

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
761035Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA #	761035
Supplement #	
Applicant	BMS
Date of Submission	June 29, 2015
PDUFA Goal Date	February 29, 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.
Applicant Proposed Indication(s)/Population(s)	for the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone ^{(b) (4)} ^{(b) (4)}
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	for the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Nicole Gormley, M.D. /Albert Deisseroth, M.D. Ph.D. Virginia Kwitkowski, M.S./ACNP-BC
Statistical Review	Chia-Wen Ko, Ph.D.
Pharmacology Toxicology Review	Michael Manning, Ph.D./ Christopher Sheth, Ph.D./John

	Leighton, Ph.D.
OPQ Review	Rachel Novak, Ph.D./Jibril Abdus-Samad, Pharm.D./ Maria Jose Lopez Barragan, Natalia Pripuzova/Linan Ha, Ph.D./Ruth Moore/Collen Thomas/Patricia Hughes/Peter Qiu/Sarah Kennett, Ph.D./Kathleen Clouse, Ph.D.
Microbiology Review	Maria Jose Lopez- Barragan and Natalia Pripuzova
Clinical Pharmacology Review	Olanrewaju Okunsanya, Pharm.D., M.S./Gene Williams, Ph.D./ Justin Earp, Ph.D./Nitin Mehrotra, Ph.D.
OPDP	Nisha Patel, Pharm.D./Kathleen Davis
OSI	Anthony Oencia, M.D./Susan D. Thompson, M.D./ Kassa Ayalew, M.D., M.P.H.
CDTL Review	Albert Deisseroth, M.D. Ph.D.
OSE/DEPI	none
OSE/DMEPA	Michele Rutledge, Pharm.D./Yelena Maslov, Pharm. D./Lubna Merchant Pharm.D.
OSE/DRISK	Mona Patel, Pharm.D./Naomi Redd, Pharm.D./Cynthia LaCivita, Pharm.D.
Other	Justin C Earp/Jiang Liu/Huifang Chen/Qianyu Dang/Michael Li/ Norman L Stockbridge LaShawn Griffiths, MSHS-PH, BSN, RN/Barbara Fuller, RN, MSN, CWOCN/Morgan Walker, PharmD, MBA

OND=Office of New Drugs

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

APPEARS THIS WAY ON ORIGINAL

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Multiple myeloma is a hematologic malignancy characterized by a neoplastic proliferation of clonal plasma cells that produce a monoclonal immunoglobulin. Clinically patients may present with signs and symptoms of anemia, bone pain or pathologic fractures, renal insufficiency, fatigue, hypercalcemia, or weight loss. Treatment options for multiple myeloma have significantly improved over recent decades with the approval and 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 (thalidomide analogues) and proteasome inhibitors. Despite these advances, patients with multiple myeloma often relapse or develop refractory disease. Multiple myeloma remains an incurable disease with the exception of an allogeneic transplant. Unfortunately few patients are candidates for this therapy.

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. 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 higher in the E-Ld arm vs. the Ld arm respectively were: pneumonia, pyrexia, respiratory tract infection, anemia, and acute renal failure. 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, constipation, vomiting, fatigue, pyrexia, peripheral edema, nasopharyngitis, upper respiratory tract infection, weight decreased, creatinine increased, decreased appetite, pain in extremity, musculoskeletal pain, headache, peripheral neuropathy, cough, and oropharyngeal pain.

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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Multiple Myeloma is a symptomatic disease with bone pain, anemia, infection, renal insufficiency, fatigue, hypercalcemia, or weight loss and is associated with significant morbidity and mortality. 	Patients with multiple myeloma experience significant morbidity and mortality.
Current Treatment Options	<ul style="list-style-type: none"> Multiple myeloma remains a mostly incurable disease with only a few patients who receive an allogeneic transplant cured of their disease. The development and approval of proteasome inhibitors and thalidomide analogues has improved the outlook for patients with multiple myeloma with a current median overall survival of approximately 5-6 years. 	Current treatment options are inadequate to control the disease. Additional therapies with differing mechanisms of action and adverse event profiles are needed.
Benefit	<ul style="list-style-type: none"> 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 	The trial results demonstrated a significant improvement in median PFS for the treatment arm containing elotuzumab. A clinically meaningful and statistically persuasive improvement in median PFS has been used as a basis for approval when the treatment has been associated with acceptable safety profile.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>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.</p>	
<p>Risk</p>	<ul style="list-style-type: none"> 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 \geq5% 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 	<p>The elotuzumab treatment arm was associated with greater risk of adverse reactions; however, these adverse reactions did not result in increased mortality as the hazard ratio for the preliminary OS result was 0.71. The infusion reaction can be managed through the use of premedication and in some cases post-medication as well.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>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%).</p>	
<p>Risk Management</p>	<p>Labeling – includes a complete description of the safety observed in the trial along with focused description in certain highlighted areas.</p>	<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 laboratory testing.</p>

2. Background

On June 29, 2015 Bristol-Myers-Squibb submitted a Biologic License Application (BLA) for elotuzumab, a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) targeted against Signaling Lymphocyte Activation Molecule Family 7 (SLAMF7). The Applicant's 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 (b) (4)

Breakthrough Therapy Designation was granted on 12-May-2014 for elotuzumab in combination with lenalidomide and dexamethasone for treatment of multiple myeloma (MM) in patients who have received one or more prior therapies.

This application was given priority review. No monoclonal antibodies directed against SLAM7 are approved at this time for treatment of multiple myeloma.

Elotuzumab is not approved in any country at this time.

3. Product Quality

No issues were identified that would preclude approval. The product presentation is single- (b) (4) vials containing 300 mg and 400 mg lyophilized powder.

From the review:

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...

The data provided in the BLA are sufficient to establish a (b) (4) month shelf life for DS when stored at (b) (4) C.

The facilities inspection is acceptable.

I concur with the recommendation for approval. Post-approval commitments are recommended as described in Section 13 of this review.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified. From the primary review:

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 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)

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 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.

I concur with the recommendation for approval.

5. Clinical Pharmacology

No issues that would preclude approval were identified. The following text is from the primary review:

EMPLICITI® (elotuzumab) is a humanized recombinant monoclonal immunoglobulin G1 (IgG1) 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) (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 mg/kg).

I concur with the Clinical Pharmacology review and the request for a PMC to review exposure-response analyses for CA204006.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

From the primary clinical and statistical joint review:

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) in the Bd arm. The ORR was (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). The median OS was NE (b) (4) in the E-Bd arm vs. (b) (4) in the Bd arm.

(b) (4)

I concur with the findings of the clinical and statistical review teams regarding both the phase 3 and phase 2 trials. 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 as required by law to support approval. (b) (4)

Only the results of the phase 3 trial will be put into the label.

8. Safety

The following text is from the joint review:

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...*
- *Infusion reactions were mitigated by protocol-required premedication 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.*

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.

I concur with the reviewers. The safety data collected is adequate for labeling with respect to warnings and precautions. Routine Pharmacovigilance should be adequate for post-approval safety monitoring.

9. Advisory Committee Meeting

This application was not referred for an Advisory Committee meeting as no clinical efficacy or safety issues arose that required an Advisory Committee meeting and discussion.

10. Pediatrics

N/A- Orphan Designation

11. Other Relevant Regulatory Issues

The Office of Scientific Investigation (OSI) did not find the data unreliable in support of the application.

Financial Disclosure information was provided and reviewed. Only one investigator had disclosable financial interests or arrangements.

12. Labeling

All disciplines made recommendations for labeling.

As discussed in section 7, the indications and usage section will reflect only an indication for use in combination with lenalidomide and dexamethasone. 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 as required by law to support approval. (b) (4)

Safety Information
No boxed warning

Warnings and Precautions subsections encompass:
Infusion reactions with a recommendation for medication

Infection Risk as increased risk seen with triple agent combination

Second Primary Malignancies increased risk seen with the triple agent combination

Hepatotoxicity observed and what is known is described

Interference with determination of complete response (laboratory testing)

I agree with the approved labeling and at the current time do not have any suggestions.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None except for the labeling

- Other Postmarketing Requirements and Commitments

PMC to address Clinical Pharmacology review concern regarding benefit of elotuzumab for patients with low exposure to elotuzumab

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.

PMCs to address previously identified OBP issues:

CMC PMC 2:

Re-evaluate elotuzumab drug substance lot release and stability specification acceptance criteria for the cell-based ADCC potency 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.

CMC PMC 3:

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.

CMC PMC 4:

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.

CMC PMC 5:

To provide additional maximum hold times (b) (4) using a surrogate solution that supports microbial growth.

CMC PMC 6:

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 (e.g., (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.

Refer to action letter for final wording and milestones of the post-marketing requirements.

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

/s/

ANN T FARRELL
11/30/2015