CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761035Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 16, 2015
From	Albert Deisseroth. MD, PhD
Subject	Cross-Discipline Team Leader Review
BLA	761035
Applicant	Bristol Myers Squibb
Date of Submission	June 29, 2015
PDUFA Goal Date	February 25, 2016
Proprietary Name / Non-Proprietary Name	Empliciti/Elotuzumab
Dosage form(s) / Strength(s)	Injection: 300 mg and 400 mg lyophilized powder in a single (b) (4) vial
Dosing Regimens	1.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 Indication(s)/Population(s)	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)
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s)	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.

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Nicole Gormley, MD
Biostatistics	Chia-Wen Ko, PhD/Lei Nie, PhD
Clinical Pharmacology	Olanrewaju Okusanya, PhD/Gene Willians, PhD
Pharmacometrics	Justin Earp, PhD/Nitin Mehrota, PhD
Pharmacology/Toxicology	Micihael Manning, PhD/Christopher Sheth, PhD
Product Quality (OBP/DMA)	Novak Rachel, PhD/Linan Ha, PhD/Sarah Kennett, PhD
OPF	Natalia Pripuzova, PhD, Maria Jose Lopez-Barragan, PhD and Patricia Hughes, PhD
Product Quality (OBP/DMA)	Jibril Abdus-Samad, PharmD
OSI	Anthony Orienca. MD
RPM	Natasha Kormanik

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1. Executive Summary: (This section is excerpted from the review of Dr. Nicole Gormley. For details, see her review.) Bristol-Myers Squibb submitted BLA 7610035 to the FDA on June 20, 2015 to support a request to have elotuzumab (Empliciti) approved for the following indications: the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone (b) (4)

The dosing regimens proposed for these indications are as follows:

1.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)

Elotuzumab: Elotuzumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody directed to 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 cell via an antibody-dependent cellular cytotoxicity (ADCC) mechanism.

Benefit Risk Assessment (This section has been excerpted from the review of Dr. Nicole Gormley. Please see her review for details.)

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. Despites 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 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. 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 ≥ 10% in either arm and had a ≥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.

Evidence and Uncertainties	Conclusions and Reasons
• 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 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.
• 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 an improvement in 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.
• 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.	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.

Evidence and Uncertainties	Conclusions and Reasons
• 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.	
• Infusion reactions were mitigated by requirement for pre-medications 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.	The Prescribing Information will include information about pre-medications for infusion reactions and management of infusion reactions should they occur. It will also include, as Warnings and Precautions, information about the risk of second primary malignancies, hepatoxicity, infections, and interference with the SPEP and IFE so that prescribers will be aware.

Conclusions about Efficacy and Safety: 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 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.

(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 comparison was to be made 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) in the Bd arm. The ORR was (b) (4) % (b) (4) in the E-Bd arm vs. (b) (4) % (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) The median OS was NE (b) (4) in the E-Bd arm vs. (b) (4) (b) (4) in the Bd arm.

(b) (4) (b) (4)

Regulatory Recommmendation of the CDTL: Regular Approval of elotuzumab for the following indication: 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.

2. Background: (This section is excerpted from the review of Dr. Nicole Gormley. For details, see her review).

Multiple Myeloma: 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. 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.

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.

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

Available Therapy: Current treatment regimens tend to consist of two to three drug combinations often including a proteasome inhibitor, an IMiD, and dexamethasone. 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.

3. Product Quality (This section was excerpted from the reviews of Drs. Rachel Novak, Jibril Abdus-Samad, Ruth Moore, Maria Jose Lopez Barragan, Natalia Pripuzova and Linan Ha. For details, please see their reviews).

Recommendation and Conclusion on Approvability: The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761035 for elotuzumab (Empliciti) manufactured by Bristol-Myers Squibb Company pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of elotuzumab is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3.A. Benefit/Risk Considerations: Elotuzumab is proposed for the treatment of multiple myeloma (MM) in patients who have received one or more prior therapies. Elotuzumab is

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administered in combination with lenalidomide and dexamethasone. Nearly all MM patients receiving currently available treatment regimens relapse, leading to the development of progressive disease resistant to both immunomodulatory agents and proteasome inhibitors. Empliciti was found to significantly improve progression free survival in heavily treated MM patients. Therefore, elotuzumab may address a currently unmet medical need.

The current potency assay for the release and stability testing of elotuzumab drug substance and drug product is a cell-based ADCC bioassay [redacted] (b) (4) This assay assesses the ability of elotuzumab to elicit NK cell-mediated ADCC in SLAMF7-expressing target cells. However, this assay was developed during a late stage of development, and the acceptance criteria for this assay were derived from retrospective testing of release and stability samples.

The cell-based ADCC assay and acceptance criteria to be approved under the BLA are sufficient to ensure adequate quality and safety of elotuzumab for the initial marketed product, because adequate information was provided to bridge the cell-based ADCC bioassay to the previous release/stability potency assay (SLAMF7 binding ELISA) and the binding assay data and to demonstrate that the ADCC bioassay is more sensitive than the SLAMF7 binding ELISA with respect to detecting product degradation.

However, the sponsor was requested to re-evaluate the elotuzumab drug substance (DS) and drug product (DP) release and stability acceptance criteria when sufficient data from commercial manufacturing and testing become available to ensure the appropriateness of the initial specification. This re-evaluation will be performed as a PMC.

Cation exchange chromatography (CEX) is a stability indicating assay and is an important control for product-related impurities, [redacted] (b) (4) However, the proposed DS and DP release and stability acceptance criteria were not sufficiently inclusive to provide adequate control over potential product degradation. The proposed specification provided a control over [redacted] (b) (4) . However, the specifications did not take into account the [redacted] (b) (4) s, which constitute approximately [redacted] (b) % of the [redacted] (b) (4) , and are comprised, in part, of [redacted] (b) (4) that significantly impact in vitro potency. The proposed criteria would allow for [redacted] (b) (4)

Therefore, during the review cycle, the sponsor was requested to implement an appropriate control(s) to limit the amount of [redacted] (b) (4) allowed in a batch. In response, the sponsor revised the control strategy for [redacted] (b) (4) to include an acceptance criterion of ≤ [redacted] (b) (4) % for the [redacted] (b) (4) for the release and stability testing of both DS and DP. This was considered to be acceptable for initial approval; however, given the limited data available for [redacted] (b) (4) , the proposed acceptance criteria should be re-assessed when sufficient information becomes available. This re-assessment will be performed as a PMC.

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The elotuzumab production cell line was developed using a [redacted] (b) (4) and a PMC was established to ensure that the sponsor will complete the ongoing studies to support the [redacted] (b) (4) of the MCB.

Validation of [redacted] (b) (4) holds was performed. However, [redacted] (b) (4) The sponsor has committed to perform supplemental validation studies using an adequate surrogate to support the proposed [redacted] (b) (4) The sponsor committed to [redacted] (b) (4) until data from the supplemental studies are provided to the Agency.

The DP manufacturing process is well controlled and should consistently deliver DP of desired quality. The microbial retention data provided thus far and microbial control of the manufacturing process indicate that the risk of microbial penetration of the sterilizing filter is very low. However, additional data should be provided to further support the parameters for the sterilizing filter. A quality microbiology PMC for a confirmatory study will be implemented; the sponsor agreed to repeat the microbial retention filter validation [redacted] (b) (4) study in accordance with PDA Technical Report #26. The sponsor will perform a repeat microbial retention study for the sterilizing filter using a suitable surrogate solution or will perform the study using a modified process, a modified formulation [redacted] (b) (4), or a reduced exposure time for the challenge organism. If any filtration parameters are changed as a result of the study, the BLA file will be updated accordingly.

3.B. Recommendation on Phase 4 (Post-Marketing) Commitments.

1. To re-evaluate elotuzumab drug substance lot release and stability specification acceptance criteria for the cell-based ADCC potency assay and cation exchange chromatography (CEX) assay after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. The corresponding

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data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

2. To re-evaluate elotuzumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

3. To complete the ongoing studies to support the (b) (4) of the elotuzumab master cell bank (MCB). The results of the (b) (4) using multiple cells from the MCB will be provided in the final study report.

4. To perform supplemental validation studies using an adequate surrogate to support the proposed (b) (4) hold times for the (b) (4) until data from the supplemental studies is provided to the FDA.

5. To repeat the microbial retention filter validation (b) (4) study in accordance with PDA Technical Report #26. Sponsor commits to providing a summary of the revised microbial retention filter validation study conducted with a modified process, a modified formulation (b) (4) or a reduced exposure time for the challenged organism used during the study. If any filtration parameters are changed as a result of the study, the BLA file will be updated accordingly.

Regulatory Recommendation: The CMC review team recommends approval of BLN 761035 for elotuzumab manufactured by Bristol-Myers Squibb. The data submitted in this application are adequate to support the conclusion that the manufacture of elotuzumab is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert. We recommend that the elotuzumab DS be stored at (b) (4) °C for (b) (4) months. We recommend that the elotuzumzb DP be stored at 2-8°C for 36 months

List Of Draft Post-Marketing Commitments:

PMC#1: To re-evaluate elotuzumab drug substance lot release and stability specification acceptance criteria for the cell-based ADCC potency assay and cation exchange chromatography (CEX) assay after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

PMC#2: To re-evaluate elotuzumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process and tested at the time

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of release using the commercial specification methods. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

PMC#3: To complete the ongoing studies to support the (b) (4) of the elotuzumab master cell bank (MCB). The results of the (b) (4) using multiple cells from the MCB will be provided in the final study report.

PMC#4: To determine the hold times for the (b) (4) using a surrogate solution that supports microbial growth. Hold times for these steps will be reported per 21CFR601.12 by December, 2016. Validation report should be submitted per 21CFR601.12 by December, 2016.

PMC#5: Perform a repeat microbial retention study for the sterilizing filter using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation (b) (4) or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any filtration parameters are changed as a result of the study, update the BLA file accordingly.

4. Nonclinical Pharmacology/Toxicology (This section was excerpted from the reviews of Dr. Michael Manning and Dr. Christopher Sheth. For details, see their reviews).

This application is a 351(a) BLA for elotuzumab (Empliciti). Elotuzumab is a first-in-class monoclonal antibody directed against the cell surface glycoprotein Signaling Lymphocyte Activation Molecule F7 (SLAMF7) which is primarily expressed on Natural Killer (NK) and normal and malignant plasma cells. The Applicant proposes elotuzumab be indicated for adult patients with multiple myeloma who have received one to three prior therapies, and be administered in combination with lenalidomide and dexamethasone. Elotuzumab has not been marketed or withdrawn in any other country.

Brief Discussion of Nonclinical Findings: Elotuzumab binds SLAMF7 expressed on human plasma cells, NK cells, NKT cells, CD8+ T cells, and CD4+ T cells, but does not bind to any other human tissue element or cross-react with SLAMF7 from any non-human species tested. Binding of elotuzumab to SLAMF7 on NK cells in vitro caused upregulation of CD69, increased cytokine production, and degranulation, implicating direct NK cell activation as a mechanism of action. Elotuzumab also binds SLAMF7-expressing multiple myeloma cell lines in vitro, and in the presence of NK cells, mediates antibody-dependent cellular cytotoxicity (ADCC). Elotuzumab does not bind or kill cells deficient in SLAMF7. Complement dependent cytotoxicity (CDC) does not contribute to elotuzumab-mediated cell killing, but other mechanisms of action cannot be definitively excluded.

The in vivo anti-tumor activity of elotuzumab and the parental murine antibody MuLuc63 was studied in xenograft mouse models with tumors grown from the human multiple myeloma cell

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lines L363 and OPM2. Both elotuzumab and MuLuc63 exhibited antitumor activity, however MuLuc63 was more potent. The Applicant attributed the difference in activity to increased ADCC mediated by MuLuc63 as murine NK cells interact more efficiently with the Fc region of MuLuc63 than elotuzumab. In the OPM2 xenograft mouse model elotuzumab mediated maximal anti-tumor activity at the 10 mg/kg dose level, the highest dose level tested. The 10 mg/kg dose level correlated with minimal and maximal elotuzumab serum concentrations of 70 µg/mL and 430 µg/mL, respectively. In subsequent clinical studies investigators sought a trough serum elotuzumab concentration of ≥70 µg/mL, which was achieved in patients at the proposed 10 mg/kg dose level.

The anti-tumor activity of elotuzumab was also studied in combination with bortezomib and in combination with lenalidomide. Elotuzumab, bortezomib, and lenalidomide each conferred similar anti-tumor activity in the OPM2 xenograft mouse model, however when elotuzumab was combined with either bortezomib or lenalidomide enhanced anti-tumor activity was observed. These nonclinical findings support the combination of elotuzumab with (b) (4) lenalidomide. (b) (4)

(b) (4) Due to the lack of a pharmacologically-relevant animal species to conduct toxicology studies, the scope of the toxicological evaluation for elotuzumab 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 100 mg/kg) was well tolerated in rhesus monkeys with no clinical signs at any dose. There were no local adverse reactions when 5 mg of elotuzumab was intravenously injected into the ears of New Zealand white rabbits, and a solution of 10 mg/mL elotuzumab did not cause hemolysis of human whole blood. An in vitro cytokine release experiment identified elevated levels of 10 cytokines in response to elotuzumab treatment.

The results of the aforementioned toxicology studies indicate elotuzumab presents little risk of off-target toxicity or a significant local adverse reaction when administered by intravenous injection. With prior agreement with the FDA, the Applicant did not conduct carcinogenicity, genotoxicity, safety pharmacology, repeat dose toxicity, or reproductive and developmental toxicity studies with elotuzumab. Carcinogenicity studies are not necessary to support the marketing of therapeutics intended to treat patients with advanced cancer as discussed in the ICH S9 guidance document. Genotoxicity studies are generally not necessary to support marketing of biotechnology-derived pharmaceuticals such as elotuzumab as discussed in the ICH S6 guidance document. Safety pharmacology, repeat dose toxicity, and reproductive and developmental toxicity studies were not conducted due to the lack of a pharmacologically-relevant animal species. The Applicant submitted a risk assessment for the potential for reproductive and

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developmental toxicity for elotuzumab based on the tissue distribution of SLAMF7 and published literature. SLAMF7 is expressed on plasma cells and immunoblasts in the uterus and cervix, however the implications for reproduction in vivo are unknown. Elotuzumab is an IgG1 monoclonal antibody, which as a class have the potential to cross the placental barrier permitting direct fetal exposure. The impact of elotuzumab on fetal development is unknown, however published reports indicate SLAMF7-deficient mice appear healthy suggesting SLAMF7 does not play a role in embryo-fetal development.

Regulatory Recommendations of the Nonclinical Review Team: Approvability. The nonclinical studies submitted to this BLA provide sufficient information to support the use of Empliciti, in combination with lenalidomide and dexamethasone, for the treatment of adult patients with advanced multiple myeloma. From the nonclinical pharmacology and toxicology perspective, Empliciti is recommended for approval.

5. Clinical Pharmacology (This section was excerpted from the review of Dr. Olanewaju Okusanya, PharmD, MS. For details, see his review).

Elotuzumab (Empliciti) is a humanized recombinant monoclonal immunoglobulin G1 (IgG2=1) that binds human Signaling Lymphocyte Activation Molecule F7 (SLAMF7) on the surface of myeloma cells and recruits circulating Natural Killer (NK) cells to the vicinity of the myeloma cell. This BLA submission is in support of the safety and efficacy of elotuzumab in combination with lenalidomide/dexamethasone (b) (4) for the treatment of patients with relapsed multiple myeloma who have received one to three prior therapies.

The clinical pharmacology data submitted with this BLA includes data from multiple-dose studies evaluating the efficacy and safety of elotuzumab as a single agent or in combination. The clinical pharmacology submission also includes population PK and exposure-response analyses for efficacy and safety. The population PK model revealed covariate relationships for elotuzumab clearance with baseline M-protein concentrations and body weight. Body weight based dosing is thus justified. Higher M-protein correlated with higher elotuzumab clearance, however the correlation was modest.

The exposure-response analysis revealed there was no difference in median PFS between patients with elotuzumab Cavgss in the lowest quartile of elotuzumab exposure (Cavgss < 209 μg/mL) and patients on active control, after controlling for potential confounding factors such as high M-protein, higher B2- microglobulin, ECOG score, and higher LDH levels. Patients with elotuzumab concentrations in the higher three quartiles of exposure showed treatment benefit in terms of PFS compared to active control after controlling for other risk factors.

As PFS in patients with Cavgss concentrations less 209 μg/mL was not better than in the control arm, even after adjusting for other risk factors, it appears reasonable to explore options to optimize dose in this subgroup of patients. We are asking for additional analyses to be conducted as a PMC. The results of the ongoing trial CA204006 will be used to conduct exposure-response analyses and determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have lower exposure to elotuzumab at the approved dose (10

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mg/kg). The applicant included data on the immunogenicity of elotuzumab. Antibody response was, in general, transient. Its impact on the PK of elotuzumab was confounded by its correlation with baseline M-protein.

Summary of Important Clinical Pharmacology Findings This BLA submission is to support the safety and efficacy of elotuzumab in combination with lenalidomide and dexamethasone (b) (4) for the treatment of patients with (b) (4) multiple myeloma who have received one to three prior therapies. The safety and efficacy of elotuzumab in this population were evaluated in two randomized trials. In the first trial, patients were randomized (1:1) to elotuzumab with lenalidomide plus dexamethasone (ELd) (n=321), or lenalidomide plus dexamethasone (Ld) (n=325). The co-primary endpoints were progression-free survival (PFS) and objective response rate (ORR). In this trial, the improvement in median PFS time between Arm ELd (19.4 months) and Arm Ld (14.9 months) was 4.5 months (p=0.0002 2-sided p-value) and the ORRs were 78.5 vs. 65.5%, respectively.

In the second trial, patients were randomized (1:1) to elotuzumab with bortezomib plus dexamethasone (EBd) (n=77), or bortezomib plus dexamethasone (Bd) (n=75). In this trial, the improvement in median PFS time between Arm EBd (9.7 months) and Arm Bd (6.9 months) was 2.8 months (b) (4). (b) (4)

A population PK analysis was submitted by the applicant incorporating data from five clinical studies: two Phase 1 studies (CA204005 and CA204007), two Phase 2 studies (CA204011 and CA204009), and one Phase 3 study (CA204004). The population PK model showed a relationship between total elotuzumab clearance and weight, co-administration of lenalidomide/dexamethasone, co-administration of bortezomib/dexamethasone, and baseline M-protein. Exposure-response analyses suggest that optimizing the dose in patients with low exposure may offer additional PFS benefit. An exposure-response relationship for elotuzuamb Cavg at steady-state and PFS was identified by both Kaplan Meier curves for PFS and the applicant's multivariate Cox proportional hazards model for exposure-response.

Findings:

1. Using a case control analysis to control for additional confounding factors (M-protein, β2-microglobulin, lactate dehydrogenase, ECOG score, prior immunomodulatory therapy, prior treatment duration, and prior stem cell transplantation) an assessment of PFS in subjects with the lowest quartile of elotuzumab Cavgss was done and compared to that in a subset of the control group with matching patient characteristics.

2. This was also perfomed for the remaining 75% of patients with higher exposure and compared to a matching subset of the control arm. The exposure-response analysis revealed there was no difference in median PFS between patients with elotuzumab Cavgss in the lowest quartile of elotuzumab exposure (Cavgss < 209 μg/mL) and patients on active control, after controlling for the potential confounding factors listed above.

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3.Patients with elotuzumab concentrations in the higher three quartiles of exposure showed treatment benefit in terms of PFS compared to active control after controlling for other risk factors.

Conclusions: This analysis in conjunction with the higher clearance of elotuzumab with higher M-protein suggests that patients who are at higher risk of PFS and have lower exposure may benefit from a dose increase.

Plan: Thus, a post-marketing commitment (PMC) is being recommended to conduct elotuzumab exposure response analysis for efficacy and safety utilizing data from the ongoing trial CA204006. The results of the exposure-response analyses from both CA204004 and CA204006 will be used to determine whether a postmarketing trial is needed to optimize the dose in patients with multiple myeloma who have lower exposure to elotuzumab at the approved dose (10 mg/kg).

Regulatory Recommendation: The Office of Clinical Pharmacology/Divisions of Clinical Pharmacology V and Pharmacometrics have reviewed the information contained in BLA 761035. This BLA is acceptable for approval from a clinical pharmacology perspective.

Post-marketing Commitments: The Applicant will conduct elotuzumab exposure-response analyses for efficacy and safety utilizing data from trial CA204006. The results of the exposure-response analyses from both CA204004 and CA204006 will be used to determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have low exposure to elotuzumab at the approved dose (10 mg/kg). The Applicant will submit a final report of the exposure-response analyses based on CA204004 and CA204006.

6. Clinical Microbiology: Non Applicable.

7. Clinical/Statistical-Efficacy: (This section is excerpted from the review of Dr. Nicole Gormley. For details, please see her review.)

Design of Trial CA204004: In study CA204004, patients were randomized to the two study arms in a 1:1 ratio. There were 3 stratification factors: β2 microglobulin (<3.5 mg/L vs. ≥ 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 in Figure 1.

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 measureable 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

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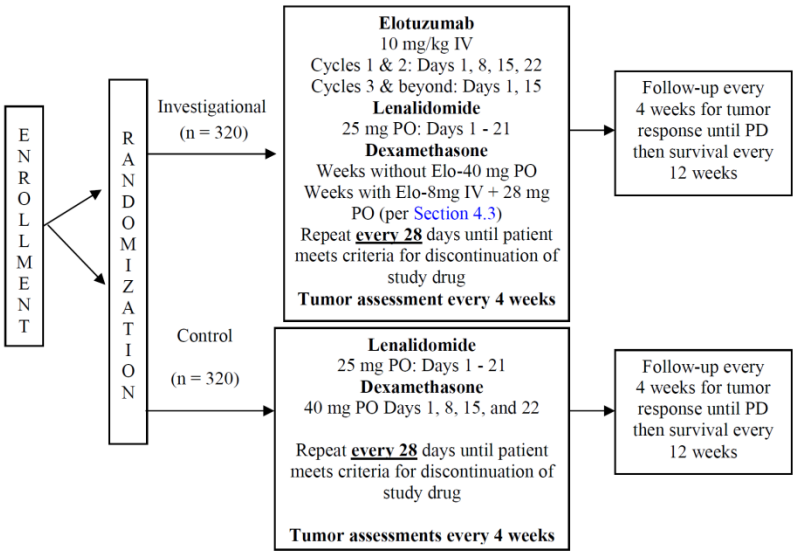
more than 9 cycles of lenalidomide, were not refractory to lenalidomide, and did not discontinue lenalidomide due to toxicity. The trial allowed no more than 10% of subjects who had prior lenalidomide exposure. The trial also allowed inclusion of patients with mild to moderate renal impairment as elotuzumab 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.

Figure 1: CA204004



Refractory myeloma was defined as disease the 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 does not meet criteria for refractory myeloma.

Results of CA 204004: Table 1 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 1: Results of CA 204004

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)

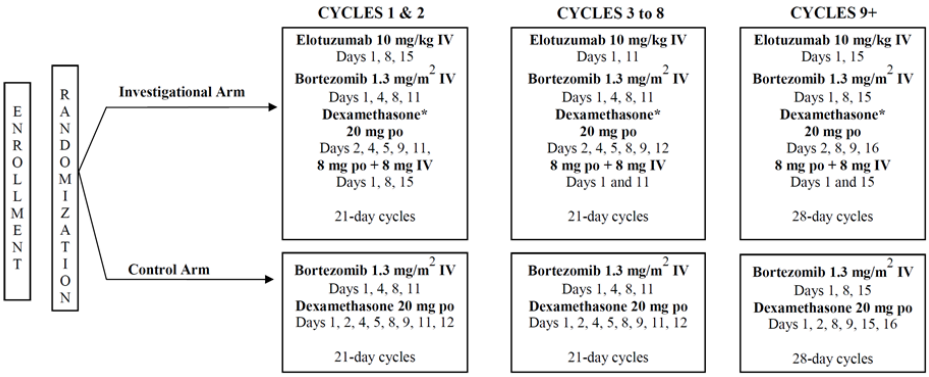
Hazard ratio[1], E+Ld/Ld (95% CI)	0.70 (0.57, 0.85)	
p-value[2]	0.0004	
IRC-assessed ORR		
Number of Responders[3]	252	213
% of Responders (95% CI)	78.5 (73.6, 82.9)	65.5 (60.1, 70.7)
Odds Ratio[4]	1.94	
95% CI	(1.36, 2.77)	
p-value	0.0002	

All Randomized Subjects
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

Reviewer Commentary: The results of the trial were positive and robust. Table 1 shows that the median duration of the PFS was 19.4 months for E+Ld and 14.9 months for Ld (HR=0.7 and p=0.0002). The ORR for E+Ld was 78.5% vs 65.5% for Ld. The median duration of the response was 20.7 months for E+Ld vs 16.6 months for Ld (p=0.0002),

Design and Efficacy Results of Trial 204009: 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 in Figure 2.

Figure 2: Study 204009



The efficacy results of CA204009 are given below in Table 2.

Table 2. Primary Efficacy Results Study CA204009

All Randomized Subjects

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

(b) (4)

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

Reviewer Commentary: (b) (4)

(b) (4)

Clinical Reviewer Comment: Study CA204009 was a phase II, open-label, investigator-assessed trial (b) (4)

(b) (4)

(b) (4) Of note, this was not the case in the CA204004 trial. The increment in median PFS improvement (2.8 months) was less than that observed in CA204004 (4.5 months), suggesting that elotuzumab may be less effective when added to bortezomib/dexamethasone as compared with lenalidomide/dexamethasone.

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. There is other evidence to suggest that the reverse is true for lenalidomide, which has been shown to increased NK cell number and activation. 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.

Regulatory Recommendation Based On Efficacy Results: Approval of the combination of elotuzumab with lenalidomide with low dose dexamethasone. (b) (4)

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8. Safety: (This section is excerpted from the review of Dr. Nicole Gormley. Please see her review for details).

Safety Population: The safety population is shown below in Table 3. This review will focus on a comparison of the two arms of Study CA 204004. This data will also be supported by data from CA204009, pooled safety data from CA2004004, HuLuc-1703, CA204005 and CA204007.

Table 3: Safety population.

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 (CA204004)	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

The safety results from CA 204004 is summarized in Table 4.

Table 4: Safety Results

	E-Ld N=318 n=(%)	Ld N=317 n=(%)
Deaths within 30 days	16 (5.0%)	20 (6.3%)
Serioius TEAE	208 (65.4%)	179 (56.5%)
Discontinuations due to TEAE	83 (23.1%)	85 (26.8%)
Any Grade 3 or 4 TEAE	272 (85.5%)	241 (76.0%)
Any TEAE	316 (99.4%)	314 (99.1%)
All Deaths as of 10//29/2014	94 (29.6%)*	116 (36.6%)

*Infection contributed to deaths in 9 patients: influenza, staphylococcus meningitis, sepsis, pneumonia (4 patients) and pseudomonas sepsis.

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

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on these criteria, there were 3 deaths considered to be primarily due to disease progression in the E-Ld arm.

Non-Fatal Serious Adverse Events: Non fatal serious adverse events (SAEs) occurred in 64.1% (204/318) of patients receiving E+Ld in Trial 204004 whereas 55.5% (175/317) of patients on the Ld arm experienced non-fatal SAEs as shown in Table 5 below.

Table 5: Non Fatal Serious Adverse Events.

	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)

Significant Adverse Events: The more common significant adverse events with ≥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%).

Treatment Emergent Adverse Events and Adverse Reactions: The following table (Table 6) includes adverse events that occurred at an incidence of ≥10% in either arm and grade 3-4 adverse events that occurred at an incidence of ≥5% in either arm.

Table 6: Treatment Emergent Adverse Events

	E+Ld Grade 1-4	E+Ld Grade 3-4	Ld Grade 1-4	Ld Grade 3-4
Neutropenia	33.6%	24.8%	42.6%	33.1%
Thrombocytopenia	27%	11.3%	22.4%	10.7%
Lymphopenia	13.2%	8.8%	6.9%	3.2%
Cataracts	11.9%	6.3%	6.3%	2.8%
Diarrhea	46.9%	5.0%	35.3%	3.8%
Pneumonia	19.2%	13.8%	13.9%	9.55
Respiratory Tract Infection	10.7%	2.5%	9.5%	1.3%

Upper Respiratory Tract Infection	22.6%	0.6%	17.4%	1.3%
Alanine Amino Transferase Increased	7.2%	0.3%	10.1%	2.5%
Hyperglycemia	17.3%	7.2%	13.6%	4.4%
Creatinine Increased	12.6%	0.9%	7.6%	0%
Peripheral Neuropathy	13.8%	1.6%	8.2%	1.6%
Rash	18.2%	0.3%	18.3	1.6%
Deep vein thrombosis	7.2%	5.7%	3.8%	2.2%

Adverse Events: The following adverse events occurred at an incidence of ≥10% greater incidence in the E+Ld arm as compared to the Ld arm: lymphopenia, cataract, diarrhea, consntipation, vomiting, pneumonia, pyrexia, fatigue, nanopharyingitis, upper respiratory tract infection, cough, weight loss, loss of appetite, headache, peripheral neuropathy, oropharyngeal pain, and increased creatinine.

The most common grade ≥3 hematologic abnormalities were lymphopenia, anemia, thrombocytopenia and neutropenia. The rates for these 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+Le arm compared with 48.5% 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 ≥5% difference between arms were increased alkaline phosphatase, creatinine, hyperkalemia, low bicarbonate, hypocalcemia and hyperglycemia (grade ≥3).

Infections: As stated above, the incidence of Grade 3-4 lymphopenia was greater on the E+Ld arm (76.7%) than on the Ld arm (48.6%). The incidence of treatment emergent infections was greater on the E+Lk arm (80.5%) than on the Ld arm (74.1%). Infectious events that were classified as serious occurred 30.5% of the time on the E+Ld arm compared to 24.9% on the Ld arm. The incidence of Grade 3 or 4 infections was 29.9% on the E+Ld arm as compared to 26.5% on the Ld arm.

Liver Function Test Abnormalities: There were 6 patients in the E+Ld arm that met criteria for potential drug-included liver injury as defined by AST/ALT > 3 times the ULN, and total bilirubin > 2 times the ULN (as shown below in Table 7).

Table 7: Hepatic Abnormalities

	E+Ld N=318 Grade 1-4	E+Ld N=318 Grade 3-4	Ld N=317 Grade 1-4	Ld N=317 Grade 3-4
Low Albumin	70.1%	3.5%	61.8%	1.9%
ALT increased	55.3%	4.4%	51.4%	4.1%
AST increased	47.2%	2.5%	42.3%	2.5%
Alk Phos Increased	37.4%	1.3%	29.0%	0%
Total Bilirubin Increased	24.2%	2.2%	25.6%	0.9%

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Immunogenicity: Among 318 patients who received elotuzumab on the E+Ld arm, 2.0% were ADA positive at baseline and 15.5% were positive on study. Of these 45 patients, 19 had neutralizing antibiodies among which 2 were persistent.

Second Malignancies: Second primary malignancies occurred in 26 subjects in the E+Ld arm (8.2%) and in 15 subjects in the Ld arm (4.7%) as shown in Table 8 below.

Table 8: Second Primaries

	E+Ld N=318 n(%)	Ld N=317 n(%)
Overall	8.2%	4.7%
Skin Cancer	3.8%	2.2%
Solid Tumors	3.1%	1.9%
Hematologic Malignancy	1.6%	1.6%

Infusion Reactions: The patients received the following medications 30-90 minutes before administration of elotuzumab: H1 blocker (25-50 mg of diphenhydramine), H2 blocker (50 mg of ranitidine), and 650 -1000 mg of acetaminophen. 10.7% experienced an infusion reaction, of these 34 subjects, 16 (5%) experienced more than 1 reaction. Grade 3 or greater occurred in 5 of 318 subjects and included angioedema, cardiac congestive failure, chest pain, diarrhea, and hypertension.

Interference of Elotuzumab with SPEP and IFE. Elotuzumab is a monoclonal immunoglobulin IgG1 kappa antibody. Therefore, elotuzumab is detected by and interferes with SPEP and IFE assays used for response evaluation in myeloma. The Applicant is in the process of developing a (b) (4) which may allow for better discrimination of protein due to elotuzumab vs myeloma.

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 ≥ 10% in either arm and had a ≥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.

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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 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.

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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.

Regulatory Recommendation: Approval of the combination of E+Ld for relapsed patients with myeloma with 1-3 prior lines of therapy.

9. Advisory Committee Meeting: No advisory committee.

10. Pediatrics: No trials indicated.

11. Other Relevant Regulatory Issues:

11.A. REMS: None.

11.B. OSI: OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS: (This section has been excerpted from the report of Dr. Anthony Orienca. Please see his report for details). Two clinical studies, Study Protocol CA204009 (Turin, Italy site only) and Protocol CA204004, respectively, were inspected for this BLA.

A single domestic clinical study site (Paul Richardson, M.D.) and two foreign sites (Antonio Palumbo, M.D. and Darrell White, M.D. were inspected. The sponsor (Bristol-Myers Squibb) was also inspected.

Clinical Inspection Summary: The preliminary regulatory classification for Dr. Richardson is No Action Indicated (NAI). The preliminary regulatory classification for Dr. Palumbo and Dr. White is Voluntary Action Indicated (VAI). The sponsor regulatory classification is No Action Indicated (NAI). The planned inspection in Greece is expected to be completed this week. When the results are received, an addendum to the CIS will be issued.

Regulatory Recommendation of OSI: In summary, OSI considers that data from the inspected clinical and sponsor sites are acceptable in support of the BLA.

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12. Labeling: Currently under negotiation.

13. Postmarketing Recommendations:
13.A. PMCs

CMC PMC 1:
Re-evaluate elotuzumab drug substance lot release and stability specification acceptance criteria for the cell-based bioassay and cation exchange chromatography (CEX) assay after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. BMS will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC Schedule Milestones	Data availability:	06/30/2017
	Final Report Submission:	09/29/2017

BMS proposes to perform this evaluation for drug substance in conjunction with the evaluation for drug product (refer to PMC 2). This approach will ensure alignment between the drug substance and drug product specifications for the cell-based bioassay and CEX assay. The milestone dates listed above are based on the current, estimated manufacturing schedule.

CMC PMC 2:
Re-evaluate elotuzumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process and tested at the time of release using the commercial specification methods. BMS will submit corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC Schedule Milestones:	Data availability:	06/30/2017
	Final Report Submission:	09/29/2017

CMC PMC 3:
Complete the ongoing studies to support the (b) (4) of the elotuzumab master cell bank (MCB). BMS will submit the results of the (b) (4) using multiple cells from the MCB.

PMC Schedule Milestones:	Final Report Submission:	04/29/2016

CMC PMC 4:
To determine the hold times for the (b) (4) using a surrogate solution that supports

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microbial growth. Hold times for these steps will be reported per 21CFR601.12 by December, 2016. Validation report should be submitted per 21CFR601.12 by December, 2016.

PMC Schedule Milestones:	Final Protocol Submission:	6/30/2016
	Study/Trial Completion:	9/30/2016
	Final Report Submission:	12/30/2016

CMC PMC 5:
Perform a repeat microbial retention study for the sterilizing filter using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation (b) (4) , or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any filtration parameters are changed as a result of the study, update the BLA file accordingly.

PMC Schedule Milestones:	Final Report Submission:	04/29/2016

Draft Clinical Pharmacology PMC 1:
Conduct elotuzumab exposure-response analysis for efficacy and safety utilizing data from trial CA204006. The result of the exposure-response analyses from both CA204004 and CA204006 will be used to determine whether a post-marketing trial is needed to optimize the dose in patients with multiple myeloma who have low exposure to elotuzumab at the approved dose (10 mg/kg). Submit a final report of the exposure-response analysis based on CA204004 and CA204006. Date of Final Report Submission: March, 2017.

13.B. PMRs: None.

14. Recommended Comments to the Applicant: None.

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/s/

ALBERT B DEISSEROTH
11/16/2015