorter than the ones based on investigator's assessments.

Table 12. IRC-assessed PFS vs. Investigator-determined PFS Study CA204004

	E+Ld (N = 321) n (%)	Ld (N = 325) n (%)	Total (N = 646) n (%)
Agree in event status and timing	112 (34.9)	140 (43.1)	252 (39.0)
As an event, by IRC and INV	55 (17.1)	70 (21.5)	125 (19.3)
As censored, by IRC and INV	57 (17.8)	70 (21.5)	127 (19.7)
Agree in event status, but not timing	177 (55.1)	163 (50.2)	340 (52.6)
As an event, IRC dated earlier	75 (23.4)	39 (12.0)	114 (17.6)
As an event, IRC dated later	0	2 (0.6)	2 (0.3)
As censored, IRC dated earlier	92 (28.7)	111 (34.2)	203 (31.4)
As censored, IRC dated later	10 (3.1)	11 (3.4)	21 (3.3)
Disagree in event status	32 (10.0)	22 (6.8)	54 (8.4)
Event by IRC, Censored by INV	10 (3.1)	9 (2.8)	19 (2.9)
Censored by IRC, event by INV	22 (6.9)	13 (4.0)	35 (5.4)
Estimated median in months (95% CI)			
IRC	19.4 (16.6, 22.2)	14.9 (12.1, 17.2)	17.0 (15.7, 18.5)
INV	22.7 (18.5, 25.8)	16.7 (13.4, 19.4)	18.9 (17.3, 20.6)

E+Ld = elotuzumab + lenalidomide and dexamethasone; IRC = independent review committee; INV = investigator; CI = confidence interval

Subsequent systemic-therapy

The protocol-specified primary analysis for the primary endpoint IRC-assessed PFS censored any subsequent systemic-therapy. However, an initiation of alternative treatment for the disease may indicate potential disease deterioration. The review team requested additional sensitivity analyses for IRC-assessed PFS treating any systemic-therapy as a PFS event with the start of the subsequent therapy as the event date for both treatment groups and for one treatment group but not the other. The results as shown in Table 13 remain supportive to the primary analysis.

Table 13. Potential IRC-PFS results with subsequent anti-myeloma therapy as an event

Treating any subsequent systemic-therapy as a PFS event		
In Ld arm only	In both E+Ld and Ld arms	In E+Ld arm only
E+Ld (events: 179/321) Ld (events: 236/325) HR (95% CI)= 0.61 (0.50, 0.74) p-value < 0.0001	E+Ld (events: 199/321) Ld (events: 236/325) HR (95% CI)= 0.68 (0.56, 0.82) p-value < 0.0001	E+Ld (events: 199/321) Ld (events: 205/325) HR (95% CI)= 0.77 (0.63, 0.97) p-value = 0.0104

E+Ld = elotuzumab + lenalidomide and dexamethasone; HR = hazard ratio; CI = confidence interval

6.2. Study CA204009

A Phase 2, Randomized Study of Bortezomib/dexamethasone with or without Elotuzumab in Subjects with Relapsed/Refractory Multiple Myeloma

6.2.1. Study Design

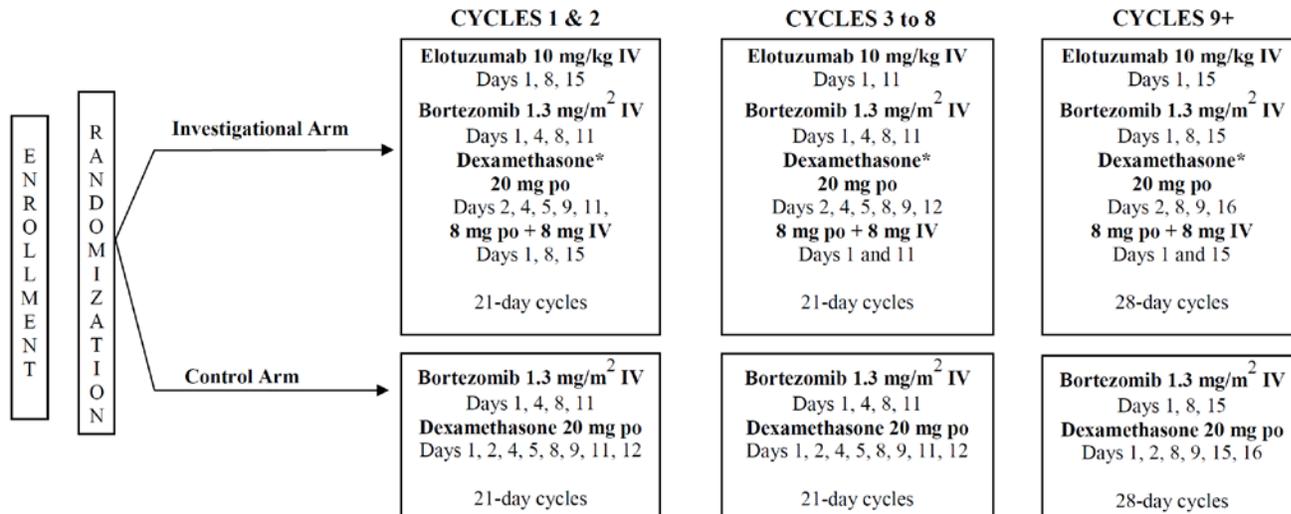
Overview and Objective

Study CA204009 was a phase 2, randomized, open-label, multicenter trial of bortezomib/dexamethasone with or without elotuzumab in patients with previously treated, relapsed or refractory multiple myeloma. The primary objective of the trial was to compare the PFS between treatment arms.

Trial Design

In Study CA204009, patients were randomized to the two treatment arms in a 1:1 ratio. There were 3 stratification factors: prior bortezomib (yes vs. no), presence of at least one FcγRIIIa V allele (yes vs. no), and number of prior lines of therapy (1 vs. 2). During cycles 1-8, subjects received E-Bd or Bd in 21 days cycles. Beginning in Cycle 9, subject received study drug in 28 day cycles. Treatment continued until disease progression, unacceptable toxicity or the subject met other criteria for study drug discontinuation. The study design for CA2040009 is included below.

Figure 11. Design Schema Study CA204009



Source: Applicant's Response to Information request received 9/10/15, Clinical Protocol pg. 5

Trial Population:

Eligible subjects included those with multiple myeloma who had documented disease progression after or during their most recent therapy, had received 1 or 2 prior lines of therapy, had measurable disease, and met other eligibility criteria. Patients were excluded if they had previously been treated with a proteasome inhibitor other than bortezomib. Given that

patients might be randomized to the control arm of bortezomib/dexamethasone, patients were excluded if they were refractory or intolerant of bortezomib defined as:

1. Progression while on bortezomib therapy or within 2 months of the last dose of bortezomib; or
2. Failed to achieve at least a PR while receiving bortezomib; or
3. Discontinued bortezomib due to a grade ≥ 3 toxicity.

Patients with primary refractory disease were also excluded. Primary refractory disease was defined as best response of stable disease to any prior therapy.

Study Treatment:

Eligible subjects received elotuzumab in combination with bortezomib and dexamethasone or bortezomib and dexamethasone alone.

Elotuzumab was administered intravenously at a dose of 10 mg/kg on Days 1, 8, and 15 in a 21 day cycle for Cycles 1 and 2. For Cycles 3-8, elotuzumab was administered at a dose of 10 mg/kg on Days 1 and 11 in 21-day cycles. For cycle 9 and beyond, elotuzumab was administered at a dose of 10 mg/kg on Days 1 and 15 in 28 day cycles.

With regards to the infusion rate, the first dose was to be administered at an initial rate of 0.5 mL per minute. If the subject did not have an infusion reaction within 30 minutes, the rate was to be increased by 0.5 mL per minute. If the subject still did not have an infusion reaction within 30 minutes, the rate was to be escalated to a maximum of 2 mL per minute. If a subject experienced a grade ≥ 2 infusion reaction, the infusion was to be interrupted.

The second dose of elotuzumab was to be initiated at an infusion rate of 1 mL per minute if no infusion reactions were reported with the first elotuzumab infusion. If the subject did not have an infusion reaction during the first 30 minutes of the second dose, the infusion rate was to be escalated by 1.0 mL per minute to a maximum infusion rate of 2 mL per minute.

If no infusion reactions were observed during the first cycle of elotuzumab, the second cycle could commence at a rate of 2 mL per minute.

Once subjects had received four consecutive cycles without grade ≥ 2 infusion reactions, the infusion rate at subsequent cycles could be increased by 1 mL per minute in a stepwise fashion in each cycle up to a maximum infusion rate of 5 mL per minute.

The following pre-medications were required 30-90 minutes before elotuzumab administration:

- H1 blocker: diphenhydramine (25 - 50 mg po or IV) or equivalent.
- H2 blocker: ranitidine (50 mg IV) or equivalent.
- Acetaminophen (650 - 1000 mg po).

Bortezomib was administered as 1.3 mg/m² intravenous bolus (subcutaneous administration was permitted after regulatory approval) on Days 1, 4, 8, and 11 in 21-day cycles for Cycles 1-8. For Cycle 9 and beyond, bortezomib 1.3 mg/m² was administered on Days 1, 8, and 15 in a 28-day cycle.

Dexamethasone (including the control arm) was to be administered at a weekly dose of 20 mg. For Cycles 1 and 2, In the control arm, dexamethasone 20mg orally was administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 in a 21-day cycle. In the investigational arm, dexamethasone 20 mg orally was administered on Days 2, 4, 5, 9, and 11. On days of elotuzumab infusion (Days 1, 8 and 15), dexamethasone was administered as a split dose of:

- 8 mg po (3-24 hours before the start of elotuzumab infusion) and
- 8 mg intravenously (at least 45 minutes before the start of elotuzumab infusion).

For Cycles 3-8, in the control arm, dexamethasone 20mg orally was administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 in a 21-day cycle. In the investigational arm, dexamethasone 20 mg orally was administered on Days 2, 4, 5, 8, 9, and 12. On days of elotuzumab infusion (Days 1 and 11), dexamethasone was administered as a split dose of:

- 8 mg po (3-24 hours before the start of elotuzumab infusion) and
- 8 mg intravenously (at least 45 minutes before the start of elotuzumab infusion).

For Cycle 9 and beyond, in the control arm, dexamethasone 20mg orally was administered on Days 1, 2, 8, 9, 15, and 16. In the investigational arm, dexamethasone 20 mg orally was administered on Days 2, 8, 9, and 16. On days of elotuzumab infusion (Days 1 and 15), dexamethasone was administered as a split dose of:

- 8 mg po (3-24 hours before the start of elotuzumab infusion) and
- 8 mg intravenously (at least 45 minutes before the start of elotuzumab infusion).

The treatment schedule is included below.

Figure 12. Treatment Schedule Study CA204009

Cycles 1 and 2 with 21-day cycles										
Day	1	2	4	5	8	9	11	12	15	16
Bortezomib	X		X		X		X			
Dexamethasone*	X	X	X	X	X	X	X	X ^C	X ^I	
Elotuzumab ⁺	X				X				X	

C: control arm only

I: investigational arm only

Table 4.3.1B: Treatment Schedule

Cycles 3 through 8 with 21-day cycles										
Day	1	2	4	5	8	9	11	12	15	16
Bortezomib	X		X		X		X			
Dexamethasone*	X	X	X	X	X	X	X	X		
Elotuzumab ⁺	X						X			

Table 4.3.1C: Treatment Schedule

Cycles 9+ with 28-day cycles						
Day	1	2	8	9	15	16
Bortezomib	X		X		X	
Dexamethasone*	X	X	X	X	X	X
Elotuzumab ⁺	X				X	

* Dexamethasone dosing:

On days when elotuzumab is administered (Investigational Arm only):

- Dexamethasone 8 mg po (3 to 24 hours prior to start of elotuzumab infusion) AND
- Dexamethasone 8 mg IV (at least 45 minutes prior to start of elotuzumab infusion).

On days when elotuzumab is NOT administered:

- Dexamethasone 20 mg po

+ Elotuzumab in investigational arm only

Source: Applicant's Final Clinical Study Report study CA204009, pg. 44

Study Endpoints

The primary endpoint was a comparison of investigator-assessed PFS between treatment arms in randomized subjects. The comparison was to be made at the one-sided, (b) (4) significance level as the trial was designed as a proof-of-concept trial, rather than a confirmatory trial.

Clinical Reviewer's comment: The Agency had communicated to the Applicant during the Type B Pre-BLA meeting held on March 9, 2015, that (b) (4)

Statistical Analysis Plan

Study CA204009 planned to randomize 150 subjects in a 1:1 ratio to receive elotuzumab + bortezomib and dexamethasone (E+Bd) or bortezomib and dexamethasone (Bd). Randomization was stratified by: prior proteasome use (yes vs. no), presence of at least one FcγRIIIa V allele (yes vs. no), and number of prior lines of therapy (1 vs. 2 or 3).

As indicated in the statistical analysis plan, this study was intended to be a proof-of-concept trial. The study targeted 103 investigator determined PFS events, in order to compare the treatment arms in PFS at a 2-sided 0.30 alpha level with 80% power to detect a median PFS time of 14.5 months in the E+Bd arm over a median PFS time of 10.0 months in the Bd alone arm (or correspondingly, a hazard ratio of (b) (4) for E+Bd over Bd in PFS). The study was not powered for any endpoints other than the primary endpoint.

The primary efficacy endpoint was PFS, as determined by investigators. PFS distribution was estimated for each treatment arm using the Kaplan-Meier product limit method. The primary analysis of PFS compared the two treatment arms via the log-rank test stratified by the treatment randomization factors. Estimation of the hazard ratio for PFS was based on a Cox proportional hazards model with stratifications by the same factors in the stratified log-rank test. Subjects who had not progressed or died were censored at the last tumor assessment. For the primary analysis, PFS was not censored for an initiation of alternative anti-myeloma treatment or for missing assessments prior to disease progression.

The study secondary efficacy endpoints included overall response rate and overall survival. Overall response rate was presented with associated 95% confidence interval for each treatment arm. Overall survival was to be analyzed using the same analysis method as for PFS as a time-to-event endpoint after 85 subjects had died.

Statistical Reviewer Comments:

- *Study CA204-009 was not designed to meet the regulatory standards, as a trial intended to support a proposed indication. First, the trial did not test any efficacy hypothesis at a type I error level ≤ 0.05 in order to make a confirmatory conclusion on treatment efficacy. Second, the primary analysis for progression-free survival did not account for potential impacts from use of alternative treatment or missing assessments. In addition, the trial did not use an independent review committee to perform blinded review of tumor assessments.*

- *At the time of clinical database lock for this BLA application, Study CA204009 had not reached 85 death events for the pre-specified formal overall survival analysis.*

Data Quality and Integrity: Sponsor's Assurance

The sponsor incorporated a strategy to assure data quality and integrity. They included selection of qualified investigators and appropriate study sites, investigational staff training prior to study initiation, and monitoring by Bristol-Myers Squibb representatives.

6.2.2. Study Results

Compliance with Good Clinical Practices

The sponsor has provided attestation that the study was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization and in accordance with the United States Code of Federal Regulations, Title 21, part 50 (21 CFR50) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC.

Financial Disclosure

The applicant submitted financial disclosure information for the investigators for this trial. There were 3 investigators that financial information to disclose. The first was (b) (6). This investigator had BMS stock valued at greater than \$50,000. There were no subjects treated at this site during that time period that (b) (6) participated in the trial. The other cases are (b) (6). Both investigators had Abbott stock valued at greater than \$50,000 each. Abbott is in a (b) (4) relationship with BMS for the elotuzumab compound. (b) (6) enrolled (b) (6) patients onto the trial and (b) (6) enrolled (b) (6) patient onto the trial. It is not anticipated that these financial interests affected the integrity of the trial.

Patient Disposition

As of the clinical database lock date 12-Sep-2014, Study CA204009 had 152 randomized subjects and 150 subjects received study treatment. At the time of database lock, 14 subjects (18.4%) were still being treated with E+Bd and 7 subjects (9.5%) were still being treated with Bd. The two most common reasons for treatment discontinuation were disease progression and study drug toxicity. The group of subjects who received E+Bd had a higher treatment discontinuation rate due to a disease progression but had a lower treatment discontinuation rate due to study drug related toxicity compared to the group of subjects who received Bd alone.

Table 14. Subject Disposition Study CA204009

(As of 12-Sept-2014)

N (%)	E+Bd Arm	Bd Arm	Total
Randomized	77	75	152
Received study treatment ¹	76 (98.7)	74 (98.7)	150 (98.7)
Still on study treatment ²	14 (18.4)	7 (9.5)	21 (14.0)
Off study treatment ²	62 (81.6)	67 (90.5)	129 (86.0)
Reason for off treatment ² :			
Disease progression	46 (60.5)	32 (43.2)	78 (52.0)
Study drug toxicity	8 (10.5)	13 (17.6)	21 (14.0)
Adverse events unrelated to study drug	1 (1.3)	9 (12.2)	10 (6.7)
Treatment refusal	1 (1.3)	5 (6.8)	6 (4.0)
Consent withdrawal	2 (2.6)	4 (5.4)	6 (4.0)
Other ³	4 (5.3)	4 (5.4)	8 (5.3)

E+Bd = elotuzumab + bortezomib + dexamethasone; Bd = bortezomib + dexamethasone

¹ Percentage based on randomized subjects

² Percentage based on subjects received study treatment

³ Other included selection criteria violation, lack of protocol compliance, and lost to follow-up

Table 15. Demographic Characteristics Study CA204009

Demographic Parameters	E-Bd (N=77) n (%)	Bd (N=75) n (%)	Total (N=152) n (%)
Sex			
Male	42 (54.5)	37 (49.3)	79 (52.0)
Female	35 (45.5)	38 (50.7)	73 (48.0)
Age			
Mean years (SD)	65.4 (9.5)	65.1 (10.3)	65.3 (9.9)
Median (years)	66	66	66
Min, max (years)	25,82	30, 82	25, 85
Age Group			
< 65 years	34 (44.2)	33 (44.0)	67 (44.1)
≥ 65 years	43 (55.8)	42 (56.0)	85 (55.9)
≥ 65 - < 75 years	28 (36.4)	28 (37.3)	56 (36.8)
≥ 75 years	15 (19.5)	14 (18.7)	29 (19.1)

Demographic Parameters	E-Bd (N=77) n (%)	Bd (N=75) n (%)	Total (N=152) n (%)
Race			
White	68 (88.3)	65 (86.7)	133 (87.5)
Black or African American	4 (5.2)	7 (9.3)	11 (7.2)
Asian	-	1 (1.3)	1 (0.7)
American Indian or Alaska Native	-	-	-
Native Hawaiian or Other Pacific Islander	1 (1.3)	-	1 (0.7)
Other	3 (3.9)	2 (2.7)	5 (3.3)
Missing ¹	1 (1.3)	-	1 (0.7)
Ethnicity			
Hispanic or Latino	7 (9.1)	4 (5.3)	11 (7.2)
Not Hispanic or Latino	44 (57.1)	47 (62.7)	91 (59.9)
Missing ¹	26 (33.8)	24 (32.0)	50 (32.9)
Region			
United States	25 (32.5)	23 (30.7)	48 (31.6)
Rest of the World	52 (67.5)	52 (69.3)	104 (68.4)
Canada	-	-	-
South America	-	-	-
Europe	52 (67.5)	52 (69.3)	104 (68.4)
Asia	-	-	-
Africa	-	-	-
Australia	-	-	-

¹ Data on race and/or ethnicity were not collected in many countries because of local regulations.
 Source: FDA Clinical Reviewer's Analysis

Table 16. Baseline Disease Characteristics Study CA204009

	E-Bd (N=77) n (%)	Bd (N=75) n (%)	Total (N=152) n (%)
Time from Initial MM Diagnosis			
Median (years)	3.8	3.7	3.7
Range	0.7, 24.7	0.7, 23.7	0.7, 24.7
Baseline ECOG performance status			
0-1	73 (94.8)	69 (92.0)	142 (93.4)
2	2 (2.6)	6 (8.0)	8 (5.3)

	E-Bd (N=77) n (%)	Bd (N=75) n (%)	Total (N=152) n (%)
Myeloma Subtype			
IgG	43 (55.8)	40 (53.3)	83 (54.6)
IgA	16 (20.8)	13 (17.3)	29 (19.1)
IgD	-	2 (2.7)	2 (1.3)
IgM	-	1 (1.3)	1 (0.7)
Light Chain Only Disease	6 (7.8)	5 (6.7)	11 (7.2)
Bi-clonal	1 (1.3)	-	1 (0.7)
Tri-clonal	-	3 (4.0)	3 (2.0)
Not Classified	3 (3.9)	1 (1.3)	4 (2.6)
Missing	8 (10.4)	10 (13.3)	18 (11.8)
Number of Prior Therapies			
Median	1	1	1
Range	1,3	1,3	1,3
Number of prior lines of therapy			
1	50 (64.9)	51 (68.0)	101 (66.4)
2-3	27 (35.1)	24 (32.0)	51 (33.6)
Prior Therapy			
Bortezomib	38 (49.4)	40 (53.3)	78 (51.3)
Lenalidomide	38 (49.4)	41 (54.7)	79 (52.0)
Prior PI therapy			
Yes	39 (50.6)	40 (53.3)	79 (52.0)
No	38 (49.4)	35 (46.7)	73 (48.0)
Prior IMiD			
Yes	55 (71.4)	58 (77.3)	113 (74.3)
No	22 (28.6)	17 (22.7)	39 (25.7)
Prior stem cell transplant			
Yes	29 (50.6)	41 (54.7)	80 (52.6)
No	38 (49.4)	34 (45.3)	72 (47.4)
Response to most recent line of therapy			
Partial or better	67 (87.0)	66 (88.0)	133 (87.5)
Minor or worse	9 (11.7)	8 (10.7)	17 (11.2)
Baseline β2 microglobulin			
< 3.5 mg/L	37 (48.1)	33 (44.0)	70 (46.1)
\geq 3.5 mg/L	28 (36.4)	32 (42.7)	60 (39.5)
ISS stage at enrollment			
I	26 (33.8)	19 (25.3)	45 (29.6)
II	23 (29.9)	20 (26.7)	43 (28.3)
III	11 (14.3)	16 (21.3)	27 (17.8)
Baseline LDH			
< 300 IU/L	42 (54.5)	45 (60.0)	87 (57.2)
\geq 300 IU/L	26 (33.8)	28 (37.3)	54 (35.5)

	E-Bd (N=77) n (%)	Bd (N=75) n (%)	Total (N=152) n (%)
ISS/Cytogenetic/FISH high risk			
Yes	0	5 (6.7)	5 (3.3)
No	36 (46.8)	28 (37.3)	64 (42.1)
Baseline creatinine clearance			
< 60 ml/min	25 (32.5)	24 (32.0)	49 (32.2)
≥ 60 ml/min	48 (62.3)	51 (68.0)	99 (65.1)

Efficacy Results - Primary Endpoint

The table below shows the results for the primary endpoint PFS as assessed by investigators. The estimated hazard ratio was 0.72 for E+Bd over Bd, and the estimated difference between treatment groups in median PFS was 2.8 months. The 2-sided p-value from stratified log-rank test comparing the distribution of PFS between treatment groups was (b) (4)

Table 17. Primary Efficacy Results Study CA204009

All Randomized Subjects

Efficacy parameter	E+Bd N = 77	Bd N = 75
Investigator-assessed PFS		
Number of events (%)		(b) (4)
1-year PFS rate (95% CI)		
Median in months (95% CI)		
Hazard ratio ¹ , E+Bd/Bd (95% CI)		
p-value ²		

E+Bd = elotuzumab + bortezomib and dexamethasone; PFS = progression-free survival; CI = confidence interval

¹ Calculated using Cox hazards model with randomization factors as stratification factors

² 2-sided p-value for stratified log-rank test

Statistical Reviewer Comment:

Although the primary endpoint result was positive at the pre-specified proof-of-concept significance level of 0.30, (b) (4)

Efficacy Results - Secondary and other relevant endpoints

The table below shows the results for investigator-assessed ORR and OS. The difference between treatment groups in ORR was only (b) (4)
 Overall survival analysis was descriptive with occurrence of only 40 events at the time of analysis.

Table 18. Secondary Efficacy Results Study CA204009

All Randomized Subjects

Efficacy parameter	E+Bd N = 77	Bd N = 75
Investigator-assessed ORR		
Investigator-assessed ORR		
Number of Responders ¹	(b) (4)	
% of Responders (95% CI)		
Difference in ORR		
Exact 95% CI		
OS		
Number of events (%)		
1-year OS rate (95% CI)		
Median in months (95% CI)		
Hazard ratio ² , E+Bd/Bd (95% CI)		

E+Bd = elotuzumab + bortezomib and dexamethasone; ORR = overall response rate; OS = overall survival; CI = confidence interval

¹ Subjects whose best overall response was partial response or better per IMWG criteria

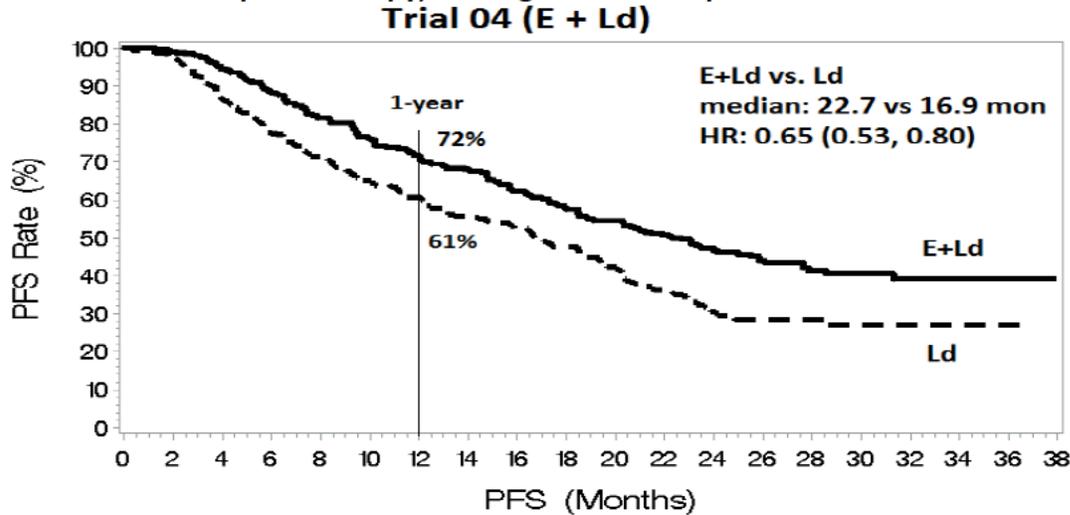
² Calculated using Cox hazards model with randomization factors as stratification factors

Additional Analyses Conducted on the Individual Trial

The figure below gives a comparison in PFS result between Study CA204004 (Trial 04) and Study CA204009 (Trial 09). The comparison was performed based on investigator–assessed PFS, because Study CA204009 did not use an independent review committee for tumor assessments. Also for making a fair comparison, censoring for a subsequent therapy or >2 missed assessments was applied to the PFS analysis in both trials. This comparison suggests that patients in Trial 09 who received elotuzumab in combination with bortezomib and dexamethasone had a worse PFS outcome when compared to the patients in Trial 04 who received elotuzumab in combination with lenalidomide and dexamethasone.

Figure 13. Study CA204004 and CA204009 comparison of Investigator-assessed PFS

(Censored for subsequent therapy, missing assessments)



Trial 09 (E + Bd)



In addition, considering that the PFS and OS analyses represented in the submitted application were based on a median follow-up time only about a year, the review team requested updated analyses for PFS and OS for Study CA204009. The table below shows the updated results provided by Applicant in comparison to the results from the initial study report. The updated results include about one more year of follow-up. The updated hazard ratio for OS is estimated at (b) (4) based on 60 death events, narrowing the difference between the two treatment arms.

Table 19. Updated PFS and OS Results for Study CA204009

	Initial CSR (DBL: 12-SEP-2014) Follow-up: 16.9 months		Updated Data (DBL: 10-AUG-2015) Follow-up: 27.8 months	
	E+Bd (n=77)	Bd (n=75)	E+Bd (n=77)	Bd (n=75)
Progression-Free Survival				
No. of Events	(b) (4)			
Median	9.7 months	6.9 months	9.7 months	6.9 months
Hazard ratio (95% CI)	(b) (4)			
Overall Survival				
No. of Events	(b) (4)			
Median	(b) (4)			
Hazard ratio (95% CI)	(b) (4)			

E+Bd = elotuzumab (E) + bortezomib and dexamethasone (Bd); CSR = clinical study report; DBL = database lock

Statistical Reviewer's Comment:

(b) (4)

Clinical Reviewer's Comment: Study CA204009 was a phase II, open-label, investigator-assessed trial.

(b) (4)

There are possibly different mechanisms of action of lenalidomide and bortezomib and their effect on NK cells which may explain some of the differences noted. A study by Feng et al demonstrated that bortezomib down-regulates cell surface expression of tumor necrosis factor apoptosis-inducing ligand (TRAIL) on primary human interleukin (IL)-2-activated NK cells(6). There is other evidence to suggest that the reverse is true for lenalidomide, which has been shown to increased NK cell number and activation(7). Given that elotuzumab's purported

primary mechanism of action is through activation of NK cells, this potential differential effect of bortezomib and lenalidomide on NK cells may explain some of the differences observed in the two trials.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The application and demonstration of efficacy primarily relies on data from Study CA204004. There was a prior phase 1b/2 study, HuLuc63-1703 which provides supportive efficacy data. Study HuLuc63-1703 was a phase 1b/2, open-label, dose-escalation study of elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma. The primary objective of the phase 1b portion was to identify the maximum tolerated dose (MTD) of elotuzumab in combination with lenalidomide and dexamethasone. The primary objective of the phase 2 portion was to evaluate the efficacy of the E-Ld combination. The primary endpoint of phase 2 was ORR based on IMWG criteria as assessed by investigators. Eligible patients included those with relapsed multiple myeloma who had received 1-3 prior treatments. The phase 1b portion of the trial evaluated elotuzumab doses of 5, 10, and 20 mg/kg administered on Days 1, 8, 15, and 22. Lenalidomide 25mg was administered orally once daily on Days 1-21 in a 28 day cycle. A total weekly dose of 40 mg dexamethasone was administered with the same schedule employed in CA204004. In the phase 2 portion, subjects were randomized in a 1:1 ratio to receive either elotuzumab 10 mg/kg or 20 mg/kg.

In total, 29 subjects were enrolled in the Phase 1b portion and 73 subjects were enrolled in the phase 2 portion. In the phase 2 portion, subjects had received a median of 2 prior lines of therapy, and 24 (32.9%) were refractory to their last prior anti-myeloma therapy. The overall response rate was 83.6%. The median time to reach response was 2.6 months. The median duration of response was 29.2 months. The median PFS was 28.6 months (95% CI: 16.6-43.1). The table below provides the response data for the phase 2 portion.

Table 20. Response Rate Study HuLuc63-1703

Assessment	Elotuzumab Dose Group		Total N = 73
	10 mg/kg N = 36	20 mg/kg N = 37	
Objective response			
Response (sCR, CR, VGPR, or PR), n (%)	33 (91.7)	28 (75.7)	61 (83.6)
95% CI ^a	77.5 – 98.2	58.8 – 88.2	73.0 – 91.2
Best confirmed response, ^b n (%)			
Stringent complete response (sCR)	2 (5.6)	1 (2.7)	3 (4.1)
Complete response (CR)	4 (11.1)	3 (8.1)	7 (9.6)
Very good partial response (VGPR)	17 (47.2)	14 (37.8)	31 (42.5)
Partial response (PR)	10 (27.8)	10 (27.0)	20 (27.4)
No confirmed response, ^b n (%)			
	3 (8.3)	9 (24.3)	12 (16.4)
Time to objective response, months			
N	33	28	61
Mean (STD)	1.4 (0.9)	2.2 (3.5)	1.8 (2.5)
Median	1.0	1.7	1.0
Min, max	0.8, 4.2	0.7, 19.2	0.7, 19.2

Source: Applicant's Interim Clinical Study Report HuLuc63-1703, pg. 158

The median duration of response was estimated using Kaplan-Meier methods.

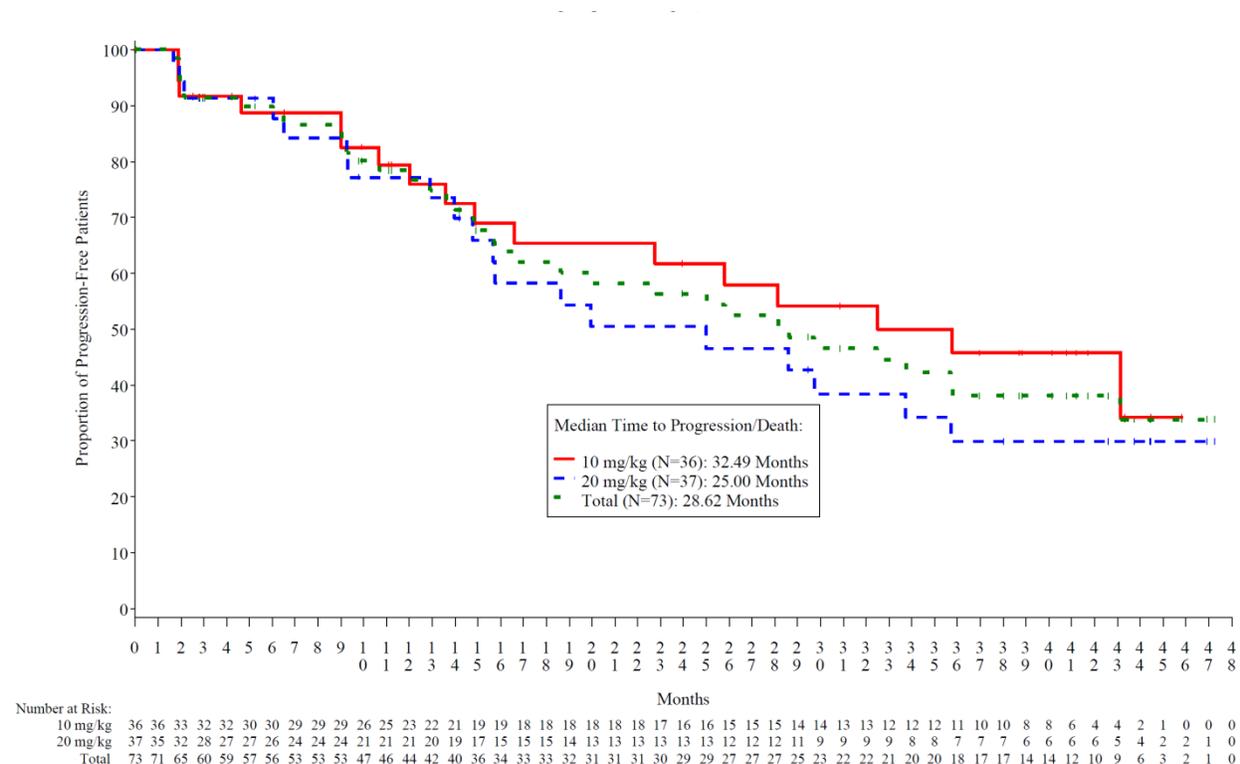
Table 21. Median Duration of Response Study HuLuc63-1703

Assessment	Elotuzumab Dose Group		Total N = 73
	10 mg/kg N = 36	20 mg/kg N = 37	
Number of responders	33	28	61
Censored subjects, n (%)	18 (54.55)	14 (50.00)	32 (52.46)
Duration of response, months			
25 th percentile	12.68	15.01	14.09
Median (95% CI)	34.83 (14.6 – NE)	29.01 (15.0 – NE)	29.24 (18.2 – NE)
75 th percentile	NE	NE	NE
Min, max	1.18, 45.11 ^a	0.95, ^a 45.37 ^a	0.95, ^a 45.37 ^a

Source: Applicant's Interim Clinical Study Report HuLuc63-1703, pg. 159

The PFS was also calculated for the phase 2 portion of the trial.

Figure 14. Progression Free Survival Study HuLuc63-1703



Source: Applicant’s Interim Clinical Study Report HuLuc63-1703, pg. 161

Table 22. Progression Free Survival Study HuLuc63-1703

	Elotuzumab Dose Group		
	10 mg/kg N = 36	20 mg/kg N = 37	Total N = 73
Confirmed Progression			
Subjects with progression (%)	17 (47.22)	19 (51.35)	36 (49.32)
95% CI ^a	30.41 – 64.51	34.40 – 68.08	37.40 – 61.28
Censored subjects (%)	19 (52.78)	18 (48.65)	37 (50.68)
Time to progression/death (months)			
25 th percentile	13.60	12.91	12.91
Median (95% CI)	32.49 (14.9 – NE)	25.00 (14.0 – 35.7)	28.62 (16.6 – 43.1)
75 th percentile	NE	NE	NE
Min, max ^b	1.91, 45.83 ^b	0.03, ^b 47.24 ^b	0.03, ^b 47.24 ^b

Source: Applicant’s Interim Clinical Study Report HuLuc63-1703, pg. 160

Clinical Reviewer's Comment: *The overall response rate of 83.6% observed in this phase 2 trial is comparable to the response rate observed in the phase 3 trial, CA204004 (78.5%). The median PFS observed in study HuLuc63-1703 exceeds that observed with E-Ld in study CA204004 (28.6 mos vs. 19.4 mos). The PFS was assessed by investigators in study HuLuc63-1703, although assessment by investigators as a possible explanation is not entirely satisfactory given the similarity of the investigator- and IRC- assessed PFS results seen in study CA204004 (19.4 and 18.5 mos respectively). The baseline disease characteristics of patient in the two trials are similar. The more robust results demonstrated in the phase 2 may be due to spurious results and relatively small number of patients. None-the-less, the results of the phase 2 trial are supportive of the results demonstrated in the pivotal CA204004 study.*

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Patients enrolled on clinical trials may differ from the broader patient population that will use the therapy after approval. There were no findings noted in this review that would suggest a different benefit in the broader patient population.

7.3. Integrated Assessment of Effectiveness

The efficacy of elotuzumab in combination with lenalidomide and dexamethasone was primarily based on results of study CA204004, a phase 3 randomized, open-label, controlled trial with supportive evidence from study HuLuc63-1703, a phase 1b/2 dose-escalation, single-arm trial. In study CA204004, a total of 646 patients were enrolled (321 in the E-Ld arm and 325 in the Ld arm). The co-primary endpoints were progression-free survival and overall response rate (both as assessed by IRC). The efficacy results are as follows:

- The estimated hazard ratio for PFS was 0.70 for E-Ld over Ld (95% CI: 0.57, 0.85; p=0.0004).
- The median PFS was 19.4 months (95% CI: 16.6, 22.2) in the E-Ld arm vs. 14.9 months (95% CI: 12.1, 17.2) in the Ld arm.
- The ORR was 78.5 % (95% CI: 73.6, 82.9) in the E-Ld arm vs. 65.5% (95% CI: 60.1, 70.7) in the Ld arm.
- The overall survival data at the time of the clinical database cutoff was not mature, with occurrence of only 49% of the total required events for the final analysis. The preliminary OS data suggests a hazard ratio of 0.71 (95% CI: 0.54, 0.93) for E-Ld over Ld. The median OS was not evaluable (NE) (95%CI: 36.2, NE) in the E-Ld arm and 34.6 (95% CI: 29.0, NE) in the Ld arm.

8 Review of Safety

8.1. Safety Review Approach

The clinical review of safety for this BLA was primarily based on safety data from Study CA204004 supported by safety findings from trial CA204009 and pooled safety data from studies CA204004, HuLuc-1703, CA204005 and CA204007.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 23. Safety Population, Size and Denominators

Safety Database for the Study Drug Individuals exposed to the study drug in this development program for the indication under review N= 569			
Clinical Trial Groups	New Drug (n= 569)	Active Control (n= 392)	Placebo (n= 0)
Normal Volunteers	0	0	0
Controlled trials conducted for this indication	318	317	0
All other than controlled trials conducted for this indication ¹	101 (Study HuLuc63-1703) 34 (Study HuLuc63-1701) 35 (Study CA204007) 6 (Study CA204005)	0	0
Controlled trials conducted for other indications	75 (Study CA204009)	75 (Study CA204009)	0

¹ - Only patients from the following studies were included in pooled analyses: CA204004, CA204005, CA204007, and HuLuc63-1703.

Table 24. Exposure in Study CA204004

	E-Ld (N=318) n (%)	Ld (N=317) n (%)
Elotuzumab Duration		
Median (mos)	17.0	-
Range (mos)	0.0, 37.7	-
Elotuzumab Dose Intensity Cycles 1 & 2		
Median (mg/kg/week)	10.0	-
Range (mg/kg/week)	(1.0, 10.8)	-
Elotuzumab Dose Intensity Cycles 3 & beyond		
Median (mg/kg/week)	4.8	-
Range (mg/kg/week)	2.4, 6.0	-
Lenalidomide Duration		
Median (mos)	17.0	12.5
Range (mos)	0.2, 37.5	0.2, 35.6
Lenalidomide Dose Intensity		
Median (mg/week)	108.0	112.3
Range (mg/week)	19.5, 137.5	13.7, 175.0

	E-Ld (N=318) n (%)	Ld (N=317) n (%)
Dexamethasone Duration		
Median (mos)	17.1	12.0
Range (mos)	0.0, 37.7	0.0, 35.9
Dexamethasone Dose Intensity		
Median (mg/week)	34.4	35.4
Range (mg/week)	2.6, 43.2	2.6, 46.7

The figures below provide the exposure distribution of patients treated with Elotuzumab in Study CA204004.

Figure 15. Distribution of Exposure (number of subjects) to Elotuzumab in months

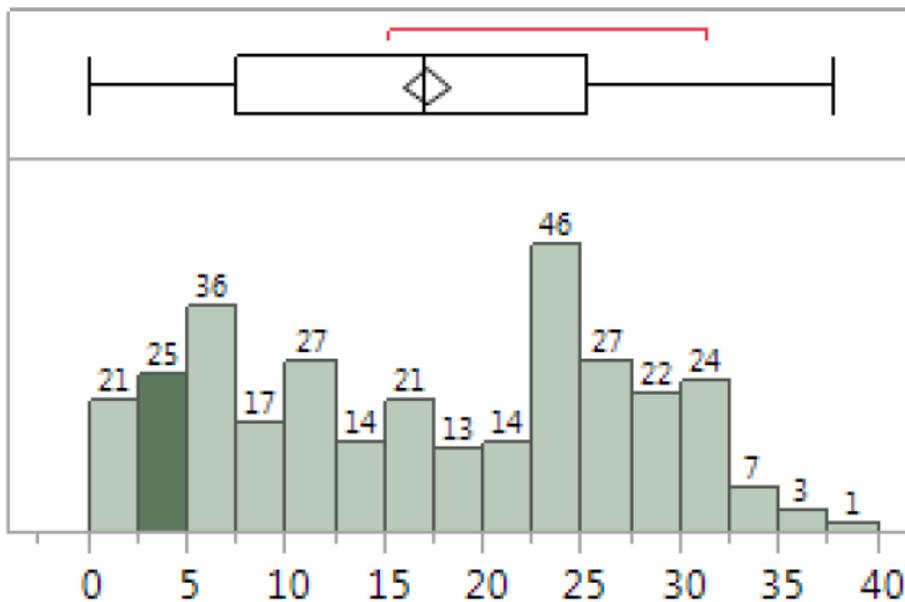


Figure 16. Distribution of Elotuzumab Dose Intensity (number of subjects) in Cycles 1 & 2 in mg/kg/week

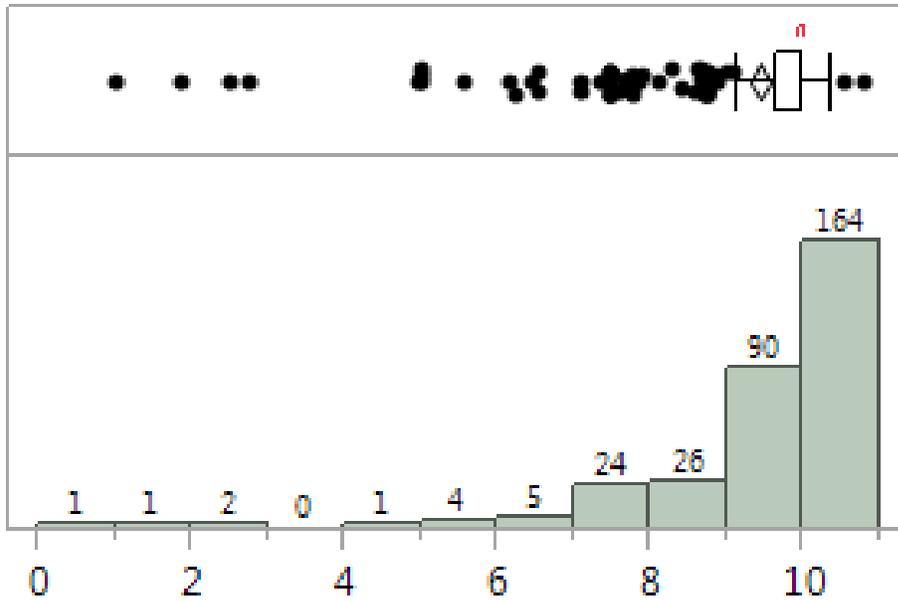
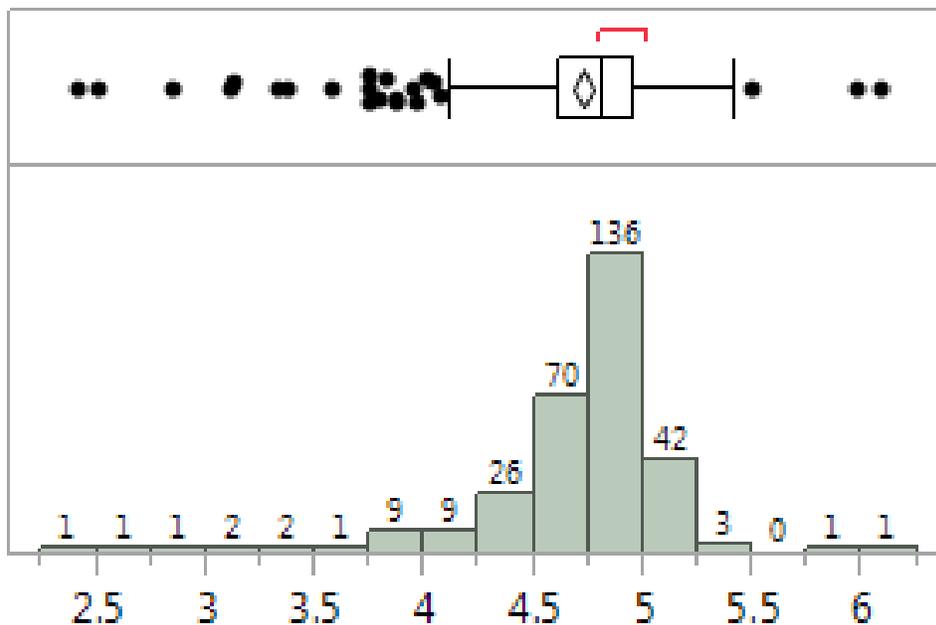


Figure 17. Distribution of Elotuzumab Dose intensity (number of subjects) in Cycles 3 & beyond in mg/kg/week



Clinical Reviewer's comments: The dose intensity of elotuzumab reflects the dosing schedule for elotuzumab. Elotuzumab is intended to be administered as 10 mg/kg/week for Cycles 1 and 2, then 10 mg/kg/2weeks in Cycles 3 & beyond.

8.2.2. Relevant characteristics of the safety population

The safety population consists of all treated patients in the trial. In total, 635 patients received treatment in study CA204004 (318 treated with E-Ld, 317 treated with Ld).

8.2.3. Adequacy of the safety database

The demographics of the safety population are adequately consistent with the demographics of the intended patient population. The necessary applicable clinical evaluations were conducted to assess the safety of the new drug.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The laboratory dataset had some deficiencies. Specifically, there was missing data with regards to reference units in some cases that prevented an assessment of grade. There were also occasional missing laboratory values. For example, one patient that had elevated transaminases that might be consistent with drug-induced liver injury (DILI), had a missing total bilirubin laboratory at the time of the transaminase elevation.

8.3.2. Categorization of Adverse Events

Adverse events were reported down to the verbatim term level. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.

8.3.3. Routine Clinical Tests

The schedule of safety evaluation for the protocol was described in Section 6. The frequency of monitoring was considered adequate within the context of the study.

8.4. Safety Results

Table 25. Safety Overview Study CA204004

	E-Ld (N=318) n (%)	Ld (N=317) n (%)	Total (N=635) n (%)
Deaths within 30 days	16 (5.0)	20 (6.3)	36 (5.6)
Progressive Disease	3 (0.9)	3 (0.9)	8 (1.3)
Serious TEAE	208 (65.4)	179 (56.5)	387 (60.9)
Discontinuations due to TEAE	83 (26.1)	85 (26.8)	168 (26.4)
Any Grade 3 or 4 TEAE	272 (85.5)	241 (76.0)	513 (80.8)
Any TEAE	316 (99.4)	314 (99.1)	630 (99.2)

Source: FDA Reviewer's analysis. Death was attributed to disease progression in cases where there was objective evidence of disease progression at the time of death.

8.4.1. Deaths

Overall there were 210 deaths as of the data cutoff of October 29, 2014. There were 94 deaths in the E-Ld arm (29.6%) and 116 deaths in the Ld arm (36.6%). Within 30 days of the last dose of treatment, there were 16 deaths in the E-Ld arm (5.0%) and 20 deaths in the Ld arm (6.3%). All narratives were reviewed to confirm the cause of death and attribution to disease progression, adverse event, or other. The cause of death was considered to be disease progression when there was objective evidence of disease progression at the time of death. Based on these criteria, there were 3 deaths considered to be primarily due to disease progression in the E-Ld arm.

Infection contributed to death in 9 patients in the E-Ld arm; infection was not the primary cause of death in all 9 cases. Infection was the primary cause of death in 6 cases. The infections associated with death were influenza, staphylococcus meningitis, sepsis, pneumonia (4 patients), and pseudomonas sepsis.

One patient died as a result of a second primary malignancy (Subject 5505-76). The patient was a 65 year old male with a history of IgG multiple myeloma. The patient had received one prior line of treatment consisting of carmustine, cyclophosphamide, dexamethasone, doxorubicin, melphalan, prednisone, and vincristine. The patient also had a prior history of prostate cancer, for which he had received radiotherapy. The patient was noted to have grade 1 constipation, grade 2 asthenia, grade 3 thrombocytopenia, and grade 4 anemia on Day 194 of treatment with E-Ld. The patient underwent a bone marrow biopsy which identified a nest of non-hematologic cells, which were identified as gastrointestinal tumor metastasis. Treatment was discontinued, and the patient died shortly thereafter.

One patient died due to a massive pulmonary embolus and granulomatous pneumonitis (Subject 5905-730). The patient was a 72 year old female with a history of IgG multiple myeloma. The patient had received 2 prior lines of therapy, consisting of cyclophosphamide, thalidomide and dexamethasone and an investigational therapy as her second treatment. Earlier in her treatment course, the patient had had prior adverse events of influenza, lower respiratory tract infection, grade 1 dyspnea, and a serious adverse event of pulmonary embolus, diagnosed on Day 58. The patient was treated with low molecular weight heparin. The patient had subsequent respiratory tract infection requiring treatment with doxycycline, and on Day 113 the patient had a witnessed collapse. She died at home. Autopsy report noted massive pulmonary embolus (despite being on therapeutic anticoagulation), deep vein thrombosis, myeloma, and granulomatous pneumonitis as causes of death.

One patient died due to pre-renal failure and pneumonia (Subject 5501-339). The patient was a 73 year old male with a 4 year history of IgA kappa multiple myeloma. The patient had received 2 prior lines of therapy. Of note, the patient had a baseline medical history of renal insufficiency

and during the course of study treatment, had one episode of renal failure grade 3 (which resolved after 8 days). On Day 187, the patient developed pre-renal failure and grade 4 pneumonia. The patient died on Day 195. The cause of death was reported as pre-renal failure; pneumonia was ongoing at the time of death.

Other causes of death in the E-Ld arm included suicide in 1 patient and unknown in 3 patients that were found dead or had loss of consciousness at home and autopsies were not performed (Subjects: 4301-622, 4600-82, 5204-441).

8.4.2. Nonfatal Serious Adverse Events

Serious adverse events occurred in 204 (64.1%) patients in the E-Ld arm compared to 175 (55.2%) patients in the control arm. The table below includes treatment-emergent serious adverse events that occurred in $\geq 2\%$ of subjects.

Table 26. Nonfatal Serious Adverse Events Study CA204004

	E-Ld (N=318) n (%)	Ld (N=317) n (%)
Infections and infestations		
Pneumonia ¹	49 (15.4)	36 (11.4)
Respiratory tract infection ²	15 (4.7)	8 (2.5)
Bronchitis	7 (2.2)	7 (2.2)
General disorders		
Pyrexia	20 (6.3)	14 (4.4)
Blood and lymphatic system disorders		
Anemia	8 (2.5)	6 (1.9)
Renal and urinary disorders		
Renal failure acute	8 (2.5)	5 (1.6)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	8 (2.5)	7 (2.2)
Gastrointestinal disorders		
Diarrhea	5 (1.6)	8 (2.5)
Cardiac disorders		
Atrial fibrillation	5 (1.6)	7 (2.2)

1- Pneumonia includes the terms: Pneumonia, bronchopneumonia, lobar pneumonia, atypical pneumonia, Pneumocystis jirovecii pneumonia, pneumonia pneumococcal, pneumonia bacterial, pneumonia fungal, and pneumonia influenza.

2- Respiratory tract infection includes the terms: respiratory tract infection, lower respiratory tract infection and upper respiratory tract infection.

Refer to Section 8.4.4 for details of specific serious adverse events presented in an issue-based format.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Treatment-emergent adverse events led to treatment discontinuation in 83 (26.1%) of patients in the E-Ld arm and 85 (26.8%) patients in the Ld arm.

8.4.4. Significant Adverse Events Study

NCI CTCAE Grade 3 and 4 (severe) adverse events are provided in Table 27 below. The most common serious adverse events with $\geq 5\%$ incidence and 2% greater incidence compared to the control arm were: lymphopenia (8.8%), cataract (6.3%), pneumonia (13.8%), hyperglycemia (7.2%), and deep vein thrombosis (5.7%).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The following table includes adverse events that occurred at an incidence of $\geq 10\%$ in either arm and grade 3-4 adverse events that occurred at an incidence of $\geq 5\%$ in either arm.

Table 27. Treatment-emergent adverse events

	E-Ld (N= 318)				Ld (N=317)			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders								
Anemia	123	38.7	47	14.8	117	36.9	52	16.4
Neutropenia	107	33.6	79	24.8	135	42.6	105	33.1
Thrombocytopenia	86	27	36	11.3	71	22.4	34	10.7
Lymphopenia	42	13.2	28	8.8	22	6.9	10	3.2
Eye Disorders								
Cataract	38	11.9	20	6.3	20	6.3	9	2.8
Gastrointestinal disorders								
Diarrhea	149	46.9	16	5.0	112	35.3	12	3.8
Constipation	111	34.9	4	1.3	85	26.8	1	0.3
Nausea	76	23.9	3	0.9	66	20.8	2	0.6
Vomiting	46	14.5	1	0.3	28	8.8	3	0.9
Abdominal Pain	39	12.3	1	0.3	27	8.5	0	0
Dyspepsia	32	10.1	0	0	19	6.0	0	0

	E-Ld (N= 318)				Ld (N=317)			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
General disorders								
Fatigue ¹	194	61	39	12.3	162	51.1	37	11.7
Pyrexia	117	36.8	8	2.5	77	24.3	8	2.5
Peripheral edema	82	25.8	4	1.3	69	21.8	1	0.3
Infections and infestations								
Nasopharyngitis	77	24.2	0	0	61	19.2	0	0
Upper respiratory tract infection	72	22.6	2	0.6	55	17.4	4	1.3
Bronchitis	54	17	5	1.6	51	16.1	7	2.2
Pneumonia ²	61	19.2	44	13.8	44	13.9	30	9.5
Respiratory tract infection	34	10.7	8	2.5	30	9.5	4	1.3
Injury, poisoning, and procedural complications								
Contusion	36	11.3	1	0.3	26	8.2	0	0
Investigations								
Weight decreased	44	13.8	4	1.3	19	6	0	0
Alanine aminotransferase increased	23	7.2	1	0.3	32	10.1	8	2.5
Creatinine increased ³	40	12.6	3	0.9	24	7.6	0	0
Metabolism and nutrition disorders								
Decreased appetite	65	20.4	5	1.6	40	12.6	4	1.3
Hyperglycemia	55	17.3	23	7.2	43	13.6	14	4.4
Hypokalemia	52	16.4	15	4.7	47	14.8	15	4.7
Hypocalcemia	43	13.5	10	3.1	31	9.8	4	1.3
Musculoskeletal and connective tissue disorders								
Muscle spasms	95	29.9	1	0.3	84	26.5	3	0.9
Back pain	89	28	16	5	89	28.1	14	4.4
Arthralgia	53	16.7	4	1.3	38	12	2	0.6
Pain in extremity	52	16.4	3	0.9	31	9.8	1	0.3
Musculoskeletal pain	40	12.6	5	1.6	27	8.5	2	0.6
Muscular weakness	37	11.6	6	1.9	24	7.6	4	1.3
Bone pain	33	10.4	1	0.3	40	12.6	3	0.9
Musculoskeletal chest pain	32	10.1	1	0.3	25	7.9	0	0

	E-Ld (N= 318)				Ld (N=317)			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Nervous system disorders								
Headache	49	15.4	1	0.3	24	7.6	1	0.3
Peripheral neuropathy	44	13.8	5	1.6	26	8.2	5	1.6
Peripheral neuropathy grouped ⁴	84	26.4	12	3.8	66	20.8	7	2.2
Dizziness	43	13.5	2	0.6	37	11.7	0	0
Dysgeusia	32	10.1	0	0	20	6.3	0	0
Paresthesia	32	10.1	1	0.3	29	9.1	1	0.3
Peripheral sensory neuropathy	29	9.1	4	1.3	35	11	2	0.6
Psychiatric disorders								
Insomnia	73	23	6	1.9	81	25.6	8	2.5
Respiratory, thoracic and mediastinal disorders								
Cough ⁵	99	31.1	1	0.3	57	18	0	0
Dyspnea	69	21.7	6	1.9	58	18.3	11	3.5
Oropharyngeal pain	32	10.1	0	0	14	4.4	0	0
Skin and subcutaneous tissue disorders								
Rash	58	18.2	1	0.3	58	18.3	5	1.6
Hyperhidrosis	37	11.6	0	0	22	6.9	0	0
Vascular disorders								
Deep vein thrombosis	23	7.2	18	5.7	12	3.8	7	2.2

1- Fatigue includes the terms: fatigue and asthenia

2- Pneumonia includes the terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, pneumonia bacterial, pneumonia fungal, pneumonia influenza, and pneumonia pneumococcal.

3- Creatinine increased includes the terms: blood creatinine increased and creatinine renal clearance decreased.

4- Peripheral neuropathy grouped includes the terms: peripheral neuropathy, axonal neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

5- Cough includes the terms: cough and productive cough

The following adverse events occurred at an incidence of $\geq 10\%$ and a 5% greater incidence than the control arm: lymphopenia, cataract, diarrhea, constipation, vomiting, pneumonia, pyrexia, fatigue/asthenia, nasopharyngitis, upper respiratory tract infection, cough, decreased weight, decreased appetite, headache, peripheral neuropathy, oropharyngeal pain, increased creatinine.

8.4.6. Laboratory Findings

Laboratory abnormalities that occurred after Day 1 and within 30 days of the last treatment are included in this discussion. There was a significant amount of missing information in the laboratory datasets. Specifically, the reference ranges, laboratory units, and/or grade were not provided in some instances. As a result, grade was not able to be assessed for approximately 7% of lab values.

The most common grade ≥ 3 hematologic abnormalities were lymphopenia, anemia, thrombocytopenia and neutropenia. The rates for these hematologic abnormalities were similar between the two arms, except in the case of lymphopenia. The rate of grade ≥ 3 lymphopenia was 76.7% in the E-Ld arm compared with 48.6% in the Ld arm. This degree of lymphopenia may have contributed to the increased rate of infections and may possibly play a role in the difference in SPM noted.

The most common non-hematologic laboratory abnormalities with a $\geq 5\%$ difference between arms were increased alkaline phosphatase, creatinine increased, hyperkalemia, low bicarbonate, hypocalcemia, and hyperglycemia (grade ≥ 3).

Table 28. Laboratory Test Abnormalities Study CA204004

	E-Ld (N= 318)				Ld (N=317)			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Hematologic								
Absolute lymphocyte low	316	99.4	244	76.7	312	98.4	153	48.6
Hemoglobin low	306	96.2	55	17.3	301	95.0	63	19.9
Platelet count low	264	83.0	56	17.6	245	77.3	57	18.0
Leukocyte low	287	90.3	103	32.4	278	87.7	80	25.2
Absolute neutrophil count low	258	81.1	107	33.6	281	88.6	136	42.9
Liver Function								
Albumin low	223	70.1	11	3.5	196	61.8	6	1.9
ALT increased	176	55.3	14	4.4	163	51.4	13	4.1
AST increased	150	47.2	8	2.5	134	42.3	8	2.5
Alk Phos increased	119	37.4	4	1.3	92	29.0	0	0
Total bilirubin increased	77	24.2	7	2.2	81	25.6	3	0.9
Electrolytes								
Creatinine increased	160	50.3	7	2.2	142	44.8	8	2.5
Sodium low	194	61.0	33	10.4	184	58.0	30	9.5
Sodium increased	50	15.7	0	0	51	16.1	1	0.3
Potassium low	162	50.9	36	11.3	159	50.2	28	8.8
Potassium increased	99	31.1	19	6.0	68	21.5	2	0.6
Bicarbonate low	151	47.5	1	0.3	106	33.4	0	0
Calcium increased	39	12.3	7	2.2	41	12.9	7	2.2
Calcium low	248	78.0	34	10.7	243	67.7	14	4.4
Glucose increased	284	89.3	54	17.0	269	84.9	31	9.8
Glucose low	44	13.8	0	0	60	18.9	1	0.3

8.4.7. Vital Signs

Clinically significant vital sign abnormalities were to be captured as adverse events. Of note, in the AE dataset, hypotension occurred at a rate of 9.4% in the E-Ld arm compared with 3.8% in the Ld arm. Hypertension was reported as an adverse event in 8.8% of patients in the E-Ld arm compared with 6.0% in the Ld arm.

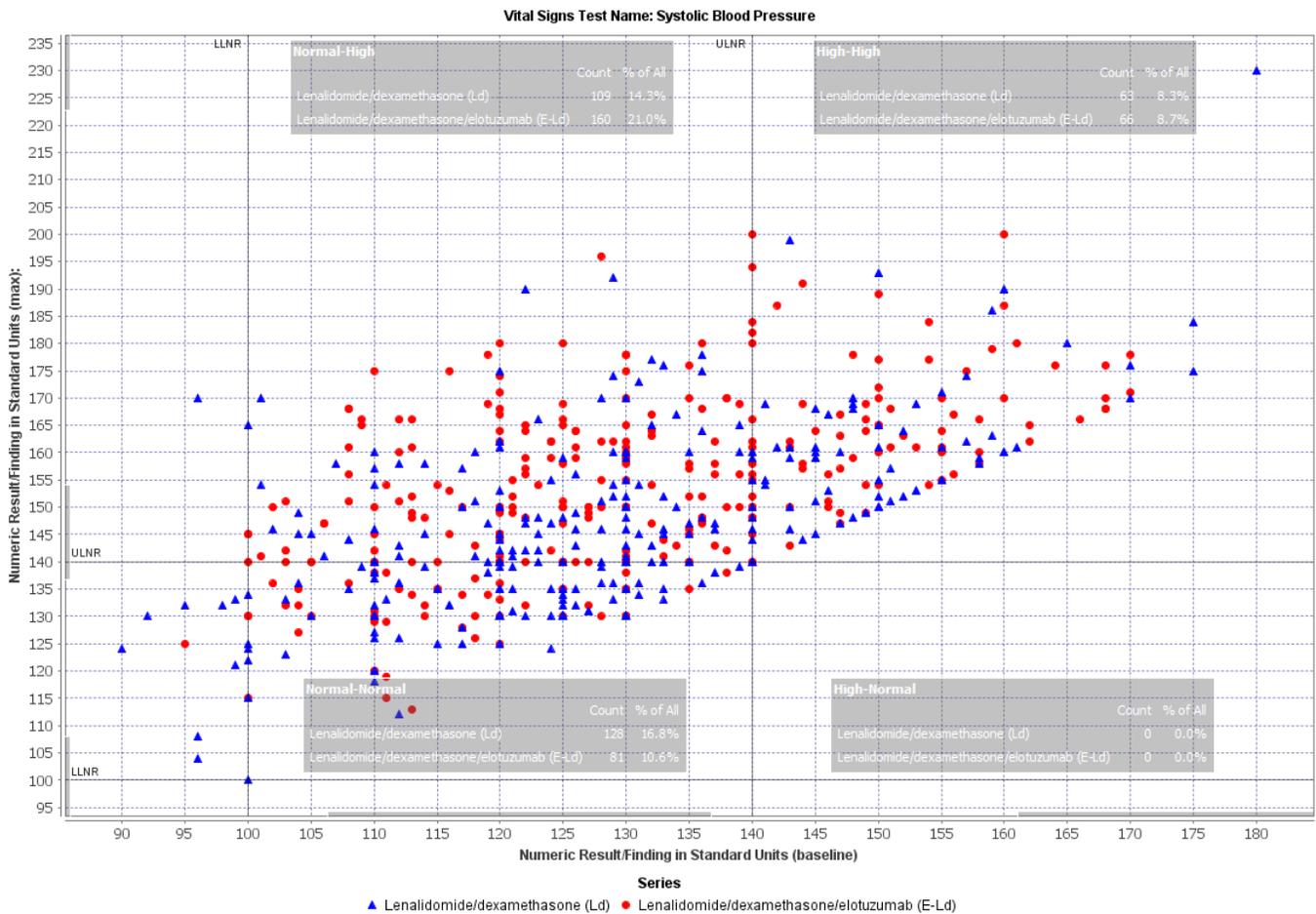
The table below includes the incidence of outlier vital signs by treatment arm based on data provided in the vital sign database.

Table 29. Outlier Vital Signs Study CA204004

	E-Ld (N= 318)		Ld (N=317)	
	n	%	n	%
Systolic BP ≥ 160 mm Hg	109	34.2	68	21.4
Systolic BP < 90 mm Hg	92	28.9	26	8.2
Diastolic BP ≥ 100 mm Hg	56	17.6	39	12.3
Heart rate ≥ 120 bpm	18	5.7	9	2.8
Hear rate ≤ 50 bpm	84	26.4	29	9.1

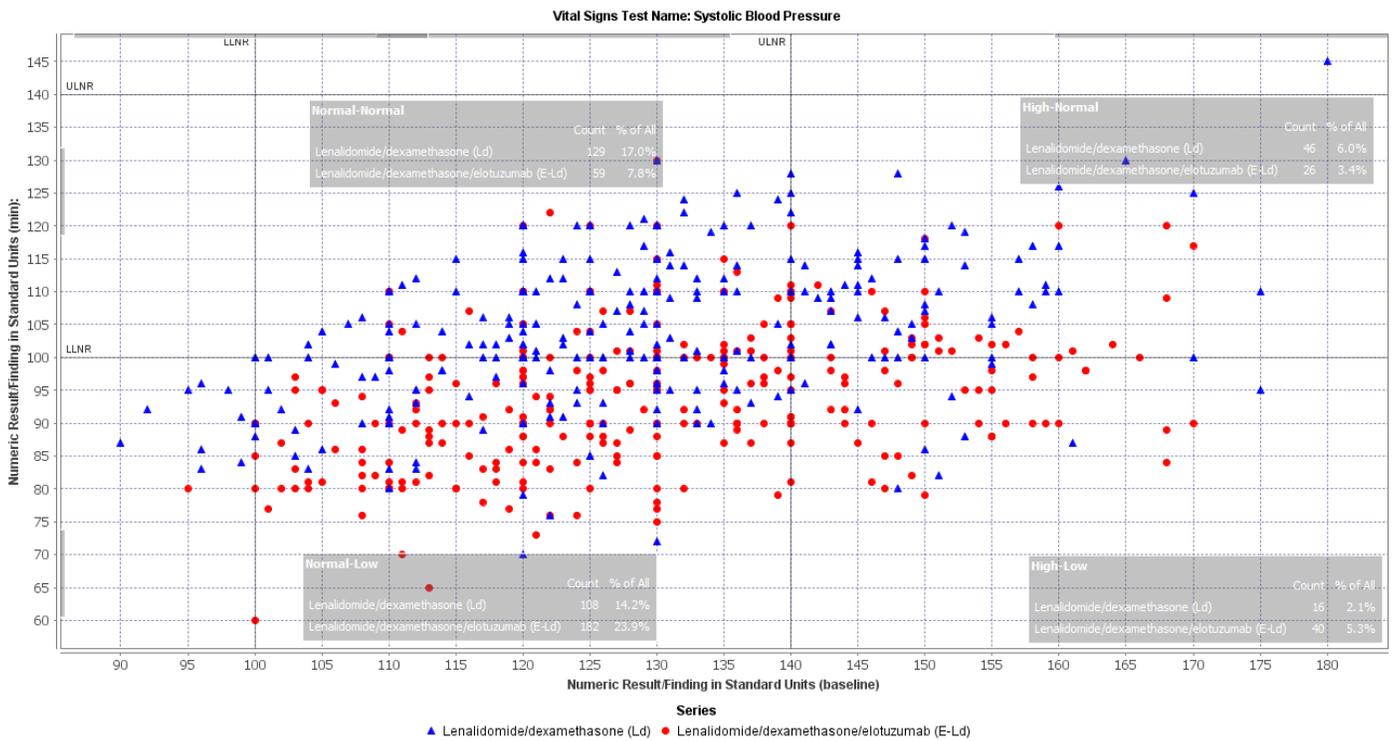
Based on an analysis of the vital sign datasets, the median systolic blood pressure (SBP) in the E-Ld arm was 120 (range: 60, 200; mean: 121.2) and 125 in the Ld arm (range: 70, 230; mean: 125.2). With regards to increases from baseline for SBP, the percentage of subjects that went from normal to high was 21.0% in the E-Ld arm and 14.3% in the Ld arm.

Figure 18. Increasing Systolic Blood Pressure Change from baseline Study CA204004



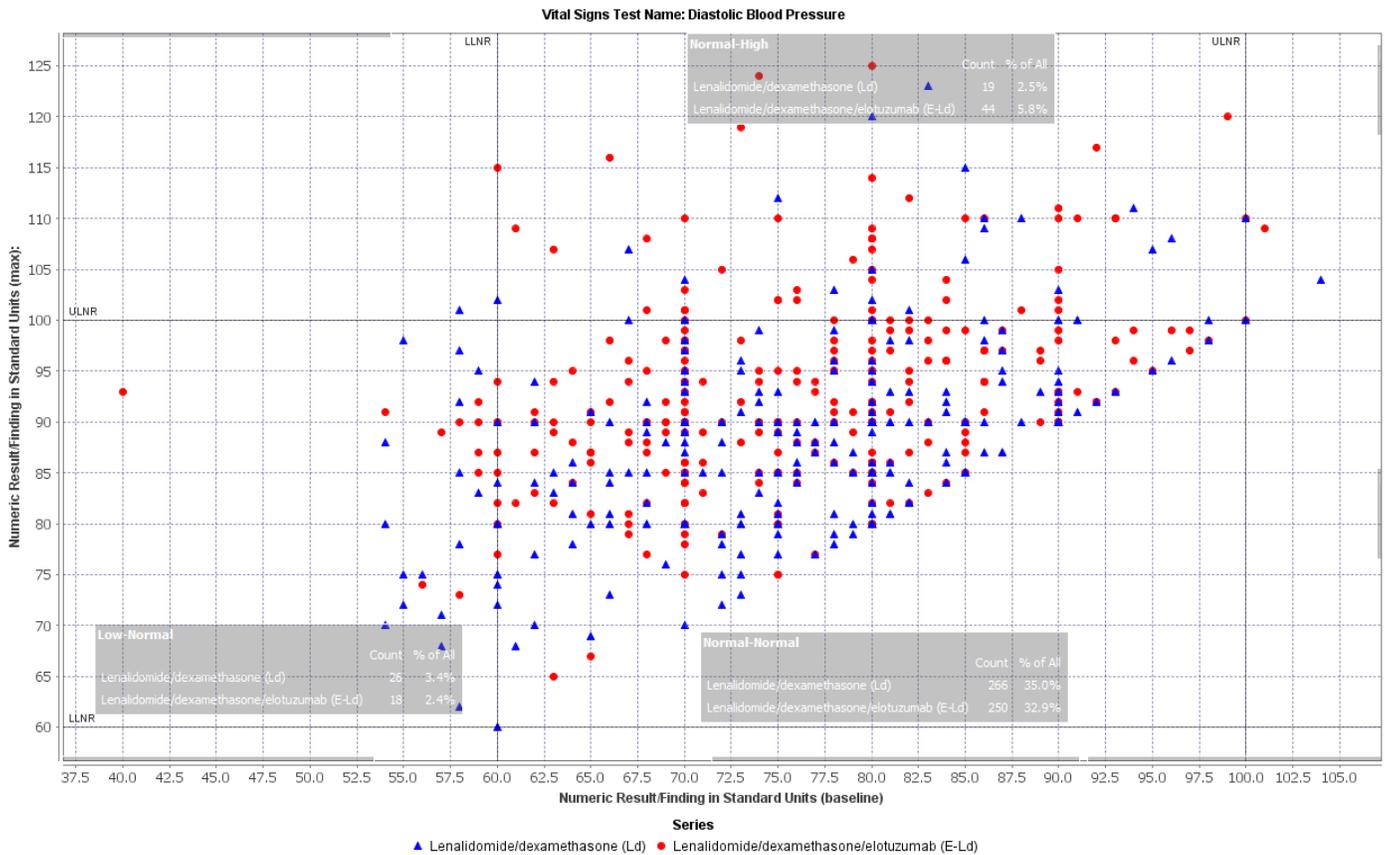
With regards to decreases from baseline for SBP, the percentage of subjects that went from normal to low was 23.9% in the E-Ld arm and 14.2% in the Ld arm and the percentage of subjects that went from high to low was 5.3% in the E-Ld arm vs. 2.1% in the Ld arm.

Figure 19. Decreasing Systolic Blood Pressure Change from Baseline Study CA204004



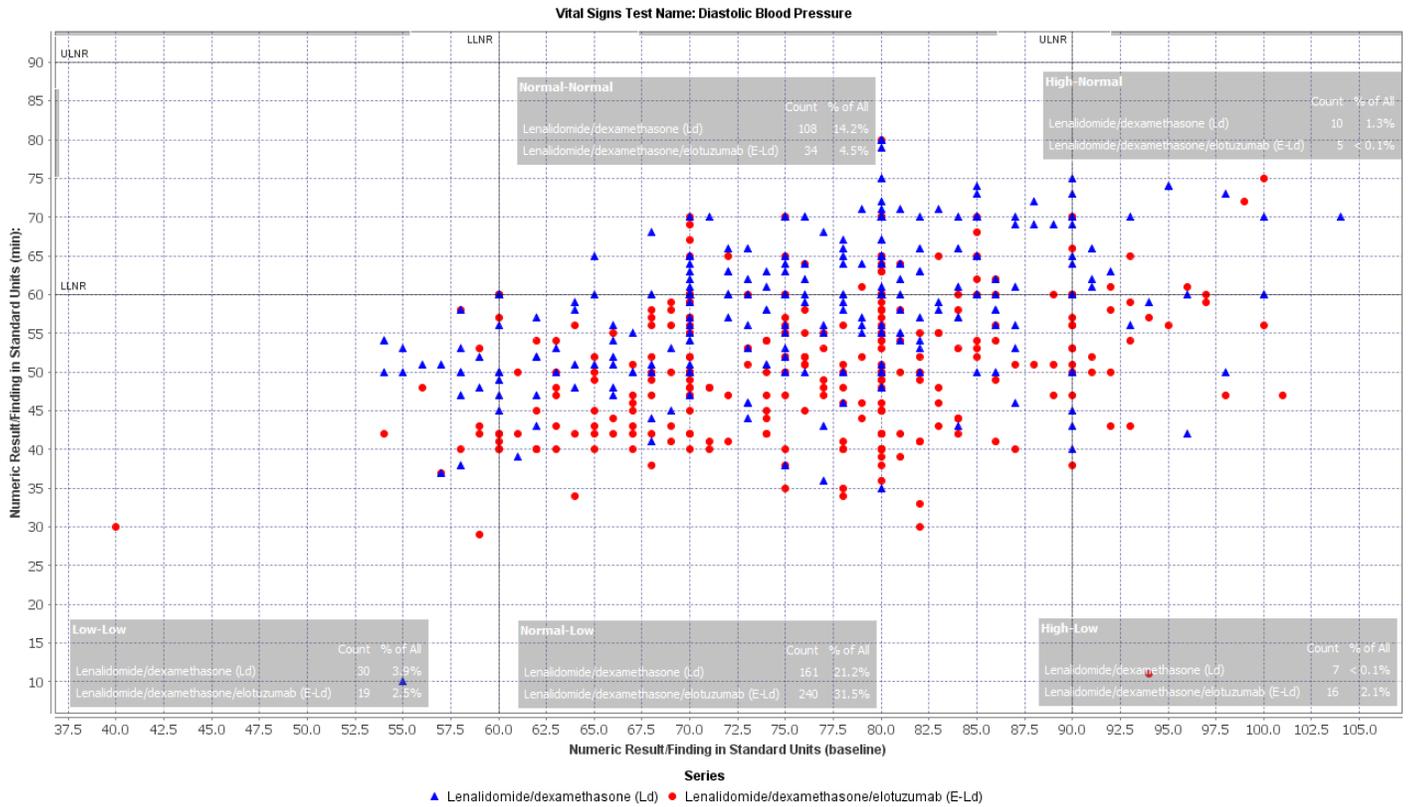
Based on an analysis of the vital sign datasets, the median diastolic blood pressure (DBP) was 70 in the E-Ld arm (range: 11, 125; mean: 71.0) and 75 in the Ld arm (range: 10, 123; mean: 74.2). With regards to increasing change from baseline for DBP, the percentage of subjects that went from normal to high was 5.8% in the E-Ld arm and 2.5% in the Ld arm.

Figure 20. Increasing Diastolic Blood Pressure Change from Baseline Study CA204004



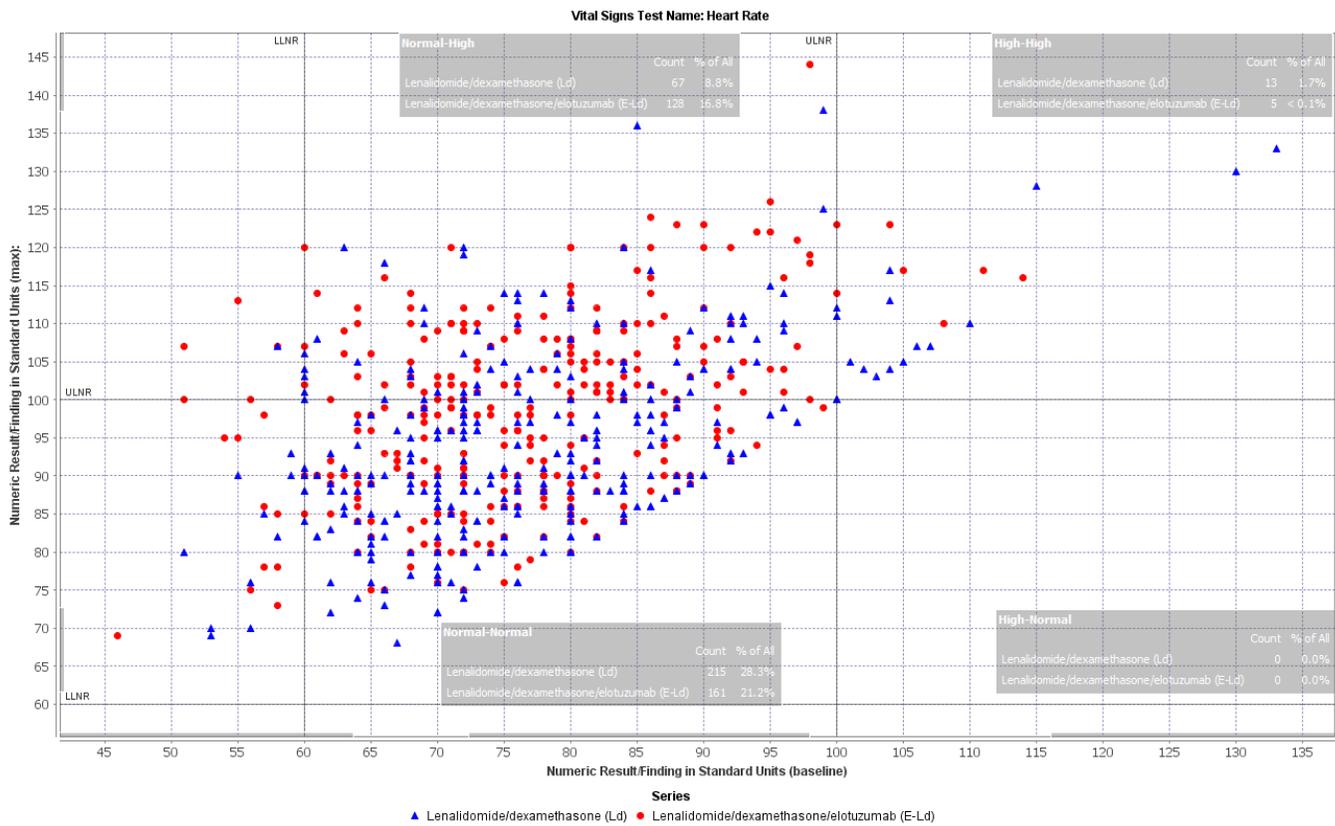
With regards to decreases from baseline for DBP, the percentage of subjects that went from normal to low was 31.5% in the E-Ld arm and 21.2% in the Ld arm and the percentage of subjects that went from high to low was 2.1% in the E-Ld arm vs. <0.1% in the Ld arm.

Figure 21. Decreasing Diastolic Blood Pressure Change from Baseline Study CA204004



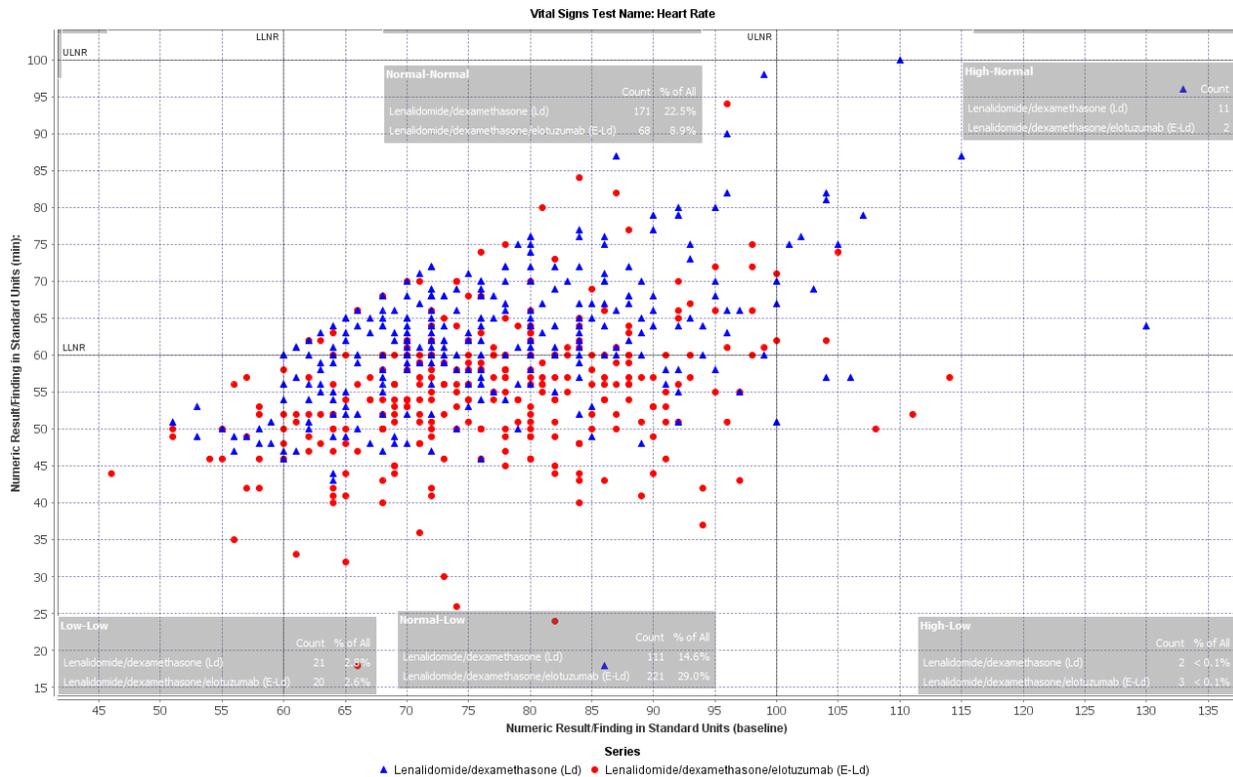
In the AE dataset, tachycardia was reported at a frequency of 2.5% in the E-Ld arm and 3.5% in the Ld arm, while bradycardia was reported in 0.3% in the E-Ld arm and 0.6% in the Ld arm. Based on data from the vital sign dataset, tachycardia, defined as heart rate greater than or equal to 100, occurred in 153 (48.1%) subjects in the E-Ld arm compared with 97 (30.6%) subjects in the Ld arm. Bradycardia defined as heart rate less than 60 occurred in 211 subjects (66.3%) in the E-Ld arm and 99 subjects (31.2%) in the Ld arm. With regards to increasing change from baseline for heart rate, the percentage of subjects that went from normal to high was 16.8% in the E-Ld arm and 8.8% in the Ld arm.

Figure 22. Increasing Heart Rate Change from Baseline Study CA204004



With regards to decreases from baseline for heart rate, the percentage of subjects that went from normal to low was 29.0% in the E-Ld arm and 14.6% in the Ld arm.

Figure 23. Decreasing Heart Rate Change from Baseline Study CA204004



Clinical Reviewer’s comment: The data reported in the AE dataset may underestimate the true incidence of hypertension, hypotension, tachycardia, and bradycardia. In the AE dataset, hypotension occurred at a rate of 9.4% in the E-Ld arm compared with 3.8% in the Ld arm, while the vital sign database showed that a SBP <90 mmHg occurred at a rate of 28.9% vs. 8.2% respectively. In the AE dataset, tachycardia was reported at a frequency of 2.5% in the E-Ld arm and 3.5% in the Ld arm, while bradycardia was reported in 0.3% in the E-Ld arm and 0.6% in the Ld arm. In the vital sign dataset, tachycardia (HR ≥ 100 bpm), occurred in 153 (48.1%) subjects in the E-Ld arm compared with 97 (30.6%) subjects in the Ld arm. Bradycardia (HR < 60) occurred in 211 subjects (66.3%) in the E-Ld arm and 99 subjects (31.2%) in the Ld arm. Based on the vital sign dataset, tachycardia had nearly an 18% greater incidence in the E-Ld arm than the Ld arm, while bradycardia had more than 30% greater incidence. These changes in heart rate or blood pressure may not have reached the threshold for clinical significance, but do clearly demonstrate a pattern of physiologic effects which can be attributed to elotuzumab. As the vital signs were primarily captured during infusions, it also raises the question of under-reporting of infusion reactions.

8.4.8. Electrocardiograms (ECGs)

In study CA204004, an ECG substudy was performed and enrolled 10 subjects. The Δ QTcF interval after elotuzumab infusion on Day 1 of Cycle 1 and Day 22 of Cycle 2 was < 10 msec compared to pre-dose levels. PR and QRS were largely unchanged during the study. No subject that participated in the ECG substudy had an AE that was thought to be related to an abnormal ECG finding. One subject (1414-108) had an SAE of grade 3 syncope during cycle 13. No ECG was recorded near the time of the event. During the ECG substudy, that subject had QTc intervals that were all < 470 msec.

8.4.9. QT

The Interdisciplinary Review Team (IRT) for QT studies was consulted to review the submitted QT data. The IRT reviewed QT data from studies CA204004 and CA204011. Per IRT, Studies CA204004 and CA204011 were not adequately designed for QT assessment. The central tendencies were not reliable. However, over the observed concentration range, there was no evidence concentration-QTc relationship. Given that elotuzumab is a large targeted protein, it was felt by IRT that elotuzumab has a low likelihood of direct ion channel interactions.

8.4.10. Immunogenicity

In study CA204004, 299 elotuzumab-treated patients had evaluable anti-drug antibody (ADA) data at baseline and post-baseline. A total of 6 patients (2.0%) were ADA positive at baseline, 45 (15.1%) were positive on study. Of these 45, 19 had neutralizing antibodies (NAbs) detected and 2 (0.7%) subjects with NAbs were also persistent ADA positive. Please refer to the CMC review for further details of the immunogenicity observed.

8.5. Analysis of Submission-Specific Safety Issues

The following safety issues were identified as those that warrant a more thorough evaluation: second primary malignancies, hepatotoxicity, infusion reactions, and infections.

8.5.1. Second Primary Malignancies

Second primary malignancies (SPM) occurred in 26 subjects in the E-Ld arm (8.2%) and in 15 subjects in the Ld arm (4.7%). Diagnosis of the SPM was made shortly after the screening visit in 3 patients in the E-LD arm and 1 patient in the LD arm. The table below lists the SPMs by subject.

Table 30. Second primary malignancy listing

Subject ID	Malignancy
E-Ld Arm	
1414-319	Breast cancer
1427-553	Basal cell carcinoma
1481-334	Squamous cell carcinoma of skin
2400-655	Squamous cell carcinoma of skin
2407-24	Thyroid neoplasm
3401-265	Squamous cell carcinoma of skin
3402-66	Pleural mesothelioma malignant
3404-628	Basal cell carcinoma
	Squamous cell carcinoma of skin
3409-267	Squamous cell carcinoma of skin
4401-48	Chronic lymphocytic leukemia
	Myelodysplastic syndrome
4409-583	Lung neoplasms malignant
4411-686	Lung adenocarcinoma, lung neoplasm malignant
4508-384	Myelodysplastic syndrome
4510-186	Erythroleukemia
4901-531	Lung neoplasms malignant
4902-213	Squamous cell carcinoma of skin
5012-105	Basal cell carcinoma
5204-744	Malignant neoplasm of unknown primary site
5505-76	Gastrointestinal neoplasm
5505-144	Basal cell carcinoma
5801-635	Bladder cancer
5900-255	Squamous cell carcinoma of skin
6003-196	Basal cell carcinoma
6008-60	Adenocarcinoma of colon
6010-547	Squamous cell carcinoma of skin
6014-36	Myelodysplastic syndrome
Ld Arm	
1414-234	Basal cell carcinoma
	Lung neoplasm malignant
2403-175	Basal cell carcinoma
2407-590	Adenocarcinoma of colon
3400-179	Tonsil cancer
3400-697	Myelodysplastic syndrome
	Squamous cell carcinoma of skin

Subject ID	Malignancy
3404-565	Basal cell carcinoma
4003-407	Squamous cell carcinoma of skin
4402-57	Myelodysplastic syndrome
4505-199	Malignant melanoma in situ
4516-366	Myelodysplastic syndrome
4517-649	Prostate cancer
4600-496	Myelodysplastic syndrome
4601-694	Endometrial cancer
5303-528	Malignant neoplasm of unknown primary site
5907-148	Basal cell carcinoma
	Myelodysplastic syndrome

Lenalidomide has been associated with the development of second primary malignancies. The prescribing information for Revlimid® (lenalidomide) includes in the warnings and precautions a section on SPM. It states that a “higher incidence of SPM were observed in controlled trials of patients with multiple myeloma receiving REVLIMID.” The malignancies noted were mostly hematological malignancies, AML and MDS, with a reported frequency of approximately 5%.

The distribution of SPMs by tumor type is included in the table below.

Table 31. Second primary malignancy categorization

	E-Ld (N=318) n (%)	Ld (N=317) n (%)
Overall	26 (8.2)	15 (4.7)
Skin Cancer	12 (3.8)	7 (2.2)
Solid Tumors	10 (3.1)	6 (1.9)
Hematologic Malignancy	5 (1.6)	5 (1.6)

Clinical Reviewer’s Comment: Lenalidomide has a recognized risk of second primary malignancies. In this trial, the E-Ld arm had a higher rate of SPM than the Ld arm. The greater incidence of SPM was most notable in the incidence of skin cancers and solid tumors, as there was no difference in the incidence of hematologic malignancies. With regards to possible mechanism, it is thought that lenalidomide may cause SPM via its immunomodulatory properties. Other immunomodulatory agents, such as thalidomide are also associated with increased incidence of SPM. Elotuzumab has myelosuppressive properties, notably severe lymphopenia. One possible mechanism for the increased SPM with elotuzumab in combination with lenalidomide is that the myelosuppression may lead to further disruption of cancer immune surveillance.

The data provided by this initial study cannot be expected to provide a complete assessment of the risk of SPM with elotuzumab. This information is best gleaned from larger numbers of patients with longer follow-up.

8.5.2. Hepatotoxicity

The Applicant identified 6 patients in the E-Ld arm that had met criteria for potential drug-induced liver injury (DILI), as defined by an AST or ALT > 3 time the ULN, total bilirubin > 2 times the ULN, and alkaline phosphatase < 2 time the ULN. There were several cases identified by this reviewer. The cases are discussed below.

- **Subject 4401-513:** The patient was a 54 year old Caucasian male with a 4 year history of IgG multiple myeloma. He had received 1 prior treatment, which consisted of bortezomib, dexamethasone, and melphalan followed by autologous stem cell transplant. The patient had a past medical history of hepatic steatosis. At baseline, the patient had the following liver lab values: AST 101 U/L (reference range: 0-50 U/L), ALT 134 U/L (reference range: 0-50 U/L), alkaline phosphatase 94 U/L (reference range: 57-120 U/L), and total bilirubin 14 µmol/L (reference range: 0-35 µmol/L). On Day 197, the patient's labs showed an increase in ALT to 190 U/L, AST 133 U/L, alkaline phosphatase 146 U/L, and total bilirubin 16 µmol/L (see table below). On Day 211, the patient was diagnosed with a SAE of grade 3 hepatitis, and was hospitalized. Study drug was discontinued. The last dose of elotuzumab and dexamethasone were received on Day 211. On Day 216, the patient experience abdominal pain and diarrhea, both grade 2. He received treatment with metronidazole and acetorphan. The patient had a CT scan performed on Day 219 which showed fatty liver disease without signs of cholelithiasis or other abnormality. The patient also had viral serology tests performed, which were negative for hepatitis A, B, C, and E. On Day 219, the diarrhea and abdominal pain resolved. The patient was discharged from the hospital on Day 224. On Day 261, the patient had a liver biopsy performed which showed findings consistent with chronic hepatitis with cirrhosis, moderate activity and ductopenia (METAVIR score A2F4). The CRF noted findings consistent with drug-related liver injury, eosinophilia. The patient's concomitant medications at the time of the event included: metformin, oxycodone, phenoxymethylpenicillin, valacyclovir, leucovorin, levothyroxine, Bactrim, sertraline, perindopril, lormetazepam, repaglinide, insulin, lysine acetylsalicylic acid, quinine, nefopam, mag/pyrxd, fenofibrate, and omeprazole.

	ALK P (U/L)	AST	ALT	TBili
Units	U/L	U/L	U/L	µmol/L
Ref. range	57-120	0-50	0-50	0-35
Day 1	94	101	134	14
Day 29	95	40	82	14
Day 197	146	133	90	16
Day 211	173	474	527	35
Day 217	-	535	713	138
Day 234	184	80	77	48
Day 253	151	42	46	31

Clinical Reviewer’s comment: *The patient described above had pre-existing liver disease in the form of hepatic steatosis, but developed acute liver injury in the setting of chronic liver disease while on treatment with E-Ld. The liver injury required permanent discontinuation of study treatment. While the patient was on other medications that could have contributed to the development of DILI, this represents a potential Hy’s law case in which DILI developed in the setting of pre-existing liver disease. Care may be needed in prescribing E-Ld to patients with pre-existing liver disease.*

- **Subject 1451-225:** The patient was a 76 year old Caucasian female with a 1 year history of IgG kappa multiple myeloma. She had received 2 prior line of therapy, including bortezomib, cyclophosphamide, dexamethasone and subsequently hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone). She had also received radiotherapy to the orbit and spine. At baseline (Day -6), the patient had the following liver lab values: AST 53 U/L (reference range: 15-32 U/L), ALT 36 U/L (reference range: 15-33 U/L), alkaline phosphatase 185 U/L (reference range: 35-104 U/L), and total bilirubin 5.1 µmol/L (reference range: 1.7-20.5 µmol/L). On Day 8, the patient was diagnosed with grade 2 drug-induced liver injury, as her AST had increased to 60 U/L, ALT increased to 85 U/L, Alkaline phosphatase to 251 U/L, and total bilirubin to 6.8 µmol/L (see table below). No action with the study drug was taken. On Day 21, the event of AST increased was considered resolved. On day 71, study therapy was discontinued due to investigator-assessed disease progression. The patient’s last dose of elotuzumab was administered on Day 58. On Day 75, the patient had a serious adverse event of grade 4 acute pancreatitis. The duration was 6 days.

On Day 87, the patient started treatment with another salvage regiment (melphalan). The patient continued to have periodic episodes of elevated LFTs.

	ALK P (U/L)	AST	ALT	TBili
Units	U/L	U/L	U/L	µmol/L
Ref. range	35-104	15-32	15-33	1.7-20.5
Day -6	185	53	36	5.1
Day 2	374	98	79	5.1
Day 8	251	60	85	6.8
Day 22	157	26	48	6.8
Day 29	307	98	142	6.8
Day 57	409	127	191	34.2
Day 70	326	60	110	10.3
Day 79	522	69	66	123.1
Day 85	538	35	26	49.6
Day 101	856	102	51	41

Clinical Reviewer's comment: *The patient above had episodic LFT abnormalities. The pattern of her LFT abnormalities are not typical of DILI in that her alkaline phosphatase was elevated more than 2 times the ULN in addition to the AST/ ALT and total bilirubin elevations. Additionally, this may not represent a case of elotuzumab-induced DILI in that the patient continued to receive treatment with elotuzumab and had continued elevations in her LFTs even on subsequent anti-myeloma treatment.*

- **Subject 4510-647:** The patient was a 76 year old Caucasian female with a 9 year history of IgA kappa multiple myeloma. She had received 3 prior lines of therapy including: 1) vincristine, doxorubicin, dexamethasone followed by cyclophosphamide, melphalan and a stem cell transplant 2) interferon maintenance therapy and a second stem cell transplant 3) bortezomib, melphalan and prednisolone. At baseline (Day 1), the patient had the following liver lab values: AST 14 U/L (reference range: 6-31 U/L), ALT 14 U/L (reference range: 6-34 U/L), alkaline phosphatase 82 U/L (reference range: 30-120 U/L), and total bilirubin 6.84 µmol/L (reference range: 5.13-20.52 µmol/L). On Day 729, the patient's lab results showed an ALT of 197 U/L, AST 97 U/L, alkaline phosphatase of 173 U/L, and total bilirubin of 11.97 µmol/L (see table below). On Day 735, the subject was determined to have disease progression. She was discontinued from study on Day 737. Her last dose of elotuzumab and dexamethasone were received on Day 729. On Day 735, a PET scan showed a soft tissue formation in the porta hepatis (presumed plasmacytoma).

	ALK P (U/L)	AST	ALT	TBili
Units	U/L	U/L	U/L	µmol/L
Ref. range	30-120	6-31	6-34	5.13-20.52
Day 1	82	14	14	6.84
Day 505	79	15	13	6.84
Day 715	117	24	36	6.84
Day 729	173	97	197	11.97
Day 756	454	234	371	94.0

Clinical Reviewer's Comment: The elevated LFTs that occurred in this patient are not typical of DILI in that the alkaline phosphatase is also elevated more than 2 times the ULN by Day 756. Additionally, the presence of a soft tissue mass in the porta hepatis may explain the LFT abnormalities.

- **Subject 2400-484:** The patient was a 54 year old Caucasian male with history of IgA kappa multiple myeloma. He had received one prior line of therapy, which consisted of velcade, cyclophosphamide, and dexamethasone followed by autologous stem cell transplant. At baseline (Day -3), the patient had the following liver lab values: AST 41 U/L (reference range: 0-40 U/L), ALT 6 U/L (reference range: 0-50 U/L), alkaline phosphatase 96 U/L (reference range: 30-130 U/L), and total bilirubin 22.23 µmol/L (reference range: 0-20.52 µmol/L). On Day 8, the patient had an increase in AST > 3 time the ULN and total bilirubin more than 2 times the ULN, with an alkaline phosphatase less than 2 times the ULN (see table below). No action was taken with the study medications. The AST and total bilirubin abnormalities improved by Day 16, although the alkaline phosphatase continued to increase.

	ALK P (U/L)	AST	ALT	TBili
Units	U/L	U/L	U/L	µmol/L
Ref. range	30-130	0-40	0-50	0-20.52
Day -3	96	41	6	22.23
Day 8	211	121	66	46.17
Day 16	241	23	26	22.23
Day 22	364	23	14	22.23
Day 36	209	27	6	27.36

Clinical Reviewer's comment: The patient had an increase in AST, total bilirubin that met criteria for possible DILI. However, the episode resolved on its own and did not require interruption of study drug.

- **Subject 4600-251:** The patient was a 79 year old Caucasian male with history of IgG lambda multiple myeloma. He had received one prior line of therapy, which consisted of

cyclophosphamide, dexamethasone, and thalidomide. At baseline (Day 1), the patient had the following liver lab values: AST 13 U/L (reference range: 5-40 U/L), ALT 14 U/L (reference range: 5-40 U/L), alkaline phosphatase 36 U/L (reference range: 40-129 U/L), and total bilirubin 13.7 (no units or reference range provided). On Day 108, the patient had an ALT elevation greater than 3 times the ULN. The AST was also elevated. The data for total bilirubin are missing on that date. No action was taken with study drug. The LFT elevations resolved by Day 122.

	ALK P (U/L)	AST	ALT	TBili
Units	U/L	U/L	U/L	-
Ref. range	30-130	0-40	0-50	-
Day 1	36	13	14	13.7
Day 93	69	15	15	-
Day 108	72	61	149	-
Day 122	81	13	17	-

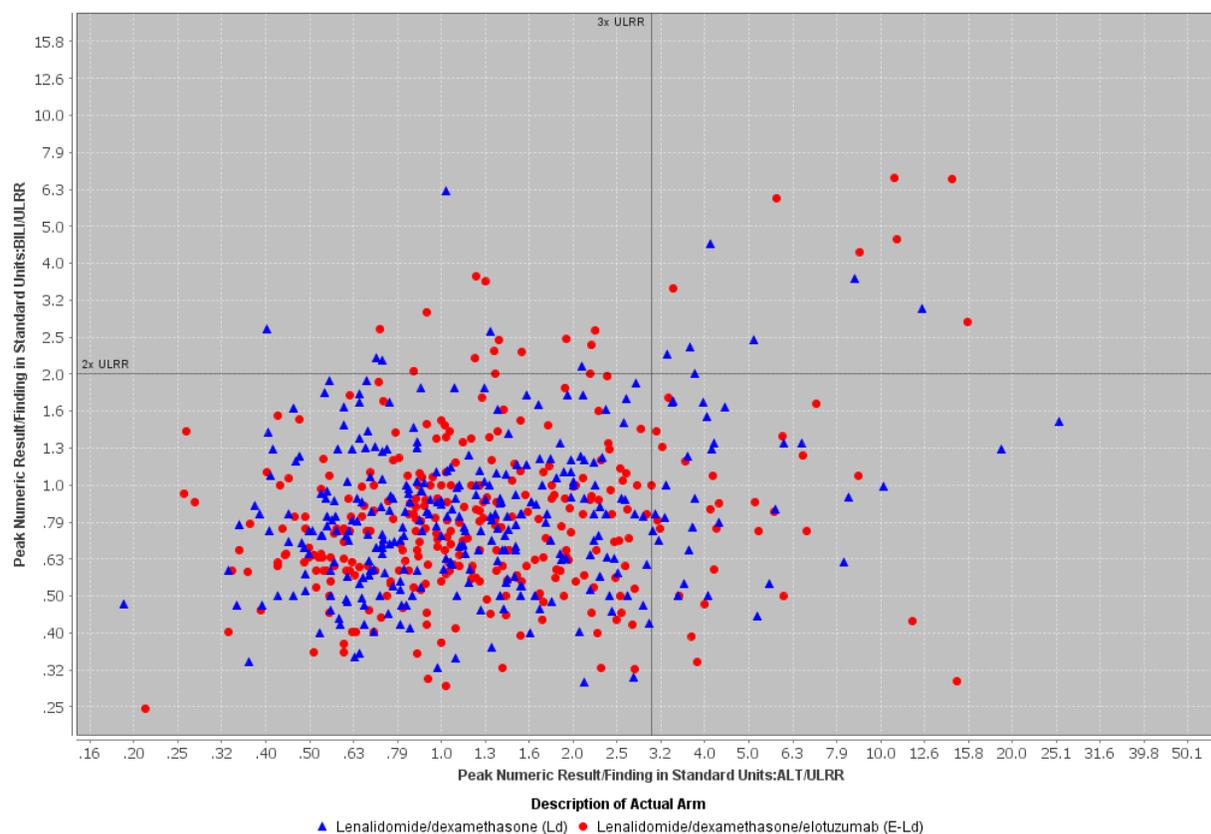
Clinical Reviewer's comment: *The patient had an increased in ALT and a normal alkaline phosphatase at the time of the event. Total bilirubin results were not provided. This case is not characteristic of DILI in that the elevations resolved despite continuation of study drug.*

There were several other cases of elevated LFTs, but these cases were confounded by evidence of cholecystitis, cholelithiasis, or cholangitis. The table below lists other cases of severe LFT abnormalities among patients in the E-Ld arm.

Subject ID	LFT abnormalities	Confounding factors
5208-568	ALT > 3x ULN, AST > 3x ULN, nml Tbili, ALP elevated but < 2x ULN	Cholangitis
1438-9	ALT > 2x ULN, AST > 2x ULN, Tbili > 3x ULN, ALP > 2x ULN	Cholecystitis
4405-759	ALT > 3x ULN, AST > 3x ULN, Tbili > 3x ULN, ALP > 3x ULN	Cholelithiasis
5501-735	ALT > 3x ULN, AST > 3x ULN, Tbili > 3x ULN, ALP > 3x ULN	Choledocus
5501-339	ALT > 3x ULN, AST > 3x ULN, Tbili > 3x ULN, ALP elevated but < 2x ULN	"cholecistolitiasys" noted on ultrasound

The figure below includes a plot of total bilirubin versus ALT. Those patients whose lab values fall within the upper right quadrant meet criteria for total bilirubin greater than 2 times the ULN and ALT greater than 3 times the ULN.

Figure 24. Potential Hy's law plot- Total bilirubin vs. ALT



Clinical Reviewer’s comment: The Potential Hy’s laws cases from this table are described above (Subjects: 4401-513, 5208-568, 1451-225, 4510-647, 5501-735, 1438-9, and 4405-759). It should also be noted from this graph that there are more cases of elevation of total bilirubin (> 2x ULN) in the E-Ld arm compared to Ld arm, 19 (6.0%) vs. 12 (3.8%).

8.5.3. Infusion Reactions

Elotuzumab is a humanized monoclonal antibody and has been associated with the development of infusion reactions. In the trial, to minimize the risk associated with infusion reactions, patients received the following pre-medications 30-90 minutes prior to administration of elotuzumab:

- H1 blocker: diphenhydramine (25-50 mg PO or IV) or equivalent
- H2 blocker: Ranitidine (50 mg IV) or equivalent
- Acetaminophen (650-1000 mg PO)

In total, 34 subjects (10.7%) experienced an infusion reaction. Of these 34 subjects, 16 subjects (5.0%) experienced more than one infusion reaction. Sixty-three (63) percent of the infusion reactions occurred in the first cycle, and 44% of the infusion reactions occurred on Cycle 1 Day

1. Elotuzumab was interrupted in 36.7% of the IR instances and resulted in permanent study drug discontinuation in 2 patients.

Grade 3 infusion reactions occurred in 5 subjects and included angioedema, cardiac congestive failure, chest pain, diarrhea, and hypertension. All grade 3 reactions occurred in Cycle 1. Three of the reactions occurred on Cycle 1 Day 1. Elotuzumab was permanently discontinued in two of these patients.

- Subject 4404-159: The patient was an 81 year old male with a 4 year history of IgG kappa multiple myeloma. His past medical history included hypertension, diabetes mellitus and ischemic cardiomyopathy, for which he had had a coronary stent placed 10 years prior. During the 3rd dose in cycle 1, elotuzumab was infused at a rate of 2 ml/min. The patient developed hypotension, bradycardia, and hypothermia (35.5° C) with rales and crackles noted on lung auscultation. The investigator assessed the event as congestive cardiac failure (grade 3). The infusion was interrupted and not resumed. The patient was hospitalized and treated with Lasix, heparin, levofloxacin and calsparine. The event was assessed as resolved 7 days later. The patient received a subsequent dose of elotuzumab 7 days after the initial event, and experienced the same signs and symptoms. The elotuzumab infusion was interrupted for 35 minutes, then resumed and completed at a rate of 0.5 ml/min. The patient remained in the hospital for 2 days. Study therapy was discontinued due to the events of congestive cardiac failure.
- Subject 1414-33: The patient was a 69 year old male with a one year history of IgA kappa multiple myeloma. His past medical history included hypertension, diabetes, and coronary artery disease, with a history of myocardial infarction. On Day 1 of Cycle 1, the patient developed grade 3 chest pain approximately 2.5 hours after the start of the infusion. The patient required hospitalization. His vital signs, ECG, and cardiac enzymes were normal. Symptoms resolved by day 2 and he was discharged from the hospital. The patient permanently discontinued treatment with elotuzumab.

In 4 subjects, the infusion reaction was classified as serious. The serious infusion reactions included the terms: diarrhea (grade 3) and fever (grade 1), congestive heart failure (grade 3), fever of unknown origin (grade 2), and chest pain (grade 3).

The table below provides the incidence of infusion reactions by system organ class and preferred term.

Table 32. Incidence of Infusion Reactions

System Organ Class Preferred Term	E-Ld (N=318)			
	Grade 1-4		Grade 3-4	
	n	%	n	%
General disorders and administration site conditions				
Pyrexia	10	3.1	0	0.0
Chills	4	1.3	0	0.0
Asthenia	1	0.3	0	0.0
Chest pain ¹	2	0.6	1	0.3
Face edema	1	0.3	0	0.0
Feeling cold	1	0.3	0	0.0
Vascular disorders				
Hypertension	4	1.3	1	0.3
Flushing	1	0.3	0	0.0
Hypotension	1	0.3	0	0.0
Injury, poisoning, and procedural complications				
Infusion related reaction	3	0.9	0	0.0
Immune system disorders				
Hypersensitivity	2	0.6	0	0.0
Skin and subcutaneous tissue disorders				
Urticaria	2	0.6	0	0.0
Angioedema	1	0.3	1	0.3
Erythema	1	0.3	0	0.0
Hyperhidrosis	1	0.3	0	0.0
Pruritus	1	0.3	0	0.0
Rash	1	0.3	0	0.0
Swelling face	1	0.3	0	0.0
Cardiac disorders				
Bradycardia	1	0.3	0	0.0
Cardiac congestive failure	1	0.3	1	0.3
Eye Disorders				
Eye edema	1	0.3	0	0.0
Eyelid Edema	1	0.3	0	0.0
Vision blurred	1	0.3	0	0.0
Gastrointestinal disorders				
Diarrhea	1	0.3	1	0.3
Dyspepsia	1	0.3	0	0.0

System Organ Class Preferred Term	E-Ld (N=318)			
	Grade 1-4		Grade 3-4	
	n	%	n	%
Musculoskeletal and connective tissue disorders				
Myalgia	1	0.3	0	0.0
Nervous system disorders				
Dizziness	1	0.3	0	0.0
Dysgeusia	1	0.3	0	0.0
Headache	1	0.3	0	0.0
Tremor	1	0.3	0	0.0
Respiratory, thoracic and mediastinal disorders				
Cough	1	0.3	0	0.0
Dyspnea	1	0.3	0	0.0

¹- Chest pain includes the terms: chest pain and chest discomfort

Infusion Rate: As noted in Section 6.1.1, for study CA204004, the protocol-specified infusion rate was changed in Amendment 12. Prior to the change the maximum infusion rate was 2 ml/min. This was changed such that with the first dose of elotuzumab, the rate of infusion could be escalated to ml/min and with the start of cycle 2 could be as high as 5 ml/min. As this Amendment occurred relatively late in the course of the study, only 40 infusions out of a total of 12,851 were administered at a rate > 2ml/min and of these only 11 were at a rate of ≥ 5 ml/min.

Clinical Reviewer Comment:

(b) (4) (b) (4)
 The Applicant has an ongoing phase 2, open-label trial, Study CA204112 to evaluate the faster infusion rate when elotuzumab is administered in combination with Ld in patients with newly diagnosed or relapsed/refractory MM.

8.5.4. Infections

Elotuzumab binds to SLAMF7, which is expressed on all plasma cells, including myeloma cells. It is also expressed on NK Cells, NK-T cells, CD56+ T cells, activated CD8 T cells, activated dendritic cells and monocytes. Based on the expression of SLAMF7, elotuzumab has the potential to affect immune cells. Additionally, it has been observed that patients in the E-Ld arm had higher rates of grade 3-4 lymphopenia compared to the control arm, 76.7% vs. 48.6%.

Overall, when evaluating the incidence of adverse events that are grouped within the system organ class of infections and infestations, 256 subjects (80.5%) in the E-Ld arm had a treatment-emergent infection compared with 235 in the Ld arm (74.1%). The incidence of grade ≥ 3 infections was 29.9% in the E-Ld arm compared with 26.5% in the Ld arm. Events that were

classified as serious occurred in 97 subjects (30.5%) in the E-Ld arm compared with 79 in the Ld arm (24.9%).

Of note, there was also an increased incidence of opportunistic infections in the E-Ld arm compared with the Ld arm, 22.0% versus 12.9%. The table below includes the opportunistic infections by grade.

Table 33. Opportunistic Infection Incidence

	E-Ld (N= 318)				Ld (N=317)			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Viral Infectious disorders								
Herpes zoster	19	6.0	5	1.6	9	2.8	2	0.6
Oral Herpes	17	5.3	0	0.0	13	4.1	0	0.0
Herpes virus infection	7	2.2	0	0.0	0	0.0	0	0.0
Genital herpes	2	0.6	0	0.0	1	0.3	0	0.0
Herpes simplex	2	0.6	0	0.0	0	0.0	0	0.0
Cytomegalovirus	1	0.3	1	0.3	0	0.0	0	0.0
Varicella	1	0.3	0	0.0	0	0.0	0	0.0
Ophthalmic herpes simplex	0	0.0	0	0.0	1	0.3	0	0.0
Ophthalmic herpes zoster	0	0.0	0	0.0	1	0.3	1	0.3
Fungal Infectious disorders								
Oral candidiasis	11	3.5	0	0.0	7	2.2	0	0.0
Candida infection	5	1.6	0	0.0	4	1.3	0	0.0
Fungal infection	3	0.9	0	0.0	1	0.3	0	0.0
Fungal skin infection	3	0.9	0	0.0	0	0.0	0	0.0
Pneumocystis jirovecii pneumonia	3	0.9	3	0.9	0	0.0	0	0.0
Oral fungal infection	2	0.6	0	0.0	3	0.6	1	0.3
Aspergillus infection	1	0.3	0	0.0	0	0.0	0	0.0
Bronchopulmonary Aspergillus	1	0.3	1	0.3	0	0.0	0	0.0

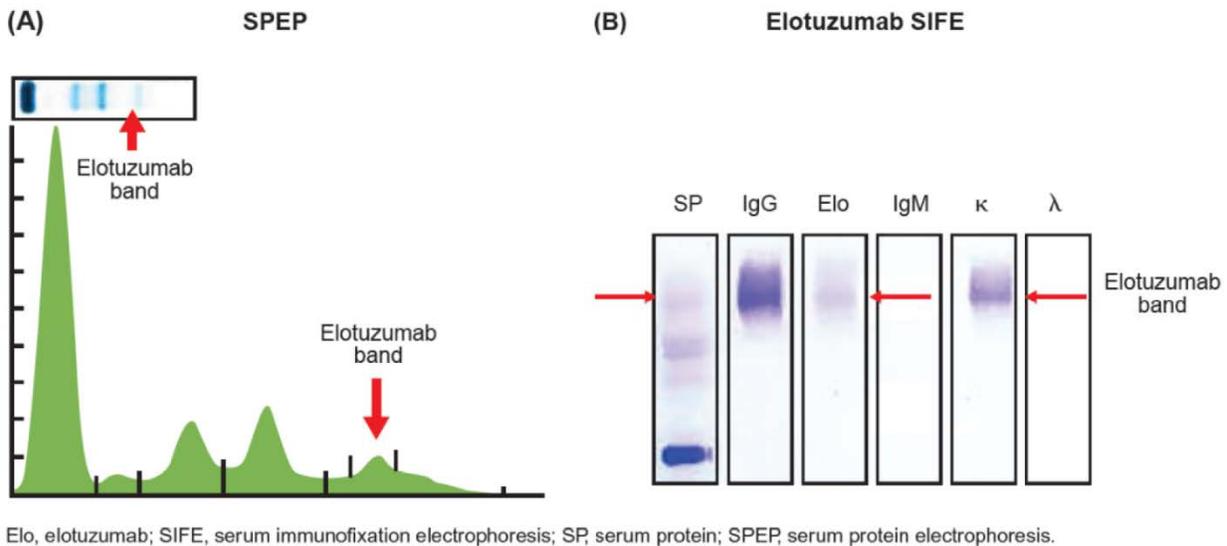
	E-Ld (N= 318)				Ld (N=317)			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Cerebral Aspergillus	1	0.3	1	0.3	0	0.0	0	0.0
Ear infection fungal	1	0.3	1	0.3	0	0.0	0	0.0
Esophageal candidiasis	1	0.3	0	0.0	0	0.0	0	0.0
Pneumonia fungal	1	0.3	0	0.0	0	0.0	0	0.0
Gastrointestinal candidiasis	0	0.0	0	0.0	1	0.3	0	0.0
Urinary tract infection fungal	0	0.0	0	0.0	1	0.3	0	0.0
Mycobacterial Infectious disorders								
Atypical mycobacterial infection	1	0.3	0	0.0	0	0.0	0	0.0

8.5.5. Elotuzumab Interference in SPEP and IFE

Elotuzumab is a humanized monoclonal immunoglobulin (IgG1) kappa antibody. Therapeutic antibodies have previously been reported to interfere with SPEP and IFE assays. This has been noted previously with ofatumumab, siltuximab and daratumumab. If a therapeutic antibody is present in a patient's sera, it can be detected on the SPEP or IFE, and can be confused with a malignant monoclonal protein.

The Applicant developed a "detection assay" for elotuzumab in which one of the anti-immunoglobulin (Ig) antibodies used to precipitate Ig was replaced by an anti-elotuzumab antibody (2 mg/ml) with reactivity to an elotuzumab epitope. If elotuzumab was present in the patient's sera, the anti-idiotypic antibody-elotuzumab complex precipitated and a band was detected on immunofixation. The sensitivity of this assay was assessed with normal human serum spiked with 8 different concentrations of elotuzumab including Cmax (1094 ug/ml), 50% Cmax, 33% Cmax, 25% Cmax, 20% Cmax, 15% Cmax, 5% Cmax and 3% Cmax (33 ug/ml). An elotuzumab band could be distinguished at all elotuzumab concentrations in the immunofixation assay. The figure below shows the SPEP and serum immunofixation of serum from a healthy donor spiked with elotuzumab (20% Cmax).

Figure 25. Elotuzumab Interference with SPEP and IFE



Source: Applicant's Response to Information Request received 10/2/15, pg. 2

Elotuzumab can be detected in the SPEP and serum IFE assays of myeloma patients treated with elotuzumab. The determination of CR or stringent CR may be confounded by the presence of elotuzumab in these assays. Ultimately, this may lead to an underestimation of complete response or an incorrect determination of relapse from CR based on the presence of an elotuzumab protein spike and not an actual M-protein.

The sponsor is in the process of developing (b) (4) which may allow for better discrimination of protein due to elotuzumab vs. myeloma. Please see section 4.6 for further assay details.

8.6. Specific Safety Studies/Clinical Trials

8.6.1. Pooled Safety Analyses

Safety data was pooled from studies CA204004, HuLuc-1703, CA204005 and CA204007 to provide further support of the safety profile of elotuzumab when combined with lenalidomide and dexamethasone. Refer to Table 3 for further details about the clinical trials. In total, there were 768 patients in the pooled analysis dataset who were included in the safety population, 451 in the E-Ld arm and 317 in Ld arm. Study CA204004 was the only controlled trial in the analysis.

Serious adverse events occurred in 277 (61.4%) patients in the E-Ld arm compared with 175 (55.2%) patients in the Ld arm. There were 18 deaths due to adverse events in the E-Ld arm compared with 19 deaths in the Ld arm. The table below includes adverse events that occurred

with an incidence of $\geq 10\%$ in either arm and grade 3-4 adverse events that occurred at an incidence of $\geq 5\%$ in either arm.

Table 34. Treatment Emergent Adverse Events Pooled Trials

	E-Ld (N= 451)				Ld (N=317)			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders								
Anemia	180	39.9	65	14.4	121	38.2	56	17.7
Neutropenia	148	32.8	110	24.4	135	42.6	106	33.4
Thrombocytopenia	124	27.5	60	13.3	73	23.0	37	11.7
Lymphopenia	76	16.9	53	11.8	22	6.9	10	3.2
Leukopenia	51	11.3	24	5.3	25	7.9	12	3.8
Eye Disorders								
Cataract	50	11.1	25	5.5	20	6.3	9	2.8
Vision blurred	48	10.6	1	0.2	16	5.0	1	0.3
Gastrointestinal disorders								
Diarrhea	228	50.6	29	6.4	115	36.3	13	4.1
Constipation	180	39.9	5	1.1	86	27.1	1	0.3
Nausea	135	29.9	4	0.9	68	21.5	2	0.6
Vomiting	73	16.2	2	0.4	28	8.8	3	0.9
Abdominal Pain	57	12.6	1	0.2	27	8.5	0	0
Dyspepsia	47	10.4	0	0	19	6.0	0	0
General disorders								
Fatigue ¹	322	71.4	53	11.8	174	54.9	38	12.0
Pyrexia	174	38.6	10	2.2	79	24.9	9	2.8
Peripheral edema	120	26.6	5	1.1	71	22.4	1	0.3
Infections and infestations								
Nasopharyngitis	105	23.3	0	0	62	19.6	0	0
Upper respiratory tract infection	121	26.8	6	1.3	55	17.4	4	1.3
Bronchitis	80	17.7	8	1.8	53	16.7	9	2.8
Pneumonia ²	91	20.2	60	13.3	43	13.6	29	9.1
Urinary tract infection	45	10.0	5	1.1	31	9.8	7	2.2
Injury, poisoning, and procedural complications								
Contusion	48	10.6	1	0.2	27	8.5	0	0

	E-Ld (N= 451)				Ld (N=317)			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Investigations								
Weight decreased	60	13.3	4	0.9	19	6	0	0
Alanine aminotransferase increased	39	8.6	5	1.1	32	10.1	8	2.5
Creatinine increased	46	10.2	5	1.1	21	6.6	0	0.0
Metabolism and nutrition disorders								
Decreased appetite	92	20.4	6	1.3	40	12.6	4	1.3
Hyperglycemia	89	19.7	36	8.0	43	13.6	14	4.4
Hypokalemia	80	17.7	22	4.9	47	14.8	15	4.7
Hypocalcemia	57	12.6	13	2.9	31	9.8	4	1.3
Musculoskeletal and connective tissue disorders								
Muscle spasms	158	35.0	3	0.7	84	26.5	3	0.9
Back pain	139	30.8	23	5.1	89	28.1	14	4.4
Arthralgia	85	18.8	7	1.6	40	12.6	3	0.9
Pain in extremity	83	18.4	3	0.7	32	10.1	1	0.3
Musculoskeletal pain	56	12.4	8	1.8	28	8.8	2	0.6
Muscular weakness	43	9.5	7	1.6	25	7.9	4	1.3
Bone pain	49	10.9	3	0.7	40	12.6	3	0.9
Musculoskeletal chest pain	45	10.0	2	0.4	27	8.5	0	0
Nervous system disorders								
Headache	79	17.5	2	0.4	24	7.6	1	0.3
Peripheral neuropathy	75	16.6	6	1.3	27	8.5	5	1.6
Dizziness	71	15.7	2	0.4	37	11.7	0	0
Dysgeusia	55	12.2	0	0	20	6.3	0	0
Paresthesia	45	10.0	1	0.2	29	9.1	1	0.3
Peripheral sensory neuropathy	39	8.6	4	0.9	35	11	2	0.6
Psychiatric disorders								
Insomnia	115	25.5	8	1.8	82	25.9	8	2.5

	E-Ld (N= 451)				Ld (N=317)			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Respiratory, thoracic and mediastinal disorders								
Cough	138	30.6	1	0.2	59	18.6	0	0
Dyspnea	103	22.8	12	2.7	59	18.6	11	3.5
Skin and subcutaneous tissue disorders								
Rash	92	20.4	3	0.7	58	18.3	5	1.6
Hyperhidrosis	54	12.0	0	0	22	6.9	0	0
Vascular disorders								
Deep vein thrombosis	33	7.3	23	5.1	12	3.8	7	2.2

1- Fatigue includes the terms: fatigue and asthenia

2- Pneumonia includes the terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, pneumonia bacterial, pneumonia fungal, pneumonia influenza, pneumonia legionella, pneumonia pneumococcal, pneumonia viral, pneumonia streptococcal, pneumonia respiratory syncytial viral, pneumonia viral.

Clinical Reviewer’s comment: *The results of the pooled safety analysis are similar to the findings observed in trial CA204004.*

8.6.2. Safety Update

The Applicant submitted a 90 day safety update on September 25, 2015. The 90 Day safety update contained updated safety information on the following trials: CA204004, HuLuc63-1703, CA204005, CA204007, CA204009, CA204010, CA204011, CA204006, and CA204116. Interim safety data was provided for studies CA204006 and CA204116, as these trials were ongoing at the time of the safety update. The safety update included pooled data from trials: CA204004, HuLuc63-1703, CA204005, and CA204007. The database lock for all studies in the safety update was May 15, 2015, except study CA204009, which had a database lock date of April 17, 2015.

A summary of treatment-emergent adverse events is included in the table below.

Table 35. Safety Update Treatment-emergent AE Summary

	Elotuzumab SCS (BLA) Number of subjects (%)						Elotuzumab SU Number of subjects (%)					
	CA204004				Pooled E-Ld ^a		CA204004				Pooled E-Ld ^a	
	E-Ld N = 318		Ld N = 317		E-Ld N=451		E-Ld N = 318		Ld N = 317		E-Ld N=451	
Deaths within 60 days of last dose	31 (9.7)		39 (12.3)		35 (7.8)		38 (11.9)		41 (12.9)		42 (9.3)	
	Worst Grade						Worst Grade					
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All SAEs	208 (65.4)	153 (48.1)	179 (56.5)	116 (36.6)	284 (63.0)	213 (47.2)	219 (68.9)	157 (49.4)	188 (59.3)	125 (39.4)	295 (65.4)	219 (48.6)
All AEs leading to DC	83 (26.1)	51 (16.0)	85 (26.8)	50 (15.8)	110 (24.4)	70 (15.5)	94 (29.6)	57 (17.9)	91 (28.7)	53 (16.7)	121 (26.8)	77 (17.1)
Infusion reactions	33 (10.4)	4 (1.3)	NA ^b	NA ^b	44 (9.8)	5 (1.1)	34 (10.7)	4 (1.3)	NA ^b	NA ^b	45 (10)	5 (1.1)
Secondary primary malignancies ^c	22 (6.9)	NA	13 (4.1)	NA	35 (7.8)	NA	25 (7.9)	NA	16 (5)	NA	38 (8.4)	NA

Source: Applicant's 90-Day Safety Update, pg. 21

Clinical Reviewer's Comment: *Of note, the incidence of SAEs, AEs leading to discontinuation, infusion reactions, and SPMs are similar to the rates noted in the initial BLA submission.*

With regards to the specific SAE, the most common SAE SOC was Infections and Infestations. In the updated information for Study CA204004, the incidence of infection was 35.5% in the E-Ld arm vs. 25.9% in the Ld arm. The incidences reported in the BLA were 31.1% and 25.2%, respectively. The updated incidence of grade 3-4 infections was 27% in the E-Ld arm vs. 20.5% in the Ld arm. The most frequently reported grade 3-4 infections were: pneumonia (10.4%), respiratory tract infection (2.2%), and sepsis (1.9%) in the E-Ld arm. The most frequently reported grade 3-4 infections in the Ld group were pneumonia (6.9%), influenza (1.6%), and urinary tract infection (1.6%).

Clinical Reviewer's Comment: *The incidence of infection seems to be increased with elotuzumab when combined with Ld when compared to Ld alone. This finding was observed in the data initially submitted with the BLA in study CA204004 and also in the pooled data.*

There were 6 new cases of SPM that were included in the updated safety information. All of the cases occurred in study CA204004. There were 3 in the E-Ld arm and 3 in the Ld arm. The new SPM cases were non-melanoma skin cancers or solid organ cancers. The table below contains the new cases.

Table 36. Safety Update- Listing of SPMs

Treatment Group Subject ID	Age/Gender/ Race	Study Day	Diagnosis (preferred term)	Diagnosis (reported term)
E-Ld group				
CA204004-3404-628	71/M/C	316	Squamous cell carcinoma of the skin	Squamous cell carcinoma of the skin
		567	Squamous cell carcinoma	Verrucous-hyperkeratotic variant of squamous cell carcinoma
		657	Basal cell carcinoma	Basal cell carcinoma of the skin
CA204004-4600-657	66/F/C	741	Squamous cell carcinoma of the skin	Squamous cell carcinoma of the skin
			Cervix carcinoma	Carcinoma of the cervix
CA204004-5906-650	61/M/C	900	Squamous cell carcinoma of the vulva	Carcinoma of the vulva
			Basal cell carcinoma	Basal cell carcinoma
Ld Group				
CA204004-1447-26	83/M/C	1147	Squamous cell carcinoma of skin	Squamous cell skin cancer
CA204004-3404-565	59/M/C	703	Basal cell carcinoma	Basal cell carcinoma
CA204004-3408-449	74/M/C	950	Squamous cell carcinoma	Squamous cell carcinoma

Source: Applicant's 90-Day Safety Update, pg. 48

Reviewer's Comment: *The updated information on SPMs does not change the interpretation of the risk of SPMs with elotuzumab in combination Ld.*

The 90-Day safety update also contains two new cases of potential DILI. Both cases occurred in study CA204004. Brief summaries of the two cases are provided below.

- Subject 5003-429: The patient was a 72 year old male with a four year history of IgG kappa multiple myeloma. He had received 2 prior regimens. At baseline, the patient had an ALT of 9 U/L (reference range: 5-40 U/L) and a total bilirubin of 11.97 µmol/L (reference range: 1.71- 20.52 µmol/L). On Day 921, on the scheduled day of elotuzumab infusion, the patient was noted to have an ALT > 3x ULN and a total bilirubin level ≥ 2x ULN. Five days later, the patient had grade 2 fever and grade 2 cough, for which he

received treatment with cefditoren pivoxil. Following the onset of these events, oral dexamethasone was interrupted. Two days later the fever resolved, and the cough was reported as resolved one week later. On Day 940, the patient met criteria for liver ALT \geq 3x ULN and total bilirubin. He was diagnosed with grade 1 biliary colic, hyperbilirubinemia and thrombocytopenia (grade 2) and was treated with ursedeoxycholic acid. Study treatment with elotuzumab and lenalidomide were interrupted. The hyperbilirubinemia improved from grade 2 to grade 1 on Day 960. Elotuzumab was resumed on Day 968.

	ALK P (U/L)	AST	ALT	TBili
Units	U/L	U/L	U/L	$\mu\text{mol/l}$
Ref. range	-	-	5-40	1.71-20.52
Day 1			9	11.97
Day 898	-	-	13	10.26
Day 926	-	-	230	15.39
Day 940	-	-	166	56.43
Day 960	-	-	67	27.36
Day 968	-	-	50	23.94
Day 982	-	-	38	15.39

Reviewer's Comment: Alkaline phosphatase and AST data were not provided. The patient resumed treatment with elotuzumab and the LFTs normalized while on treatment, which is not typically seen with drug-induced liver injury.

- Subject 5900-572: The patient was a 59 year old male with a three year history of IgG kappa multiple myeloma. He had received three prior therapies. At baseline, the patient had normal ALT and total bilirubin. On Day 846, the patient was hospitalized for grade 3 fever. Study drug was interrupted because of this event. On Day 855, 14 days after the 63rd dose of elotuzumab, the patient had ALT \geq 3x ULN and total bilirubin \geq 2x ULN. On Day 857, the patient was diagnosed with hematophagic lymphohistiocytosis and progressive myeloma. A CT scan and MRI showed evidence of a hepatic mass. The patient died on Day 875. An autopsy was performed which showed myeloma progression and tumor deposits in the liver and spleen.

	ALK P (U/L)	AST	ALT	TBili
Units	U/L	U/L	U/L	µmol/l
Ref. range	-	-	0-40	1.71-20.52
Day 0			20	10
Day 840	-	-	66	4
Day 855	-	-	138	103
Day 859	-	-	81	131

Clinical Reviewer's comment: The patient's autopsy demonstrated evidence of myeloma hepatic involvement. This confounder makes a determination of drug-induced liver injury difficult.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Refer to section 8.5.1

8.7.2. Human Reproduction and Pregnancy

There has not been any exposure to elotuzumab in pregnant or lactating women.

8.7.3. Pediatrics and Assessment of Effects on Growth

There has not been any exposure to elotuzumab in pediatric patients.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There has not been overdose experience with elotuzumab. Its use has been evaluated in clinical trials which have dose-escalated up to 20 mg/kg. The MTD was not reached in these trials.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Elotuzumab is not marketed in any country.

8.8.2. Expectations on Safety in the Postmarket Setting

It is not expected that the safety profile of elotuzumab in combination with lenalidomide and dexamethasone in the postmarket setting will differ from that observed in the clinical trials.

8.9. Additional Safety Issues From Other Disciplines

There are no other safety concerns from other disciplines.

8.10. Integrated Assessment of Safety

The assessment of safety was primarily based on the safety dataset from study CA204004 and the pooled datasets from studies CA204004, HuLuc-1703, CA204005 and CA204007. The safety population from study CA204004 consisted of 318 patients and the pooled safety dataset contained 451 patients.

In study CA204004, as of the data cutoff of October 29, 2014, there were 210 deaths, 94 (29.6%) in the E-Ld arm and 116 (36.6%) deaths in the Ld arm. Nonfatal serious adverse events occurred in 204 (64.1%) of patients in the E-Ld arm compared with 175 (55.2%) in the Ld arm. The most frequent SAEs were in the E-Ld arm vs. the Ld arm respectively were: Pneumonia (15.4% vs. 11.4%), pyrexia (6.3% vs. 4.4%), respiratory tract infection (4.7% vs. 2.5%), anemia (2.5% vs. 1.9%), pulmonary embolism (2.5% vs. 2.2%), and acute renal failure (2.5% vs. 1.6%).

Treatment-emergent adverse events occurred in 99.4% of patients in the E-Ld arm and 99.1% in the Ld arm. Grade 3-4 TEAEs occurred in 85.5% of patients in the E-Ld arm compared with 76.0% of patients in the Ld arm. TEAEs that occurred at an incidence $\geq 10\%$ in either arm and had a $\geq 5\%$ higher rate in the E-Ld arm compared with the Ld arm respectively were: diarrhea (46.9% vs. 35.5%), constipation (34.9% vs. 26.8%), vomiting (14.5% vs. 8.8%), fatigue (61 vs. 51.1%), pyrexia (36.8% vs. 24.3%), peripheral edema (25.8% vs. 21.8%), nasopharyngitis (24.2% vs. 19.2%), upper respiratory tract infection (22.6% vs. 17.4%), weight decreased (13.8% vs. 6%), creatinine increased (12.6% vs. 7.6%), decreased appetite (20.4% vs. 12.6%), pain in extremity (16.4% vs. 9.8%), musculoskeletal pain (12.6% vs. 8.5%), headache (15.4% vs. 7.6%), peripheral neuropathy (13.8% vs. 8.2%), cough (31.3% vs. 18%), and oropharyngeal pain (10.1% vs. 4.4%).

For laboratory data, the most common grade ≥ 3 hematologic abnormalities were lymphopenia, anemia, thrombocytopenia and neutropenia. The rate of grade ≥ 3 lymphopenia was 76.7% in the E-Ld arm compared with 48.6% in the Ld arm.

Vital sign abnormalities as identified in the vital sign dataset revealed significantly more abnormalities than that which was identified in the adverse event dataset. For example, in the AE dataset, hypotension occurred at a rate of 9.4% in the E-Ld arm compared with 3.8% in the Ld arm, while the vital sign database showed that a SBP < 90 mmHg occurred at a rate of 28.9% vs. 8.2% respectively. In the AE dataset, tachycardia was reported at a frequency of 2.5% in the E-Ld arm and 3.5% in the Ld arm, while bradycardia was reported in 0.3% in the E-Ld arm and 0.6% in the Ld arm. In the vital sign dataset, tachycardia (HR ≥ 100 bpm), occurred in 153 (48.1%) subjects in the E-Ld arm compared with 97 (30.6%) subjects in the Ld arm. Bradycardia

(HR < 60) occurred in 211 subjects (66.3%) in the E-Ld arm and 99 subjects (31.2%) in the Ld arm. Based on the vital sign dataset, tachycardia had nearly an 18% greater incidence in the E-Ld arm than the Ld arm, while bradycardia had more than 30% greater incidence. These differences suggest that there may be significant underreporting of adverse events and possibly underreporting of infusion reactions, as many of these vital changes likely occurred during the or shortly thereafter the infusion. The clinical significance of these vital results is not likely to be substantial, but more likely reflect physiologic effects of elotuzumab.

Other safety issues of importance include second primary malignancies, infusion reactions, hepatotoxicity, and infections (especially opportunistic infections). SPMs occurred in 8.2% in the E-Ld arm vs. 4.7% of patients in the Ld arm. Lenalidomide has a recognized risk of SPMs. Elotuzumab when combined with lenalidomide and dexamethasone seems to increase the rate of SPM. Infusion reactions occurred in 10% of patients treated with E-Ld. Overall the infusion reactions were tolerable, such that only 2 infusion reactions resulted in permanent discontinuation of study drug. Hepatotoxicity was also noted in this trial and there was 1 case that met Hy's law criteria and had biopsy findings consistent with drug-induced hepatitis. This case developed in the setting of underlying hepatic steatosis. Care should be taken when elotuzumab is administered to those patients with liver disease at baseline. Infection also occurred more commonly in patients with E-Ld compared to those with Ld. In the trial, 80.5% of subjects in the E-Ld arm had a treatment-emergent Infection compared to 74.1% of subjects in the Ld arm. Serious adverse events of infection occurred in 30.5% in the E-Ld arm vs. 24.9% Ld arm. Opportunistic infections occurred at a rate of 22% of subjects in the E-Ld arm vs. 12.9% in the Ld arm. These additional safety issues require that investigators be aware of these effects and monitor patients carefully.

The safety findings observed in the pivotal trial and in the pooled safety data are risks that providers should be aware of, but are not uncommon or unacceptable risks for therapies used in the treatment of cancer.

9 Advisory Committee Meeting and Other External Consultations

This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

10 Labeling Recommendations

10.1. Prescribing Information

The following are recommended major changes to the proposed elotuzumab prescribing information based on this review:

1 Indications and Usage: The Applicant proposed that elotuzumab is indicated for the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone (b) (4). It is recommended by these reviewers that (b) (4)

(b) (4) Additionally, study CA204004 was conducted in patients that had received 1 to 3 prior lines of therapy. The indication should be limited to those that have received 1 to 3 prior therapies, not one or more as proposed by the Applicant.

5 Warnings and Precautions: In the initial proposed label, the Applicant proposed infusion reaction and (b) (4) to be included in this section. The (b) (4) were removed. The additional recommended W&P are: second primary malignancies, Infections, hepatotoxicity, and interference with determination of complete response.

6 Adverse Reactions: The initial proposed label contained the following adverse reactions:

(b) (4)
The Applicant was instructed to include a table which listed adverse reactions which occurred at a frequency of $\geq 10\%$ in the E-Ld arm and $\geq 5\%$ higher than the Ld arm. It is also the recommendation of this reviewer to include a table of laboratory data and a discussion of vital sign abnormalities given the possible underreporting of labs and vitals as AEs.

14 Clinical Studies: Minor changes were made to the proposed clinical studies section, with the exception of removal of (b) (4)

10.2. Patient Labeling

Review of Patient labeling by the Division of Medical Policy Programs in the Office of Medical Policy is ongoing.

11 Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of this drug, there are no additional risk management strategies beyond recommended labelling. Based on the review of the application and the findings of the review team, the Division of Risk Management in the Office of Surveillance and Epidemiology agrees that a REMS is not needed to ensure the benefits of elotuzumab exceed its risks

12 Post-marketing Requirements and Commitments

There are no Clinical PMCs or PMRs proposed for elotuzumab. A Clinical Pharmacology PMC is being considered to evaluate if poor response among patients with a low exposure to elotuzumab can be overcome by using a higher dosing strategy. Please refer to Clinical Pharmacology Review for further details.

13 Appendices

13.1. References

1. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2014;28(5):1122-8. doi: 10.1038/leu.2013.313. PubMed PMID: 24157580; PubMed Central PMCID: PMC4000285.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65(1):5-29. doi: 10.3322/caac.21254. PubMed PMID: 25559415.
3. Howlader N, NA, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA SEER Cancer Statistics Review, 1975-2012, National Cancer Institute http://seer.cancer.gov/csr/1975_2012/2015. based on November 2014 SEER data submission posted to the SEER web site April 5.].
4. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003;78(1):21-33. doi: 10.4065/78.1.21. PubMed PMID: 12528874.
5. Waxman AJ, Mink PJ, Devesa SS, Anderson WF, Weiss BM, Kristinsson SY, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. *Blood*. 2010;116(25):5501-6. doi: 10.1182/blood-2010-07-298760. PubMed PMID: 20823456; PubMed Central PMCID: PMC3031400.
6. Feng X, Yan J, Wang Y, Zierath JR, Nordenskjöld M, Henter JI, et al. The proteasome inhibitor bortezomib disrupts tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)

expression and natural killer (NK) cell killing of TRAIL receptor-positive multiple myeloma cells. Mol Immunol. 2010;47(14):2388-96. doi: 10.1016/j.molimm.2010.05.003. PubMed PMID: 20542572.

7. Krieg S, Ullrich E. Novel immune modulators used in hematology: impact on NK cells. Front Immunol. 2012;3:388. doi: 10.3389/fimmu.2012.00388. PubMed PMID: 23316191; PubMed Central PMCID: PMC3539673.

13.2. Financial Disclosure

Covered Clinical Study: CA204004

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>166</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in Sponsor of covered study: <u>1</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>10</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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

/s/

NICOLE J GORMLEY
11/16/2015

CHIA-WEN KO
11/16/2015

ALBERT B DEISSEROTH
11/16/2015

**Clinical Review
Breakthrough Therapy Designation
IND 100043**

Summary Box

1. IND Number: **IND 100043**
2. Company name: **Bristol-Myers Squibb**
3. Drug name: **Elotuzumab**
4. Indication: **Elotuzumab in combination with lenalidomide and dexamethasone for treatment of multiple myeloma in patients who have received one or more prior therapies.**
5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition? **Yes**
6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints? *[brief statement]* **Yes, there is credible evidence for substantial improvement over available therapy in a sufficient number of patients. There is an ORR of 80 to 95% compared to 60% in historical controls from 3 trials and a duration of response approximately twice that of historical controls without a significant increase in toxicity.**

Division: **Division of Hematology Products**
Medical officer: **Thomas Herndon, MD**
Clinical Team Leader: **Albert Deisseroth, MD, PhD**

1. Brief description of the drug

- Elotuzumab (BMS-901608) is a humanized monoclonal immunoglobulin G1 (IgG1) antibody product directed to human SLAMF7 (also known as CS1), a cell surface glycoprotein with homology to the CD2 family of cell surface proteins. SLAMF7 is expressed in greater than 95% of all MM cells. There is little expression on normal cells, with the exception of subsets of normal leukocytes in humans (natural killer, natural killer T-cells, a subset of CD8+ T cells and plasma cells). The proposed mechanism of action of elotuzumab involves NK cell-mediated antibody dependent cellular cytotoxicity.

2. Brief description of the disease and intended population

- Multiple myeloma (MM) is an incurable malignancy associated with high morbidity and mortality with a 5-year relative survival rate of 43%.^{1,2} Nearly all patients relapse from initial therapy and remissions with second, third and fourth-line therapies become progressively shorter. Remissions with second line therapy extend for a median of 6-11 months while

remissions during third line therapy continue for a median of 4-5 months. Most of the available therapies for relapsed MM are from two classes of agents, proteasome inhibitors and immunomodulatory drugs (IMiDs). Despite the current treatments, relapsed MM remains essentially incurable and an area of unmet medical need.

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

- The endpoints considered by the sponsor as supporting the breakthrough therapy designation are overall response rate (ORR), (b) (4) and median Duration of Response (mDOR). (b) (4)
- The endpoint(s) that are accepted by the division as a clinically significant endpoint (outcome measure) for patients with the disease are:
 - PFS which is a clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval) and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit. Overall survival is usually a secondary endpoint in trials that lead to traditional approval or confirmatory trials following accelerated approval.
 - ORR with a prolonged DOR are earlier clinical endpoints considered reasonably likely to predict the clinical benefit of a drug and are the current standard for supporting an application for patients with MM under the accelerated approval pathway.
- There are no other biomarkers the division would consider likely to predict a clinical benefit (e.g., metastatic effect), even if not yet a basis for accelerated approval.

4. Brief description of available therapies

The approved agents for relapsed or refractory MM that are commonly used to treat this patient population are listed in Table 1. In addition to those agents listed in Table 1, thalidomide, melphalan, cyclophosphamide, carmustine, and dexamethasone have approval or are accepted agents for the treatment of MM. These agents are rarely used as single agents and carmustine is seldom used for the treatment of patients with MM.

Agent	Current Approval	Trials	ORR (%)	DOR/TTP* (months)
Lenalidomide	Regular	MM-009	61	14*
		MM-010	60	12*
Bortezomib	Regular	APEX	38	6*
Liposomal doxorubicin**	Regular	MMY3001	48	9*
Pomalidomide	Accelerated	MM-002	8	NA

Agent	Current Approval	Trials	ORR (%)	DOR/TTP* (months)
Carfilzomib	Accelerated	PX-171-003A1	24	8

Table 1: Approved agents for relapsed refractory MM.

*Time To Progression

**Data is liposomal doxorubicin plus bortezomib

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

Daratumumab, a monoclonal antibody was granted breakthrough therapy designation for the treatment of patients with MM who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or are double refractory to a proteasome inhibitor and an immunomodulatory agent. This was based on the results of a Phase 1/2, open-label trial of single-agent daratumumab in patients with MM relapsed or refractory to at least two prior therapies. Preliminary efficacy information was provided for 12 patients in 4 cohorts receiving doses of 4-24mg/kg. The ORR of 42% was compared to an expected ORR of <24% expected using existing approved therapies in the same patient population.

6. Description of preliminary clinical evidence

- An overview of the clinical development program including completed and planned studies is shown in Figure 1. Phase 1 and 2 studies have been conducted to evaluate the pharmacokinetic (PK), safety, and preliminary efficacy of elotuzumab as monotherapy and combination therapy. The development plan includes 2 ongoing Phase 3 studies evaluating elotuzumab in combination with lenalidomide and low-dose dexamethasone in subjects with relapsed or refractory MM (CA204-004) and in subjects with newly diagnosed MM (CA204-006). Phase 2 studies of elotuzumab in combination with bortezomib and thalidomide are ongoing. The Phase 3 dose of 10 mg/kg was selected based on FDA feedback, safety and efficacy data, PK, and SLAMF7 saturation results in these studies. As of 17 May 2013, elotuzumab has been administered to approximately 887 subjects in 10 completed or ongoing clinical studies. The initial BLA is anticipated to be based on the Phase 3 study, CA204-004, with the proposed indication of elotuzumab in combination with lenalidomide and low-dose dexamethasone for the treatment of MM in patients who have received at one or more prior therapies, the same indication as the request for breakthrough therapy designation.

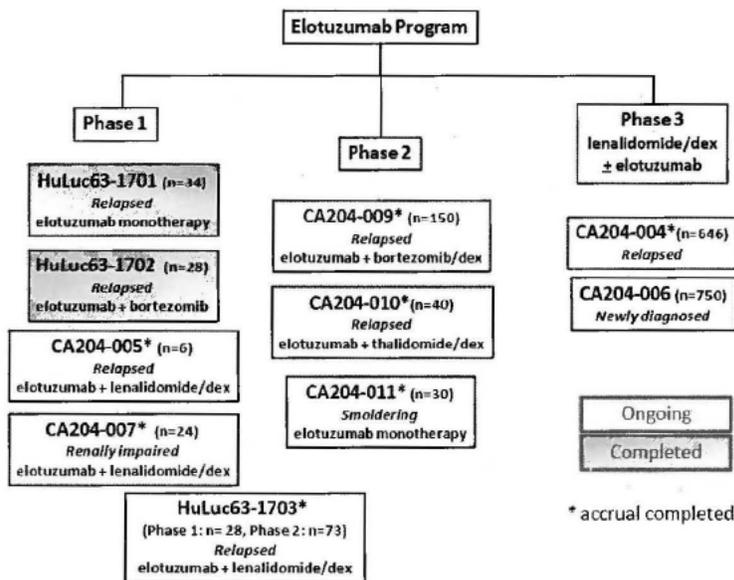


Figure 1: Development program for elotuzumab (appended from the submission)

- The preliminary efficacy data available to support breakthrough therapy designation is summarized in Table 2. In the Phase 2 portion of the HuLuc-63-1703 study, 73 subjects with relapsed/refractory MM were randomized 1:1 to receive either elotuzumab 10 mg/kg or elotuzumab 20 mg/kg IV combined with lenalidomide 25 mg orally and low-dose weekly dexamethasone 40 mg orally. The primary endpoint was ORR (\geq partial response (PR) per International Myeloma Working Group with key secondary endpoints assessing safety. As of 12 Dec 2013, the median DOR for the subjects in the 10 mg/kg dose group was 34.8 months and 29 months for the 20 mg/kg dose group. The combined ORR of the 10 and 20 mg/kg dose groups was 84% (61/73) with a DOR of 29 months.
- To justify that elotuzumab in combination with lenalidomide and low-dose dexamethasone has the potential to provide patients with a substantial clinical benefit over the existing standard of care for MM patients who have received at least one prior therapy, Phase 2 data from the HuLuc-63-1703 study is compared to the available published data from 3 historical trials evaluating lenalidomide in combination with dexamethasone in this population.^{3,4,5,6,7} The 3 historical trials that were used as the basis of the comparison are summarized in Table 2. MM-009 is a phase 3 study of lenalidomide /high-dose dexamethasone (177 patients from US and Canada) with relapsed and/or refractory MM with 1–3 prior therapies. MM-010 is a phase 3 study of lenalidomide /high-dose dexamethasone (176 patients from EU, Australia, Israel) with relapsed and/or refractory MM with 1–3 prior therapies. MM-021 is a phase 2 study of lenalidomide /low-dose dexamethasone (187 patients from China) with relapsed and/or refractory MM with >1 prior therapy; 50 (27%) patients with 1-2 prior therapies

	Study HuLuc63-1703 Elotuzumab with Low-Dose Dexamethasone		Historical Data Lenalidomide with Dexamethasone		
	10 mg/kg n=36	10 + 20 mg/kg n=73	MM-009 HIGH DOSE DEX n=177	MM-010 HIGH DOSE DEX n=176	MM-021 LOW DOSE DEX n=50
ORR, n (%)	33 (92%)	61 (84%)	108 (61%)	106 (60%)	29 (58%)
CR/sCR, n (%)	5 (14%)	9 (12%)	25 (14%)	28 (16%)	NA
mDOR, months	34.8	29.2	15.8	16.5	NA

Table 2: Summary of efficacy data supporting breakthrough therapy designation

- Safety data from HuLuc63-1703 (Phase 1 dose escalation and Phase 2) indicated treatment with elotuzumab in combination with lenalidomide and low-dose dexamethasone was well tolerated and toxicities were similar to what is observed with lenalidomide plus dexamethasone. No MTD was reached. The safety profile of elotuzumab was consistent across doses and does not appear to be dose dependent.

7. Reviewer's recommendation and rationale

- Recommendation: **Grant**
- Rationale:
 - Granted because the disease is a serious condition and preliminary clinical evidence indicates a substantial improvement over available therapy.

8. References

1. Kumar SK, Rajkumar SV, Dispenzieri A, et. al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008; 111(5):2516-20.
2. Myeloma - SEER stat fact sheets. National Cancer Institute (2014). Available at seer.cancer.gov/statfacts/html/mulmy.html Accessed 3/11/2014.
3. Weber DM, Chen C, Niesvizky R, et. al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007;357:2133-2142.
4. Dimopoulos M, Spencer A, Attal M, et. al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;357:2123-2132.
5. Dimopoulos MA, Chen C, Spencer A, et. al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia*. 2009; 23: 2147-2152.
6. Hou J, Du X, Jin J, et. al. A multicenter, open-label, phase 2 study of lenalidomide plus low-dose dexamethasone in Chinese patients with relapsed/refractory multiple myeloma: the MM-021 trial. *J Hematol Oncol*. 2013;6(1):41.

7. Jin J, Du X, Cai Z, Chen F, et. al. The MM-021 trial of lenalidomide plus low-dose dexamethasone in Chinese patients with relapsed and refractory multiple myeloma: Impact of prior therapies on efficacy and safety. *Blood*. 2013;122:3227.

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

/s/

THOMAS M HERNDON
05/06/2014

ALBERT B DEISSEROTH
05/08/2014