

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761035Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 761035
Product Name: Empliciti® (elotuzumab)

PMC #5 Description: Conduct a study to determine the hold times for the (b) (4) using a surrogate solution that supports microbial growth. Hold times will be reported per 21CFR601.12.

PMC Schedule Milestones: Final Report Submission: 12/2016

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Microbial quality attributes (bioburden and endotoxin) are appropriately monitored (b) (4) and therefore, the risk of unacceptable bioburden levels in the (b) (4) is deemed low.

2. Describe the particular review issue and the goal of the study.

The data submitted in the original BLA described the use of (b) (4) as a surrogate for elotuzumab (b) (4) during maximum hold time validation studies. This (b) (4) was not an adequate surrogate because (b) (4). Sponsor is currently performing new maximum hold time validation studies using a different surrogate solution that will be more representative of the microbial growth promotion properties of elotuzumab (b) (4). The goal of these studies will be to confirm that the proposed maximum hold times for elotuzumab (b) (4) are adequate to support microbial quality.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The agreed-upon study will consist of additional validation studies using an adequate surrogate solution to support the proposed (b) (4) hold times for the (b) (4)

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

NATASHA L KORMANIK
11/20/2015

PATRICIA F HUGHES TROOST
11/20/2015

During the review of this application, it was noted that there is a subgroup of patients (lower exposure and sicker patients) who do not appear to derive any benefit with the addition of elotuzumab to the lenalidomide/dexamethasone regimen. We are requesting additional analysis to be conducted based on the data from the ongoing CA2040006 trial in newly diagnosed multiple myeloma. The goal of the requested analysis is to evaluate if the observation of lower efficacy in a subgroup of patients is also evident in the 06 trial. Based on the analysis conducted for the CA204004 trial and additional analysis requested from the CA204006 trial, the determination of need for additional trial(s) to explore dose optimization will be made.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

There is no request to conduct a study or trial at this time. Additional exposure-response analysis is requested based on the CA204006 trial data. A need and subsequent request to conduct a study or trial will be determined based on the results of the requested analysis.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Additional exposure-response analysis based on the 06 trial is requested
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Additional exposure-response analysis based on the 06 trial is requested

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

NATASHA L KORMANIK
11/19/2015

NITIN MEHROTRA
11/19/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 18, 2015

TO: Natasha Kormanik, MSN, RN, OCN[®], Regulatory Project Manager
Nicole Gormley, M.D., Medical Officer
Albert Deisseroth, M.D., Ph.D., Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice K. Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: **Evaluation of Clinical Inspections: Addendum**

BLA: 761035

APPLICANT: Bristol-Myers Squibb Company

DRUG: elotuzumab

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority Review

INDICATIONS: Treatment of (b) (4) relapsed multiple myeloma

CONSULTATION REQUEST DATE (signed): July 28, 2015

INSPECTION SUMMARY GOAL DATE (original): November 30, 2015
 INSPECTION SUMMARY GOAL DATE (revised): November 6, 2015
 DIVISION ACTION GOAL DATE (original) December 14, 2015
 DIVISION ACTION GOAL DATE (revised): November 30, 2015
 PDUFA DATE: December 14, 2015

I. BACKGROUND:

See CIS in DARRTS (November 5, 2015)

II. RESULTS:

Name of CI Location	Study Site/Protocol/ Number of Subjects Enrolled	Inspection Date	Classification*
Meletios Dimopoulos, M.D. 80 Vas Sofias Avenue Athens, Greece 11528	Site #4600 Protocol CA204004 Subjects = 33	November 2-6, 2015	Preliminary: VAI
Antonio Palumbo, MD Via Genova, 3 Torino, Italy 10126	Site #4934 Protocol CA204009 Subjects=19	October 19-23, 2015	Preliminary: VAI
Darrell White, M.D. Bethune Bldg. Room 433 1276 South Park Street Halifax, Nova Scotia B3H2Y9 Canada	Site #2407 Protocol CA204004 Subjects=24	October 19-23, 2015	Preliminary: VAI
Paul Richardson, M.D. 450 Brookline Ave. Boston, MA 02215	Site #1414 Protocol CA204004 Subjects=10	September 1-8, 2015	Preliminary: NAI
Sponsor: Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492	Protocol CA204004 Protocol CA204009	September 8-17, 2015	Preliminary: NAI

***Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. Meletios Dimopoulos M.D., Protocol CA204004/Site #4600

Athens, Greece

a. What was inspected:

The inspection was conducted from November 2 to 6, 2015.

A total of 35 subjects were screened, and 33 subjects were enrolled and randomized. Twenty seven subjects completed the treatment period phase of the study. A total of three enrolled subjects' records were audited for adverse events. Additionally, three subjects' serious adverse events (SAEs) were verified. An audit of 10 enrolled subjects' records for efficacy endpoints was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

At the end of the inspection a single item 483 was issued for not accurately reporting source document adverse events in the electronic case report form (eCRF) at the time of the data cut-off date (October 19, 2014) for the study analysis. For example, source records for Subject #00222 (76 total adverse events reported for this subject randomized to the elotuzumab treatment group), the adverse event of "diarrhea" was originally reported as "constipation and the event of "hyperglycemia grade 2" judged "related" (by the investigator), was reported as "unrelated" in the eCRF".

The clinical site personnel informed the ORA investigator that this site had entered multiple corrections to the eCRF after their Quality Assurance advisor conducted a "quality check" of tumor response, concomitant medications, and adverse event data entered in the eCRF. Based upon review of clinical site monitoring reports, the ORA investigator observed that original inaccurate data entries detected during this "quality check" were not detected in any of the monitoring visits conducted by the contract research organization (CRO) from February 2, 2012 to the present.

OSI Reviewer Comments:

Based upon review of a limited number of subjects' AE records, the ORA investigator observed a few discrepancies between AEs recorded on source documents and data listings submitted to the BLA. The site acknowledged that eCRF corrections had been made by the site after the study data cut-off date of

October 19, 2014 following a quality check by the site's Quality Assurance Advisor. None of the initially incorrect entries had been detected during monitoring visits by the CRO subcontracted by (b) (4) to monitor CI sites in Greece. Although the ORA investigator obtained a spread sheet containing an audit trail of changes made to the AE dataset from study data cutoff (October 19, 2014) through November 5, 2015, it is not entirely clear the exact quantity or nature of changes made because variables and codes in the spread sheet are not defined and the dataset is not locked so that changes can be made as the study continues.

Based on subject records assessed by the ORA investigator, the data corrections made following the quality check had no impact on efficacy assessment.

The CRO monitor for this site in Greece, (b) (4) was subcontracted by (b) (4) for site management and monitoring only in Greece. Dr. Dimopoulos site enrolled the majority of subjects in Greece (33 out of a total of 43) and it is unclear if similar monitoring deficiencies affected the other two sites enrolling subjects.

c. Assessment of data integrity:

Based upon inspection of this site, efficacy data submitted by this clinical site appear acceptable in support of this specific indication. The inspection covered limited comparisons of subject source documents and BLA data listings for safety. For adequate review of reliability of the safety information, OSI recommends that DHP consider sending an information request to the sponsor to obtain information about any changes made to the safety data for AEs occurring before the data cut-off date of October 19, 2014 for subjects enrolled at the site prior to this date or doing sensitivity analyses with a set of plausible possibilities regarding the data from this site.

2. **Antonio Palumbo, M.D., Protocol CA204009/Site #4934**
Turin, Italy

SEE CIS report in DARRTS entered on November 4, 2015.

3. **Darrell White, M.D., Protocol CA204004/Site #2407**
Nova Scotia, Canada

SEE CIS report in DARRTS entered on November 4, 2015.

4. **Paul Richardson, M.D., Protocol CA204004/Site #1414**
Boston, MA

SEE CIS report in DARRTS entered on November 4, 2015.

SPONSOR INVESTIGATION

4. **Bristol-Myers Squibb Company**

Wallingford, CT 06492

SEE CIS report in DARRTS entered on November 4, 2015.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

A single foreign clinical site was inspected for Study Protocol CA204009 (Antonio Palumbo, M.D., Turin, Italy). For Study Protocol CA 204004, a single domestic clinical study site (Paul Richardson, M.D.) and two foreign sites (Meletios Dimopoulos M.D., and Darrell White, M.D. were inspected. The sponsor (Bristol-Myers Squibb) was also inspected.

The preliminary regulatory classification for Dr. Richardson is No Action Indicated (NAI). The preliminary regulatory classification for Drs. Palumbo, White, and Dimopoulos is Voluntary Action Indicated (VAI). The sponsor regulatory classification is No Action Indicated (NAI).

OSI considers that data from the inspected clinical and sponsor sites are acceptable in support of the BLA. OSI recommends that DHP consider sending an information request to the sponsor to obtain information about any changes made to the safety data base after the data cut-off date of October 19, 2014 for subjects enrolled at the Site #4600 (Dr. Dimopoulos, Athens, Greece) prior to this date or doing sensitivity analyses, as some discrepancies between BLA data listings and source documentation were detected in a limited number of subjects during inspection and to assess any significant impact changes may have on the overall safety or risk:benefit assessment.

Note: The inspectional observations for the sponsor and the clinical investigators are based on preliminary communications with the field investigator. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly, upon receipt and review of the Establishment Inspection Report (EIR). The CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.

Branch Chief

Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation

Office of Scientific Investigations

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/s/

JANICE K POHLMAN
11/18/2015

KASSA AYALEW
11/18/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 761035

Product Name: Elotuzumab (Humanized anti-CS1 Monoclonal IgG1 antibody)

PMC #6 Description: 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.

PMC Schedule Milestones: Final Report Submission: 04/2016

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor provided microbial retention data for the sterilizing filter. The acceptance criteria were met. However, the study design was deficient. The protocol has to be modified and the study should be repeated with a suitable surrogate for elotuzumab Drug Product (DP) (b)(4). The sponsor agreed to repeat the microbial retention filter validation (b)(4) study in accordance with PDA Technical Report #26.

2. Describe the particular review issue and the goal of the study.

It was clear from the submitted Filter Validation Summary Report that both Elotuzumab DP and Elotuzumab placebo were determined to (b) (4). The sponsor provided microbial retention data for the sterilizing filter using (b) (4) as a substitute for Drug Product (b) (4). However, in accordance with PDA Technical Report # 26 for cases where the challenge organism is not viable under process conditions, a modified process, or a modified formulation (b) (4) or a reduced exposure time for the challenge organism can be used during the microbial retention filter validation studies. The sponsor agreed to perform the comprehensive evaluation of the most appropriate option. The goal of the study is to perform the filter validation studies, as recommended by the Agency.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The Sponsor will 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) (b) (4), or a reduced exposure time for the challenged organism used during the study.

5. To be completed by ONDQA/OBP Manager: (Completed by the Quality Microbiology Acting Branch Chief)
- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

ANDREW J SHIBER
11/16/2015

PATRICIA F HUGHES TROOST
11/16/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # BLA 761036/ elotuzumab
Product Name: _____

PMC #2 Description: 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 Final Report Submission: 09/2017

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The drug substance lot release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of elotuzumab for the initial marketed product. Additional manufacturing and testing experience gained post licensure can facilitate improved acceptance criteria for the cell-based ADCC assay and the CEX assay.

2. Describe the particular review issue and the goal of the study.

The current potency assay for the release and stability testing is a cell-based ADCC bioassay (b) (4). However, this assay was implemented at a late stage of development and the acceptance criterion for this assay is derived from retrospective testing of release and stability samples. Therefore, the release and stability acceptance criteria for the cell-based ADCC potency assay should be re-evaluated when sufficient data from real-time testing become available to ensure the adequacy of the initial acceptance criterion.

The CEX assay is a stability indicating assay. The initial acceptance criteria for the CEX peaks did not take into account (b) (4) product related impurities that could significantly impact potency are detected in peaks included in this group. During the review cycle, the sponsor agreed to implement a criterion for this (b) (4) peak group as part of release and stability testing. However, given the limited data provided for these peaks, the proposed acceptance criteria should be re-assessed when sufficient information becomes available.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Statistical analysis of data acquired at the time of release following manufacture and testing of additional commercial lots

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

ANDREW J SHIBER
11/16/2015

LINAN HA
11/16/2015

PMR/PMC Development Template: Product Quality (CMC)

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NDA/BLA # BLA 761036/ elotuzumab
Product Name: _____

PMC #3 Description: 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: Final Report Submission: 09/2017

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The drug product lot release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of elotuzumab for the initial marketed product. Additional manufacturing and testing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

The drug product lot release and shelf-life specifications are based on clinical and manufacturing experience provided in the BLA and assessed during the BLA review; however, the limited number of lots manufactured and tested to date using commercial process do not allow for a robust analysis of the data.

The current potency assay for the release and stability testing is a cell-based ADCC bioassay (b) (4). However, this assay was implemented at a late stage of development and the acceptance criterion for this assay is derived from retrospective testing of release and stability samples. Therefore, the release and stability acceptance criteria for the cell-based ADCC potency assay should be re-evaluated when sufficient data from real-time testing become available to ensure the adequacy of the initial acceptance criterion.

The CEX assay is a stability indicating. The initial acceptance criteria for the CEX peaks did not take into account (b) (4) product related impurities that could significantly impact potency are detected in peaks included in this group. During the review cycle, the sponsor agreed to implement a criterion for this (b) (4) peak group as part of release and stability testing. However, given the limited data provided for these peaks, the proposed acceptance criteria should be (b) (4) when sufficient information becomes available.

In addition, some acceptance criteria have a statistical component that should be reassessed when a sufficient number of marketed product lots have been tested.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Statistical analysis of release data acquired following manufacture and testing of additional commercial lots

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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ANDREW J SHIBER
11/16/2015

LINAN HA
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PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # BLA 761036/ elotuzumab
Product Name:

PMC #4 Description: 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: 04/2016

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The (b) (4) studies are on-going and data were not available by the end of the review cycle.

2. Describe the particular review issue and the goal of the study.

The elotuzumab master cell bank (MCB) was developed using (b) (4)

Additional data were provided during the review cycle. Data from Southern blot analysis identified that there are (b) (4)

However, these studies should be completed as support for the (b) (4) of the MCB.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

BMS will continue to perform the studies and submit the results of the study when the data are available.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

ANDREW J SHIBER
11/16/2015

LINAN HA
11/16/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 16, 2015

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nisha Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): EMLICITI (elotuzumab)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761035

Applicant: Bristol-Myers Squibb

1 INTRODUCTION

On June 29, 2015, Bristol-Myers Squibb submitted for the Agency's review a Biologics License Application (BLA) 761035 for EMPLICITI (elotuzumab) for injection. The proposed indication for EMPLICITI is for the treatment of multiple myeloma in combination with lenalidomide and dexamethasone (b) (4) in patients who have received one or more prior therapies.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on August 11, 2015, and July 7, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for EMPLICITI (elotuzumab) for injection.

2 MATERIAL REVIEWED

- Draft EMPLICITI (elotuzumab) PPI received on June 29, 2015, and received by DMPP and OPDP on November 10, 2015.
- Draft EMPLICITI (elotuzumab) Prescribing Information (PI) received on June 29, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 10, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
11/16/2015

NISHA PATEL
11/16/2015

BARBARA A FULLER
11/16/2015

LASHAWN M GRIFFITHS
11/16/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: November 12, 2015

To: Natasha Kormanik, Regulatory Project Manager
Division of Hematology Products (DHP)

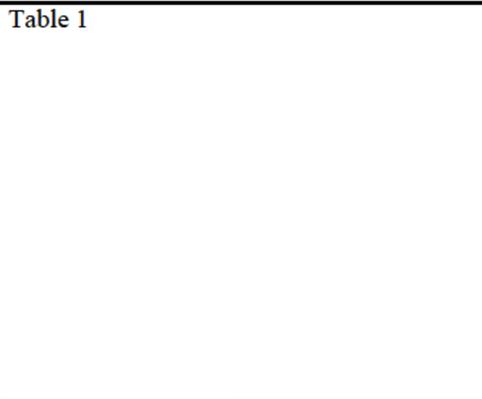
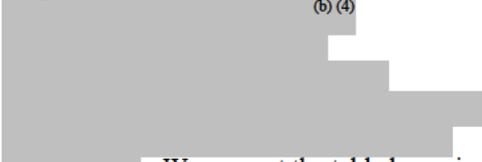
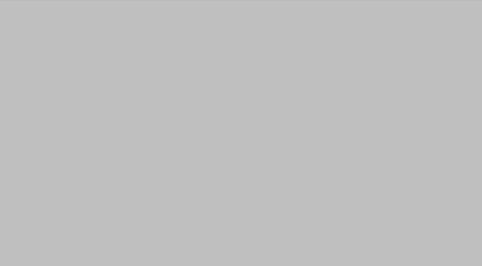
From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for
EMPLICITI™ (elotuzumab) for injection, for intravenous use
BLA 761035

In response to your consult dated July 7, 2015, we have reviewed the draft Package Insert (PI) for EMPLICITI™ (elotuzumab) for injection, for intravenous use (Empliciti) and offer the following comments. Please note that OPDP has made these comments using the version e-mailed to OPDP on November 10, 2015.

Section	Statement from draft	Comment
Highlights, Indications and Usage	EMPLICITI is a SLAMF7-directed immunostimulatory antibody indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies. (emphasis added)	We note that the Indications and Usage section in the Highlights section differs from the Indications and Usage section in the full PI. Please revise to ensure consistency between both sections.
1 Indications and Usage	EMPLICITI is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received one to three prior therapies. (emphasis added)	

Section	Statement from draft	Comment
Highlights, Warnings and Precautions 2 Dosage and Administration	Permanently discontinue for (b) (4) severe reaction. (emphasis added) (b) (4) severe infusion reactions may require permanent discontinuation of EMPLICITI therapy and emergency treatment. (emphasis added)	The bolded term is non-specific. Please consider revising, if possible, to give specific guidance (e.g., "Grade 3 or 4 infusion reactions...")
Highlights, Warnings and Precautions	Infections: (b) (4) 	The bolded statement could be used promotionally to minimize the risk of infections. OPDP recommends deleting this statement since descriptive data (i.e., percentages) are already included in the Warnings and Precautions section of the full PI.
2 Dosage and Administration	Table 1 	We note that the text above Table 1 describes giving 28 mg of dexamethasone orally plus 8 mg IV dexamethasone before administering Empliciti. However, Table 1 purports to show (b) (4)  . We suggest the table be revised to include the administration schedule for IV dexamethasone.
2 Dosage and Administration	(b) (4) infusion rate may be increased in a stepwise fashion as described in Table 2. (emphasis added)	The bolded term is promotional in tone and could be used to minimize the risks of Empliciti. Please consider revising or deleting this term.
5 Warnings and Precautions	Fatal infections were (b) (4) reported in 2.5% and 2.2% of E-Ld and Ld treated patients. (emphasis added)	Is the bolded term needed? It could be used promotionally to minimize the risk of infections.
5 Warnings and Precautions	 (b) (4)	Is this statement needed? It could be used promotionally to minimize the risk of infections in the Empliciti arm.
6 Adverse Reactions		This statement could be used promotionally to minimize the risks associated with Empliciti. OPDP recommends deleting this statement.
6 Adverse Reactions		Please consider adding quantitative data, if possible, to describe this group as the bolded

Section	Statement from draft	Comment
	(b) (4)	phrase could be used promotionally to downplay the risk of immunogenicity.
12 Clinical Pharmacology	In preclinical models, the combination of elotuzumab and lenalidomide resulted in enhanced activation of Natural Killer cells that was greater than the effects of either agent alone and increased anti-tumor activity <i>in vitro</i> and <i>in vivo</i> . (emphasis added)	Is the term “enhanced” needed? If not, please consider deleting as it is promotional in tone.
14 Clinical Studies	The cytogenetic categories of del 17p and t(4;14) were present in 32% and 9% of patients, respectively. (b) (4)	Has (b) (4) been adequately demonstrated? If not, please consider deleting as the sponsor will most likely use these efficacy results in promotional materials. (b) (4)
14 Clinical Studies	The 1- and 2-year rates of PFS for EMLICITI in combination with lenalidomide and dexamethasone treatment were 68% and 41%, respectively, compared with 57% and 27%, respectively, for lenalidomide and dexamethasone treatment. At the time of the interim analysis, there were 94 (29%) deaths in the EMLICITI in combination with lenalidomide and dexamethasone study arm compared to 116 (36%) in the lenalidomide and dexamethasone study arm.	Have these results been adequately demonstrated? If not, please consider deleting as the sponsor will most likely use these efficacy results in promotional materials.

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/s/

NISHA PATEL
11/12/2015

Table 1: Proposed Product Characteristics of Empliciti (elotuzumab)

Proprietary Name:	Empliciti
Proper Name:	elotuzumab
Indication:	treatment of multiple myeloma in patients who have received one or more prior therapies: in combination with lenalidomide and dexamethasone.
Dose:	10 mg/kg administered via intravenous infusion every week for the first two cycles and every 2 weeks thereafter until disease progression or unacceptable toxicity
Route of Administration:	Intravenous infusion
Dosage Form:	for Injection
Strength and Container-Closure:	300 mg and 400 mg in single-dose vials
Storage and Handling:	Refrigerate at 2°C to 8°C (36° F-46°F). Protect EMPLICITI from light by storing in the original package until time of use. Do not freeze or shake.

Materials Reviewed:

- Container Labels
- Carton Labeling

Start of Sponsor Material

(b) (4)



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *does not conform*.

OBP Request: Relocate the dosage form "for Injection" to appear below the proper name. For CDER-regulated biological products, the proper name should not include the finished dosage form. The finished dosage form, for Injection, can appear on the line below the proper name.¹ *Applicant revised as requested.*

¹ Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft Guidance) April 2013, page 9. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

(2) The name, address, and license number of manufacturer; *conforms*.

(3) The lot number or other lot identification; *conforms*.

(4) The expiration date; *conforms*.

(5) The recommended individual dose, for multiple dose containers. *Not applicable*.

(6) The statement: "Rx only" for prescription biologicals; *conforms*.

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *Not applicable*.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable*.

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Not applicable*.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable*.

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; does not conform.

OBP Request: Confirm there is no text on top of the ferrule and cap overseal of the vials to comply with United States Pharmacopeia (USP) General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals. *Applicant's response is acceptable.*

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms. However, we recommended the Applicant update the placeholders (0003-xxxx-11) with actual NDC numbers. Applicant revised as requested.*

C. 21 CFR 201.5 Drugs; adequate directions for use; *does not conform.*

OBP Request:

Add the statement "Reconstitute and Further Dilute Prior to Use" to appear under the route of administration. *Applicant revised as requested.*

D. 21 CFR 201.6 Drugs; misleading statements; *conforms.*

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *does not conform.*

OBP Request: Increase font size of proper name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) to increase readability of this important information on the principal display panel (PDP). *Applicant revised as requested.*

F. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform.*

OBP Request:

If space permits, increase the prominence of the route of administration "For Intravenous Infusion Only" by using larger font size. *Applicant revised as requested.*

Additionally, we concur with DMEPA's recommendation to reduce the size of wave image and consider moving away from the proprietary name. *Applicant revised as requested.*

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*

H. 21 CFR 201.25 Bar code; *conforms*.

I. 21 CFR 201.50 Statement of identity; *conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *does not conform. See below for discussion of 21 CFR 610.61(g) - The Amount of Product in the container.*

K. 21 CFR 201.55 Statement of dosage; *conforms*.

L. 21 CFR 201.100 Prescription drugs for human use. *conforms*.

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II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *does not conform.*

OBP Requests:

Relocate the dosage form "for Injection" to appear below the proper name. For CDER-regulated biological products, the proper name should not include the finished dosage form. The finished dosage form, for Injection, can appear on the line below the proper name. *Applicant revised as requested.*

b) The name, addresses, and license number of manufacturer; *conforms.*

c) The lot number or other lot identification; *conforms.*

d) The expiration date; *conforms.*

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms.*

f) The number of containers, if more than one; *not applicable.*

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *does not conform. The labeling does not appropriately inform end-users of the excess volume of reconstituted solution. The total volume (including overfill) appears in the labeling.*

Table 2 below displays the reconstitution instructions from the proposed PI.

Table 2: Reconstitution Instructions in the PI section 2

Strength	Amount of Sterile Water for Injection (SWFI), USP Required for Reconstitution	(b) (4)	Postreconstitution Concentration
300 mg vial	13.0 mL		25 mg/mL
400 mg vial	17.0 mL		25 mg/mL

Based on these instructions, the Applicant claims there is (b) (4) mL of overfill in the 300 mg and 400 mg vials which is excessive when compared to (b) (4)



Although, Empliciti is a lyophilized product, the concepts provided in FDA Guidance: Allowable Excess Volume and Labelled Vial Fill Size in Injectable Drug and Biological Products should be applied. Specifically for injectable products requiring reconstitution, the product should be designed to meet the label claim and acceptable overfill, and allow for correct dosing. Deviations from the recommended excess volumes should be justified. In this case, the product meets the label claim (300 mg/12 mL or 400 mg/16 mL of reconstituted solution), however the overfill of (b) (4) mL appears excessive for a product whose final volume after reconstitution is (b) (4) mL and (b) (4) mL, respectively. The Applicant claims the (b) (4). See the product quality review for an evaluation of the VNS of (b) (4) mL.

Subsequent to our request for detailed extractable volume study data, the data provided a wide range of volumes. The average volume extracted from the 400 mg vial after reconstitution was (b) (4) mL. The Applicant noted one study subject retrieved a recoverable volume of (b) (4) mL. The Applicant proposed to label the product 400 mg based upon 16 mL of reconstituted solution (concentration of 25 mg/mL) reliably withdrawn from the vial in the extractable volume study.

My concern is that in some instances, after reconstitution, there may be excessive volume above the labeled amount (16 mL of reconstituted solution) in the 400 mg vial that is available for withdrawal. Therefore, I recommend the labeling contains a statement that after reconstitution, the product contains overfill in order to meet the labeling claim. This will help to inform end-users of the additional overfill and also help minimize the likelihood that end-users withdraw the entire contents of the vial during preparation. Additionally, the labeling should state the intended labeled volume (12 mL and 16 mL) while deleting the excessive volume, which should not appear in labeling (see Table 4 for revised reconstitutions instructions). *Applicant revised as requested.*

Table 4: Revised Reconstitution Instructions in the PI section 2

Strength	Amount of Sterile Water for Injection, USP Required for Reconstitution	Deliverable Volume of Reconstituted EMLICITI in the Vial	Postreconstitution Concentration
300 mg vial	13 mL	12 mL*	25 mg/mL
400 mg vial	17 mL	16 mL*	25 mg/mL

* After reconstitution, each vial contains overfill to allow for withdrawal of 12 mL (300 mg) and 16 mL (400 mg), respectively.

Furthermore, we added reconstitution instructions on the carton labeling at the end of the list of ingredients.

OBP Request: Revise the statement of contents to appear as:

Contents: Each single-dose vial delivers 300 mg elotuzumab, citric acid monohydrate (2.44 mg), polysorbate 80 (3.4 mg) sodium citrate (16.6 mg), sucrose (510 mg). After reconstitution with 13 mL of Sterile Water for Injection, USP, the reconstituted solution concentration is 25 mg/mL and the vial contains overfill to allow for withdrawal of 12 mL.

Use a similar format for the 400 mg vial.

Applicant revised as requested. DMEPA and DHP concurred with these labeling recommendations.

- h) The recommended storage temperature; *conforms.*
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms.*
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable.*
- k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms.*
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable.*
- m) The type and calculated amount of antibiotics added during manufacture; *not applicable.*
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable.*
- o) The adjuvant, if present; *not applicable.*

p) The source of the product when a factor in safe administration; *not applicable*.

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals. *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels; *not applicable*.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Empliciti (elotuzumab) is a monoclonal antibody.*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor; *not applicable*.

E. 21 CFR 610.67 Bar code label requirements: *conforms*.

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms. However, we recommended the Applicant update the placeholders (0003-xxxx-11) with actual NDC numbers. Applicant revised as requested*

G. 21 CFR 201.5 Drugs; adequate directions for use; *does not conform*.

OBP Request: If space permits, increase the prominence of the route of administration "For Intravenous Infusion Only" by using larger font size. *Applicant revised as requested.*

Add the statement "Reconstitute and Further Dilute Prior to Use" to appear under the route of administration. *Applicant revised as requested.*

Consider deleting the statement from the side panel "Prior to Use, EMPLICITI must be reconstituted and further diluted." *Applicant revised as requested.*

Note the instructions for reconstitution were placed at the end of the list of ingredients. See above discussion of 21 CFR 610.61(g) - The Amount of Product in the container.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms.*

I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] *does not conform.*

OBP Request: Increase font size of proper name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) to increase readability of this important information on the principal display panel (PDP). *Applicant revised as requested.*

J. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform.* See 201.5 above. *Applicant revised as requested.*

Additionally, we concur with DMEPA's recommendation to reduce the size of wave image and consider moving away from the proprietary name. *Applicant revised as requested.*

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*

L. 21 CFR 201.25 Bar code label requirements; *conforms.*

M. 21 CFR 201.50 Statement of identity; *conforms.*

N. 21 CFR 201.51 Declaration of net quantity of contents; *does not conform.* See above discussion of 21 CFR 610.61(g) - The Amount of Product in the container.

O. 21 CFR 201.55 Statement of dosage; *conforms.*

P. 21 CFR 201.100 Prescription drugs for human use; *conforms*.

CDER Labeling Recommendations:

This section describes additional recommendations provided to the Applicant that address CDER Labeling preferences. The Applicant's response to these recommendations was acceptable.

A. General Comments

1. Confirm there is no text on top of the ferrule and cap overseal of the vials to comply with United States Pharmacopeia (USP) General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals.
2. Update the NDC numbers.

B. Carton Labeling

1. Revise the dosage form "FOR INJECTION" to appear as "for Injection".
2. Revise the statement "Single-Use Vial" to read "Single-Dose Vial. Discard Unused Portion". Note the change from "Single-Use" to "Single-Dose". Single-Dose is the appropriate package term for a container designed for use with a single patient as a single injection or infusion per USP General Chapters: <7> Packaging and Storage Requirements. Therefore the PDP should appear as:

Empliciti
(elotuzumab)
for Injection

300 mg per vial
For Intravenous Infusion Only
Reconstitute and Further Dilute Prior to Use
Single-Dose Vial. Discard Unused Portion

C. Vial Container Label

1. See comments B1 and B2.
2. Rotate the orientation of the text on the side panel so that it appears horizontally in the same direction as the information on the PDP to help ensure the safe use of this product.

Conclusions:

The container labels and carton labeling for Empliciti (elotuzumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [August 1, 2015 to November 30, 2015]. Labeling deficiencies were identified and resolved. The container labels and carton labeling submitted on November 10, 2015 are acceptable(see below).

BEST AVAILABLE COPY

Container Labels

(b) (4)

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 4, 2015

TO: Natasha Kormanik, MSN, RN, OCN[®], Regulatory Project Manager
Nicole Gormley, M.D., Medical Officer
Albert Deisseroth, M.D., Ph.D., Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 761035

APPLICANT: Bristol-Myers Squibb Company

DRUG: elotuzumab

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority Review

INDICATIONS: Treatment of (b) (4) relapsed multiple myeloma

CONSULTATION REQUEST DATE (signed): July 28, 2015

INSPECTION SUMMARY GOAL DATE (original):	November 30, 2015
INSPECTION SUMMARY GOAL DATE (revised):	November 6, 2015
DIVISION ACTION GOAL DATE (original)	December 14, 2015
DIVISION ACTION GOAL DATE (revised):	November 30, 2015
PDUFA DATE:	December 14, 2015

I. BACKGROUND:

Elotuzumab (HuLuc63/BMS-901608) is a humanized monoclonal IgG1 antibody product directed to human CS1 (CD2 subset-1, also known as CRACC and SLAMF7), a cell surface glycoprotein with homology to the CD2 family of cell surface proteins. Although the exact mechanism is unknown, the proposed mechanism of elotuzumab involves natural killer cell mediated antibody dependent cell-mediated cytotoxicity. Elotuzumab could kill multiple myeloma cell lines and primary myeloma cells *in vitro* in the presence of peripheral blood mononuclear cells or purified natural killer cells.

Treatment options for subjects with primary resistant or relapsed multiple myeloma may include combination therapies with glucocorticoids and cytotoxic chemotherapeutic agents, more recently combined with autologous stem cell transplantation (ASCT). Two open-label randomized clinical trial studies were submitted in support of the applicant's BLA. For this NME BLA under the PDUFA V program review with priority therapy designation, CDER DHP requested two domestic sites and two international sites to be inspected. The sites enrolled large numbers of patients and showed a good response to treatment.

Study CA204004

Study CA204004 was a Phase 3, multi-center, open-label, randomized trial investigating lenalidomide/low-dose dexamethasone with and without elotuzumab in subjects with previously treated, relapsed or refractory multiple myeloma. The primary study objective was to compare progression free survival (PFS) of lenalidomide/low-dose dexamethasone plus elotuzumab versus lenalidomide/low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma, and to compare the overall response rate of lenalidomide/low-dose dexamethasone plus elotuzumab versus lenalidomide/low-dose dexamethasone. A cycle was defined as 28 days. Treatment with study drug continued until disease progression, unacceptable toxicity or subject met other criteria for discontinuation of study drug. Tumor response assessments were evaluated during the trial for all randomized subjects. An Independent Review Committee conducted a blinded, independent review of these tumor assessments. The co-primary endpoints of treatment overall response rate and progression free survival was based on the Independent Review Committee assessment. Treatment with elotuzumab-lenalidomide significantly improved PFS compared to lenalidomide. Per sponsor's submission, there was a 30% reduction in the risk of progression. The hazard ratio was 0.70.

Study CA204009

Study CA204009 was Phase 2, multicenter, open-label, randomized study that assessed the effect of bortezomib, dexamethasone, and elotuzumab (investigational arm) compared with bortezomib and dexamethasone (control arm) in subjects with relapsed/refractory multiple myeloma. The primary study objective was to compare progression free survival between treatment arms in the overall population. A cycle was defined as 21 days for Cycles 1 through 8 and 28 days for Cycles 9 and beyond. Treatment with study drug continues until disease progression, unacceptable toxicity or subject meets other criteria for discontinuation of study drug. The primary efficacy endpoint was treatment response. Per sponsor's submission, the trial met its primary endpoint of PFS - the hazard ratio was 0.72.

II. RESULTS:

Name of CI Location	Study Site/Protocol/ Number of Subjects Enrolled	Inspection Date	Classification*
Meletios Dimopoulos, M.D. 80 Vas Sofias Avenue Athens, Greece 11528	Site #4600 Protocol CA204004 Subjects = 33	November 2-4, 2015-ongoing	Inspection Pending
Antonio Palumbo, MD Via Genova, 3 Torino, Italy 10126	Site #4934 Protocol CA204009 Subjects=19	October 19-23, 2015	Preliminary: VAI
Darrell White, M.D. Bethune Bldg. Room 433 1276 South Park Street Halifax, Nova Scotia B3H2Y9 Canada	Site #2407 Protocol CA204004 Subjects=24	October 19-23, 2015	Preliminary: VAI
Paul Richardson, M.D. 450 Brookline Ave. Boston, MA 02215	Site #1414 Protocol CA204004 Subjects=10	September 1-8, 2015	Preliminary: NAI
Sponsor: Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492	Protocol CA204004 Protocol CA204009	September 8-17, 2015	Preliminary: NAI

***Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. Meletios Dimopoulos, M.D., Protocol CA204004/Site #4600

Athens, Greece

The inspection was conducted from November 2 to 4, 2015 and is ongoing.

A total of 35 subjects were screened, and 33 subjects were enrolled and randomized. Twenty seven subjects completed the treatment period phase of the study. At this stage of the inspection, an audit of 19 enrolled subjects' records for efficacy endpoints was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects, whose records were reviewed, were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

c. Assessment of data integrity:

NOTE: The field inspection is ongoing, although no regulatory violations have been noted thus far. Per field staff at this juncture, the site inspection did not reveal evidence of "non-compliance or data integrity". A review update will be provided upon completion of the inspection.

2. Antonio Palumbo, M.D., Protocol CA204009/Site #4934

Turin, Italy

a. What was inspected:

The inspection was conducted from October 19 to 23, 2015.

A total of 20 subjects were screened, and 19 subjects were enrolled and randomized. Ten subjects completed the treatment period phase of the study. An audit of 19 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects, whose records were reviewed, were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

Although the FDA field investigator did not issue a Form FDA 483 (Inspectional Observations), a one item inspectional observation was noted. Specifically, the study was not conducted according to the investigational plan. For example: (a) Subject 034 in the “elotuzumab” group had the date of disease progression reported as September 18, 2013. The source document recorded date was April 9, 2013, and (b) Subject 079 in the “non-elotuzumab” group had the date of disease progression reported as May 30, 2013. The source document recorded date was February 11, 2013.

Reviewer’s Comment: For this regulatory deficiency, a determination as to the definitive date of disease progression that affected Subject 034 and Subject 079 cannot be determined. DHP was notified and stated that the efficacy assessment impact was unlikely to be significant in efficacy outcome, given the small number of cases. In addition, since one subject in each treatment arm was impacted by this situation, the overall outcome should be minimally affected.

Form FDA 483 (Inspectional Observations) was not issued because a Turbo citation generator was not available for the field investigator at the end of the inspection. Although a Form FDA 483 was not issued at the end of the inspection, the field investigator recommended a regulatory classification of Voluntary Action Indicated (VAI) for the deficiency noted above.

c. Assessment of data integrity:

Despite the above regulatory deficiencies that were not critical, data submitted by this clinical site appear acceptable in support of this specific indication.

3. Darrell White, M.D., Protocol CA204004/Site #2407

Nova Scotia, Canada

a. What was inspected:

The inspection was conducted from October 19 to 23, 2015.

A total of 25 subjects were screened, and 24 subjects were enrolled and randomized. Twenty four subjects completed the treatment period phase of the study. An audit of 24 enrolled subjects’ records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects, whose records were reviewed, were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Specifically, the study was not conducted according to the investigational plan. For instance, vital signs, from August 30, 2011 through August 29, 2012 inclusive, were periodically not obtained at various times for Subjects #004, #006, #015, #019, #024, #465, and #554.

Reviewer's Comment: Per study protocol, these were considered regulatory deficiencies. Clinical vital signs were not the primary efficacy outcome variable of the study. The efficacy endpoint, progression free survival (not clinical vital signs), was weighted as principally relevant to the study objective (as described in Study Protocol CA204004), for application review.

After the sponsor monitor noticed lapses in site monitoring, corrective actions to Dr. White's site were implemented. A full documentation process for patient vital signs recording was implemented, and subsequent clinical monitoring resulted in improved data reporting to the BLA submission.

c. Assessment of data integrity:

Despite the above regulatory deficiency, it is unlikely that the occasional omission of vital signs would impact subject safety, and data submitted by this clinical site appear acceptable in support of this specific indication.

**4. Paul Richardson, M.D., Protocol CA204004/Site #1414
Boston, MA**

a. What was inspected:

The inspection was conducted from September 1 to 8, 2015.

A total of 11 subjects were screened and 10 subjects enrolled. Ten subjects completed the treatment period phase of the study. An audit of 11 screened subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects, whose records were reviewed, were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR INVESTIGATION

4. Bristol-Myers Squibb Company

Wallingford, CT 06492

a. What was inspected:

The inspection was conducted from September 8 to 17, 2015. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

Monitoring, in general, was considered adequate. At the close out meeting with the inspected clinical study site, the following deviations were discussed with the sponsor: (1) although there was verbal confirmation with the study site personnel, the monitors did not confirm GCP training through a review of training documentation, and (2) the application sponsor provided a guidance document for conducting qualifying visits that asks whether or not the staff had documented GCP training. However, GCP training and confirmation were not clearly defined in the applicant's procedures. OSI considered these as protocol deviations, not regulatory violations.

Noncompliant sites were not noted. There was no evidence of under-reporting of adverse events.

A Form FDA 483 was not issued at the end of the sponsor inspection.

c. Assessment of data integrity:

Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

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.

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.

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

Note: The inspectional observations for the sponsor and the clinical investigators are based on preliminary communications with the field investigator. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly, upon receipt and review of the Establishment Inspection Report (EIR). The CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
11/04/2015

SUSAN D THOMPSON
11/04/2015

KASSA AYALEW
11/05/2015

Division of Hematology Products (DHP) Labeling Review Of NME

BLA Number	761035
Applicant	Bristol-Myers Squibb
Proprietary Name (nonproprietary name)	EMPLICITI (elotuzumab)
Receipt Date	06/29/2015
PDUFA Goal Date (Internal Goal Date)	02/29/2016 (11/30/2015)
Review Classification	Priority (expedited); Breakthrough Designated Product
Proposed Indication	Elotuzumab in combination with lenalidomide and dexamethasone [REDACTED] ^{(b) (4)} for the treatment of patients with MM who have received one or more prior therapies.
Indication (modified from requested)	EMPLICITI is a SLAMF7-directed immunostimulatory antibody indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.
Dosing Regimen	10 mg/kg IV weekly x 2 cycles and every 2 weeks thereafter (until PD or toxicity) in combination with lenalidomide and dexamethasone
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application: (example text below)

The BLA for elotuzumab, a SLAMF7-directed immunostimulatory antibody, was submitted on June 29, 2015. The Applicant is seeking approval in patients with Multiple Myeloma who had received one or more prior therapies based upon CA204004, a Phase 3 randomized, open-label trial of lenalidomide/dexamethasone (Ld) with or without elotuzumab and CA204009, a Phase 2 randomized study of bortezomib/dexamethasone (Bd) with or without elotuzumab. The dosing regimen in the Phase 3 trial was Ld ± elotuzumab 10 mg/kg IV weekly x 2 cycles and q2 weeks thereafter.

In this review, I propose labeling recommendations and edits in the EMPLICITI labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of EMPLICITI.

The following table summarizes my recommendations by section of labeling:

Labeling Section	Recommendation	Justification
Highlights	<ol style="list-style-type: none"> 1. Add white space before each major heading in HL. 2. Dosage forms and strengths: use “single-dose” not (b) (4) 	<ol style="list-style-type: none"> 1. Labeling Review Tool (LRT): “White space should be present before each major heading in HL”. 2. LRT: “Appropriate package terms for injectable drugs include “single-dose, single-patient use, and multiple-dose”.
Throughout Labeling	<ol style="list-style-type: none"> 1. Changed language to “command language” throughout. 2. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone symbols in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows: Spell out all >, <, or ≤ symbol appearing in the Dosage and Administration section to instead read ‘greater than’, 	<ol style="list-style-type: none"> 1. LRT page3. 2. Institute of Safe Medication Practice List of Error-Prone Abbreviations, Symbols and Dose Designations and Labeling Review Tool (page 1).

	'less than', or 'less than or equal to'.	
(2) Dosage and Administration	<p>1. Section Revised to provide the information most relevant to prescribers first:</p> <ul style="list-style-type: none"> • Recommended Dosing • Premedication • Dose Modifications • Administration • Reconstitution and Preparation <p>2. Recommended inclusion of the following reference to labels for combination drugs: “Refer to the dexamethasone and lenalidomide prescribing information for additional information.”</p>	<p>1. The most important information for prescribers is the dosing and premedication, followed by dose modifications, administration, and reconstitution/preparation. LRT (page 19): “Provide basic dosing first, followed by other information relevant to dosage and administration. The sequence of information should reflect the relative importance of the information to safety and effectively administer the drug.</p> <p>2. The drugs used in combination with Empliciti have important safety concerns that should be communicated to prescribers, however, this label is intended to describe the safe and effective use of Empliciti, and should therefore not contain information that is not specific to Empliciti. References to the lenalidomide and dexamethasone label were added to sections 2,4, 5, 7, 8, & 17.</p>
(4) Contraindications	Recommended: “There are no contraindications to EMPLICITI. Because EMPLICITI indicated for use in combination	There are important contraindications for the drugs used in combination with

	with lenalidomide and dexamethasone, healthcare providers should consult the prescribing information of these products for a complete description of contraindications before starting therapy.”	Empliciti.
(5) Warnings and Precautions	Recommended including a warning for “Interference with laboratory tests” because elotuzumab interferes with the measurement of myeloma protein, which may prevent determination of stringent Complete Response. This information is recommended to be included in Sections 7, 5, and 2.	Per CFR201.57(c)(8), WARNINGS and PRECAUTIONS must note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section.
(6) Adverse Reactions and (14) Clinical Studies	1.Applicant had numbered studies as (b) (4) ”. The review team removed (b) (4) from the labeling, so recommend that (b) (4) be described as (b) (4) 2. Spell out ECOG acronym at first appearance.	1.LRT (page 39) regarding study description. 2. Good writing practice.
(8) Use in Specific Populations	Revised section to be consistent with Final Rule for Pregnancy and Lactation Labeling Rule. Added pregnancy testing and contraception subheading of 8.3 to refer prescribers to lenalidomide labeling.	21 CFR 201.57; PLLR Final Rule.
(10) Overdosage	1. Removed Applicants proposed text (b) (4) Added this general statement about the lack of data and management recommendations: “The dose of EMLICITI at which severe toxicity occurs is not known. In case of overdosage, patients should be closely monitored for signs or symptoms of adverse reactions and	LRT: The OVERDOSAGE section must be based on human overdosage data. If human data are unavailable, appropriate animal and in vitro data regarding overdosage may be included. Alternatively, if no specific overdosage data are available that would be useful to the prescriber, omit this section.

	<p>appropriate symptomatic treatment instituted.”</p> <p>2. Asked applicant to add information as to whether Empliciti is removed by dialysis (if available)</p>	
(14) Clinical Studies	Added “+” symbol to reference the European Group for Blood Marrow Transplantation (EBMT) criteria.	To make it clear that all categories of response (not just ORR) were by those criteria.

Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP’s final recommendations for the EMPLICITI labeling.

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/s/

VIRGINIA E KWITKOWSKI
10/26/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: October 14, 2015

Requesting Office or Division: Division of Hematology Products (DHP)

Application Type and Number: BLA 761035

Product Name and Strength: Empliciti
(Elotuzumab)
for Injection,
300 mg/vial, 400 mg/vial

Product Type: Single Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Bristol Myers Squibb

Submission Date: June 29, 2015

OSE RCM #: 2015-1374

DMEPA Primary Reviewer: Michelle Rutledge, PharmD

DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling and prescribing information for Empliciti (elotuzumab) for areas of vulnerability that could lead to medication errors. The Sponsor is proposing a product 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).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Bristol Myers Squibb is seeking approval of Empliciti (Elotuzumab) for injection, a humanized immunoglobulin G1 monoclonal antibody, for the treatment of patients with multiple myeloma who have received one or more prior therapies in combination with lenalidomide and dexamethasone (b) (4). The proposed breakthrough therapy will provide an alternate treatment option for this indication.

We reviewed the proposed label and labeling and identified the following areas of vulnerability to errors:

- Readability of the Dosage and Administration in the prescribing information, label, and labeling.

4 CONCLUSION & RECOMMENDATIONS

We reviewed the label and labeling and identified that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on this review, DMEPA provides the following comments for consideration by the review division prior to the approval of this BLA:

A. PRESCRIBING INFORMATION, SECTION 2, DOSAGE AND ADMINISTRATION

- a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone symbols in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:
 - i. Spell out all \geq symbol appearing in the Dosage and Administration section to instead read such as, greater than or equal to.
 - ii. Remove trailing zeros in the Dosage and Administration section, for example, Table 4 Reconstitution Instructions and Dilution
- b. Revise the heading of Section 2.4 (b) (4) to "Preparation and Administration".
- c. Relocate Infusion Rate information from Section 2.1, Recommended Dosage to Section 2.4, Preparation and Administration, as it appears that this information should belong to administration that should follow preparation of the product.
- d. (b) (4)
- e. In Section 2.4, add bullet points or numbering to add clarity to the multiple steps of the process of reconstitution and dilution.
- f. In Section 2.4, it is unclear why the Applicant states "(b) (4)" when the dosing is weight-based. Thus, revise Dilution instructions for clarity and to allow flexibility in calculating individualized dosing, such as: "Withdraw the required volume needed for patient's dose and further dilute in either Dextrose 5% Water (D5W) or 0.9% Sodium Chloride for a resulting concentration between 1 mg/mL and 6 mg/mL."

- g. In Section 2.4, in Table 4: Reconstitution Instructions for Empliciti, we recommend removing the third column, (b) (4) as this information and the column title may cause confusion when preparing the product.

4.2 RECOMMENDATIONS FOR THE BRISTOL MYERS SQUIBB

We recommend the following be implemented prior to approval of this BLA:

A. CARTON LABELING

1. Increase font size of proper name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) to increase readability of this important information on the principal display panel (PDP)¹.

2.



3. Change the presentation of the following format:

Empliciti

(Elotuzumab)

For Injection

4. Add the statement “Discard Unused Portion” after the statement “Single-(b) (4) Vial”.
5. Move and bold the “Prior to use, must be reconstituted and further diluted” sentence from the side panel to the PDP to help ensure the correct use of this product. In addition, this is important product safety information.
6. If space permits, increase the prominence of the route of administration “For Intravenous Infusion Only” by using larger font size.

¹ Labeling, 21 CFR 201.10(g)(2), 2015

B. VIAL LABEL

1. See A.1 –A.5 and revise vial label accordingly.
2. If space allows, add the “Prior to use, must be reconstituted and further diluted” sentence to the PDP to help ensure the correct use of this product. If space does not allow, add this information to the side panel.
3. We recommend changing the direction of the information on the side panel to read horizontal in the same direction as the information on the PDP to help ensure the safe use of this product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Empliciti that Bristol Myers Squibb submitted on June 29, 2015.

Table 2. Relevant Product Information for Empliciti	
Initial Approval Date	N/A
Active Ingredient	Elotuzumab
Indication	In combination with lenalidomide and dexamethasone (b) (4) for the treatment of patients with MM who have received one or more prior therapies
Route of Administration	Intravenous
Dosage Form	For Injection
Strength	300 mg/vial, 400 mg/vial
Dose and Frequency	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. (2.1) (b) (4)
How Supplied	Lyophilized powder in a single-use vial, 300 mg and 400 mg
Storage	Store EMPLICITI under refrigeration at 2C to 8C (36F-46F). Protect EMPLICITI from light by storing in the original package until time of use. Do not freeze or shake.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On September 10, 2015, we searched the L:drive using the terms, Empliciti, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous label and labeling reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 12, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care
Search Strategy and Terms	Match Exact Word or Phrase: Empliciti

D.2 Results

We found no related articles.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MICHELLE K RUTLEDGE
10/14/2015

YELENA L MASLOV
10/15/2015

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	BLA 761035
Brand Name	EMPLICITI
Generic Name	Elotuzumab
Sponsor	Bristol-Myers Squibb
Indication	(b) (4) Multiple Myeloma
Dosage Form	300 mg and 400 mg lyophilized powder in a single-use vial for IV Infusion
Drug Class	Immunostimulatory Monoclonal Antibody
Therapeutic Dosing Regimen	10 mg/kg IV
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	20 mg/kg (highest studied, no MTD defined)
Submission Number and Date	SDN 001; 29 Jun 2015
Review Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Studies CA204004 and CA204011 were not adequately designed for QT assessment. Central tendency analyses were not reliable. However, over the observed concentration range, there is no evident concentration-QTc relationship. Elotuzumab as a large targeted protein has a low likelihood of direct ion channel interactions. There is no evidence from nonclinical or clinical data to suggest that elotuzumab has the potential to delay ventricular repolarization.

CA204004:

In this phase 3, randomized, open-label trial of lenalidomide/dexamethasone with or without elotuzumab (10 mg/kg IV) in patients with relapsed or refractory multiple myeloma, 646 patients were randomized to receive lenalidomide/dexamethasone with elotuzumab (E-Ld) or lenalidomide/dexamethasone without elotuzumab (Ld). Of the 646 randomized patients, 318 patients were treated with E-Ld and 317 patients were treated with Ld. Ten patients in the E-Ld group participated in the ECG sub-study.

CA204011:

In this phase 2 biomarker study of elotuzumab monotherapy, 31 patients received elotuzumab in 2 cohorts. Enrollment in the 2 cohorts occurred in a sequential manner: the

20-mg/kg IV cohort followed by the 10-mg/kg IV cohort. All 31 patients were included in the ECG population.

Premedications were administered in both studies. Overall summary of findings is presented in Table 1 and Table 2.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for E-Ld (FDA Analysis for Study CA204004)

Cycle	Day	Time	N	QTcF (ms) (SD)	ΔQTcF (ms) (SD)	ΔQTcF 90% CI (ms)
2	22	-1 Hour	7	419.9 (21.9)	13.0 (18.5)	(-0.6, 26.5)
		0 Hour (predose)	7	436.2 (24.6)	29.3 (22.9)	(12.4, 46.1)
		EOI	7	435.3 (23.9)	28.3 (23.1)	(11.3, 45.3)
		2 Hour Post EOI	7	430.7 (21.1)	23.8 (20.4)	(8.8, 38.7)

Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Elotuzumab (10 mg/kg IV and 20 mg/kg IV) (FDA Analysis for Study CA204011)

Treatment	Cycle	Day	Time	N	QTcF (ms) (SD)	ΔQTcF (ms) (SD)	ΔQTcF 90% CI (ms)
Elo-10mg/kg	1	1	2 Hour Post EOI	16	425.2 (26.8)	10.4 (23.1)	(0.3, 20.5)
Elo-20mg/kg	1	1	0.5 Hour Post EOI	15	427.7 (17.7)	2.7 (12.0)	(-2.7, 8.2)
Total	1	1	0.5 Hour Post EOI	31	425.3 (22.0)	5.6 (18.8)	(-0.1, 11.3)

Both the 20 mg/kg once monthly regimen and the 10 mg/kg every 2-week regimen achieved similar therapeutic exposure at the steady state. At the observed concentration range, there is no evident concentration-QTc relationship.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Elotuzumab is a humanized IgG1 monoclonal antibody that specifically targets the SLAMF7 (Signaling Lymphocytic Activation Molecule Family member 7) protein. It is indicated for the treatment of patients with multiple myeloma who have received one or more prior therapies: in combination with lenalidomide and dexamethasone (b) (4)

3.2 MARKET APPROVAL STATUS

Elotuzumab is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of elotuzumab's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 100043. The sponsor submitted the study report CA204004 and CA204011 for

lenalidomide/dexamethasone with or without elotuzumab and elotuzumab monotherapy, including electronic datasets and most of the waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

CA204004:

A phase 3, randomized, open-label trial of lenalidomide/dexamethasone with or without elotuzumab in relapsed or refractory multiple myeloma

CA204011:

A phase 2 biomarker study of elotuzumab (humanized anti-CS1 monoclonal IgG1 antibody) monotherapy to assess the association between NK Cell status and efficacy in high risk smoldering myeloma

4.2.2 Study Dates

CA204004: 14 Jun 2011 -- 01 Sep 2014

CA204011: 20 Feb 2012 -- 30 May 2014

4.2.3 Objectives

CA204004:

Primary Objectives: To compare progression-free survival (PFS) and objective response rate (ORR) of lenalidomide/low-dose dexamethasone + elotuzumab (E-Ld) versus lenalidomide/low-dose dexamethasone (Ld) in subjects with relapsed or refractory multiple myeloma (MM).

Secondary Objectives:

- To compare overall survival (OS) of E-Ld versus Ld.
- To compare the change from baseline of the mean score of pain severity and the change from baseline of the mean score of pain interference using the Brief Pain Inventory- Short Form (BPI-SF) of E-Ld versus Ld.

CA204011:

Primary Objective: To explore the association between baseline percent CD56dim/CD16+/CD3-/CD45+ (CD56dim) Natural Killer (NK) cells in bone marrow and the maximal change in serum monoclonal protein in subjects with high-risk smoldering myeloma treated with elotuzumab (10 mg/kg or 20 mg/kg) monotherapy.

Secondary objectives:

- To estimate the objective response rate (ORR) by modified International Myeloma Working Group (IMWG) criteria;
- To evaluate the effects of elotuzumab on electrocardiogram (ECG) intervals, including corrected QT (QTc) intervals;
- To estimate the 2-year PFS rate (Note: This objective will be presented after either all subjects have progressed or died or 2 years after the initiation of study therapy of the last subject enrolled, whichever comes first)

4.2.4 Study Description

4.2.4.1 Design

CA204004:

This is a phase 3, randomized, open-label trial of lenalidomide/dexamethasone with or without Elotuzumab.

CA204011:

This is a phase 2, open-label, biomarker study of elotuzumab monotherapy. Patients were enrolled for 2 cohorts and the 2 cohorts occurred in a sequential manner: the 20 mg/kg cohort followed by the 10 mg/kg cohort.

4.2.4.2 Controls

There were no placebo and positive (moxifloxacin) controls in both studies.

4.2.4.3 Blinding

The two studies were both open-label.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

CA204004:

There were two treatment arms:

- Lenalidomide/dexamethasone without elotuzumab (Ld).
- Lenalidomide/dexamethasone with elotuzumab (E-Ld).

Elotuzumab was administered as a 10 mg/kg (based on the subject's body weight assessed at each visit) IV infusion weekly during Cycles 1 and 2, and every 2 weeks during Cycle 3 and beyond.

Elotuzumab dose reductions were not permitted. Premedication with dexamethasone, an H1 blocker (diphenhydramine, 25-50 mg PO or IV, or equivalent), H2 blocker (ranitidine, 50 mg IV), and acetaminophen (650-1000 mg PO) was required 30-90 minutes prior to the elotuzumab infusion.

On weeks of elotuzumab dosing in the E-Ld group:

- Lenalidomide was administered at a dose of 25 mg PO QD for the first 3 weeks of the 4-week cycle on Days 1 – 21
- Dexamethasone was administered weekly as a split dose of 28 mg PO (3 - 24 hours prior to the start of elotuzumab infusion) + dexamethasone 8 mg IV (on the day of elotuzumab infusion at least 45 min prior to the start of infusion)

On weeks when elotuzumab was not administered,

- Lenalidomide was administered at a dose of 25 mg PO QD, Days 1 - 21 and

- Dexamethasone was administered at the weekly dose of 40 mg PO on Days 1, 8, 15, and 22.

For the Ld arm, lenalidomide was administered daily at a dose of 25 mg per os (PO) (Days 1-21) and dexamethasone was administered weekly at a dose of 40 mg PO on Days 1, 8, 15, and 22.

CA204011:

There were two cohorts:

- Elotuzumab 20 mg/kg
- Elotuzumab 10 mg/kg

20 mg/kg cohort: subjects received elotuzumab at 20 mg/kg/dose in 28-day cycles. In Cycle 1, elotuzumab was administered as an intravenous (IV) infusion on Days 1 and 8. In Cycle 2 and beyond, elotuzumab was administered as an IV infusion once monthly.

10 mg/kg cohort: subjects received elotuzumab at a dose of 10 mg/kg in 28-day cycles. In Cycles 1 and 2, elotuzumab was administered as an IV infusion weekly. In Cycles 3 and beyond, elotuzumab was administered every 2 weeks (twice monthly).

Elotuzumab dose reductions were not permitted. Premedication methylprednisolone (50 mg IV) was administered at least 45 minutes prior to the start of the elotuzumab infusion. Additionally, an H1 blocker (diphenhydramine, 25-50 mg PO or IV, or equivalent), H2 blocker (ranitidine 50 mg IV or equivalent), and acetaminophen (650 to 1000 mg po) or equivalent analgesic/antipyretic were also administered 30 to 90 minutes prior to elotuzumab infusion. Based on the severity of infusion reaction, 4 mg po dexamethasone or 8 mg po dexamethasone might be administered 3 to 24 hours before elotuzumab as an additional premedication.

In both studies, treatment with study drug continued until disease progression, unacceptable toxicity, or subject met other criteria for discontinuation of study drug.

4.2.5.2 Sponsor's Justification for Doses

In Study CA204011, elotuzumab will be administered to two cohorts of study subjects who receive different doses and schedules of elotuzumab. However, both regimens use 28 day cycles and have similar elotuzumab dose intensity. Both regimens have a loading period where elotuzumab is administered at 40 mg/kg per cycle (2 loading cycles for Cohort 2 and 1 loading cycle for Cohort 1) followed by continued administration at 20 mg/kg per cycle. This dose intensity was chosen because it matches the dose intensity in the cohort with the higher response rate in the phase 2 portion of study 1703. Testing two regimens which arrive at similar dose intensity in different ways will allow a preliminary evaluation of each regimen and inform subsequent development of elotuzumab without compromising the primary endpoint.

Cohort 1 will receive elotuzumab at a dose of 20 mg/kg on Days 1 and 8 during Cycle 1 followed by Day 1 only (every 4 weeks) beginning at Cycle 2. This is different than the schedule used in Study 1701 but will be identical (following loading doses in Cycle 1) to

the dose and schedule used after Cycle 18 in ELOQUENT-1, the study of lenalidomide/dexamethasone ± elotuzumab in previously untreated myeloma [CA204006 (NCT01335399)]. This monthly regimen was selected based on the following:

- 1) Patient and schedule considerations: Subjects do not have active myeloma and require fewer scheduled clinic visits. Therefore, selection of a monthly maintenance regimen is preferable to the twice monthly schedule administered in Study 1701.
- 2) Steroid dose: Monthly premedication using 50 mg methylprednisolone prior to infusion is unlikely to affect M protein levels, whereas high doses of steroids could have detectable antitumor activity.
- 3) Elotuzumab safety: In a randomized Phase 2 study (Study 1703), the incidence and severity of general AEs/serious adverse events (SAEs) and infusion-related AEs/SAEs were generally similar at both 10 mg/kg and 20 mg/kg doses of elotuzumab. In Phase 1 dose escalation of elotuzumab as monotherapy and in combination with bortezomib or lenalidomide, doses up to 20 mg/kg elotuzumab were well tolerated and a maximum tolerated dose (MTD) was not reached.
- 4) Elotuzumab dose: Based on modeling data (Figure 1.1.5-1; top), a dose of 20 mg/kg elotuzumab on Day 1 and Day 8 of Cycle 1 and then every 4 weeks starting in Cycle 2 will maintain elotuzumab trough levels above 70 µg/mL. A concentration of 70 µg/mL is the minimum trough concentration at which maximum efficacy was seen in preclinical studies and was sufficient to maintain saturation of CS1 in Study 1701 by elotuzumab (Figure 1.1.5- 2).

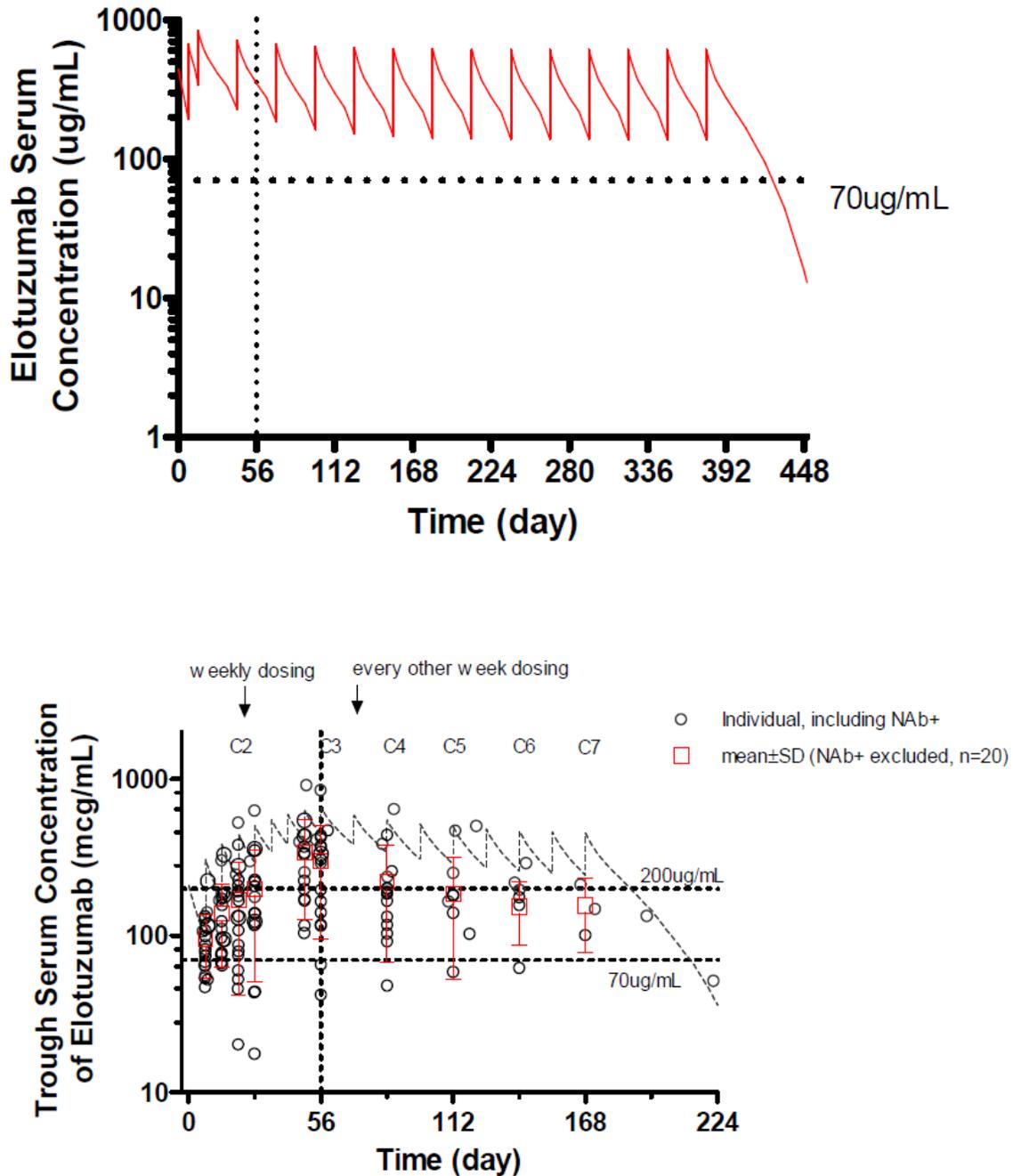
Cohort 2 will receive elotuzumab at a dose of 10 mg/kg weekly for Cycles 1 and 2 and then every 2 weeks starting in Cycle 3. Although the amount of elotuzumab infused per administration is 1/2 as much as in Cohort 1, the frequency of administration is generally twice that in Cohort 1. Therefore, except for the presence of two loading cycles (instead of one), the dose intensity of this regimen is the same as in Cohort 1. The schedule of elotuzumab administration is similar to study 1701 and identical to study 1703. Both the dose and schedule are identical to the first 18 cycles in ELOQUENT-1 and ELOQUENT-2, the phase 3 studies of lenalidomide/dexamethasone +/- elotuzumab [CA204-004 (NCT01239797) and CA204-006 (NCT01335399)]. This regimen was selected based on the following:

- 1) Patient and schedule considerations: Although requiring more frequent dosing than in Cohort 1, this dose and schedule demonstrated an 92% overall response rate in a Phase 2 trial of elotuzumab with lenalidomide and dexamethasone.
- 2) Steroid dose: Premedication prior to elotuzumab infusion using 50 mg methylprednisolone on this schedule remains well below the dose of steroids typically used for antitumor activity in smoldering myeloma (for example 40 mg dexamethasone Days 1 - 4 on a 28-day cycle³¹ and is unlikely to affect M protein levels.
- 3) Elotuzumab safety: This regimen uses elotuzumab below the maximally tolerated dose and has been previously characterized in a Phase I trial. (ref 1701 Zonder et al).
- 4) Elotuzumab dose: 10 mg/kg on the schedule defined will maintain elotuzumab trough levels above 70 µg/mL and provide near complete CS1 saturation. In the

Phase 2 portion of study 1703, 10 mg/kg had a higher response rate than 20 mg/kg on the same schedule.

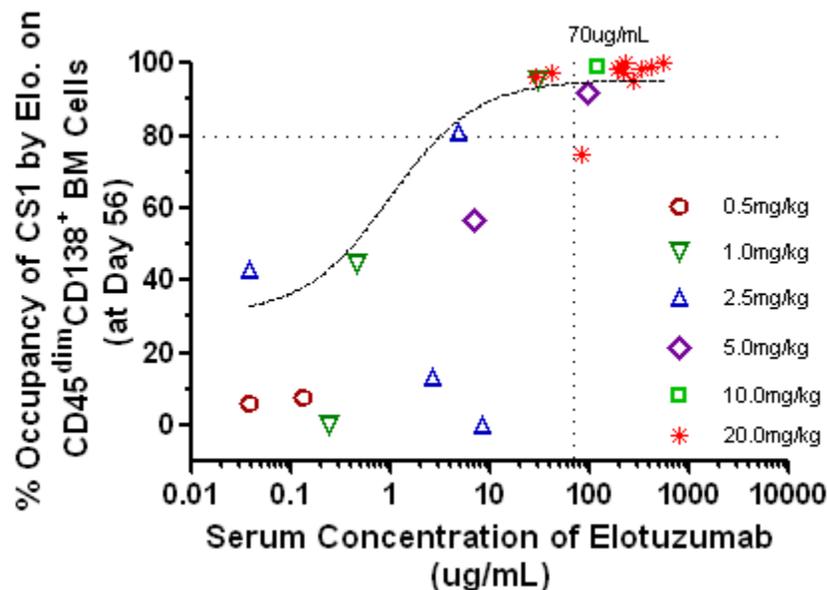
(Source: Applicant's Clinical Study Report Protocol CA204011)

Figure 1. Model predicted Elotuzumab serum concentrations for regimens in Cohort 1 (top), and for regimens in Cohort 2 overlaid with observed concentrations from 1703 study (bottom).



(Source: Sponsor's Clinical Study Report CA204011, Figure 1.1.5-1)

Figure 2. Saturation of CS1 Target on Bone Marrow Myeloma Samples from Subjects Treated in 1701



(Source: Sponsor’s Clinical Study Report, Figure 1.1.5-2)

Reviewer’s Comment: The studied doses appear reasonable to cover the anticipated therapeutic exposure.

4.2.5.3 Instructions with Regard to Meals

No instructions were given with regards to meals as elotuzumab is a product for IV administration.

Reviewer’s Comment: As the route of administration is IV, this appears reasonable.

4.2.5.4 ECG and PK Assessments

Electrocardiogram assessment for subjects treated with elotuzumab was added through amendments at selected sites for Study 204004. Day 1 of Cycle 1 had assessments at predose and immediately after the end of the elotuzumab infusion as well as 30 minutes and 2 hours post infusion on Day 1 of the cycle.

ECG and PK Assessments were to be collected according to the following schedule for Study 204011 (Table 3).

Table 3. PK, ADA, and ECG sampling schedule for Study 204011

Cycle Number	Study Day	Time (Event)	PK Collection	ADA Collection	ECG Measurement
1	1	-1.5 to -0.5 H (prior to pre-medication regimen administration)			X
		0 H (pre-dose)	X	X	X
		30 minutes post-end of infusion	X		X
		2 hours post-end of infusion	X		X
	8 ^a	0 H (pre-dose)	X		X
		2 hours post-end of infusion	X		X
2	1	0 H (pre-dose)	X	X	
3	1 ^b	0 H (pre-dose)	X	X	X
		30 minutes post-end of infusion	X		X
		2 hours post-end of infusion	X		X
4	1	0 H (pre-dose)	X	X	
6	1	0 H (pre-dose)	X	X	
9	1	0 H (pre-dose)	X	X	
12	1	0 H (pre-dose)	X	X	
15	1	0 H (pre-dose)	X	X	
18	1	0 H (pre-dose)	X	X	
-	-	End of Study/ Discontinuation	X	X	
-	-	30-Day Follow-up	X	X	
-	-	60-Day Follow-up	X	X	

^a If the Cycle 1 Day 8 elotuzumab dose is skipped, on Cycle 2 Day 1 follow the Cycle 1 Day 8 sampling schedule for PK collection and ECG measurement.

^b If the Cycle 3 Day 1 elotuzumab dose is skipped, on Cycle 4 Day 1 follow the Cycle 3 Day 1 sampling schedule for PK and ADA collection and ECG measurement.

(Source: Sponsor's Clinical Study Report CA204011, Table 5.5-1)

Reviewer's Comment: Given this is a monoclonal antibody with a half-life of 9 days, it appears reasonable to sample early (day 1) and later (day 8) during cycle 1.

4.2.5.5 Baseline

The average of QT/QTc values from after premedication and prior to elotuzumab infusion time points was used as baseline in both studies.

4.2.6 ECG Collection

Standard 12-Lead ECGs were obtained while subjects were recumbent in both studies.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

CA204004:

A total of 646 patients were randomized to receive E-Ld or Ld. Of the 646 randomized patients, 318 patients were treated with E-Ld and 317 patients were treated with Ld. Overall, 10 patients from E-Ld group participated in the optional ECG substudy.

The average age of the 10 participants was 68 years ranging from 56 to 76 years. The majority were white (90.0%) and were females (60.0%).

CA204011:

A total of 31 patients received elotuzumab at 20 mg/kg (N=15) or 10 mg/kg (N=16). All of the 31 patients were included in the ECG dataset and the PK dataset.

The average age of the 31 patients was 59 years ranging from 39 to 75 years. Most patients (74.2%) were <65 years of age. The majority were white (93.5%) and were males (54.8%).

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

CA204004:

The Δ QTcF interval after elotuzumab infusion on Day 1 of Cycle 1 and Day 22 of Cycle 2 was < 10 msec compared to pre-dose values, and was associated with a large degree of variability (range of Δ QTcF was -12.3 to 56 msec).

Δ QTcF values after pre-medication and prior to elotuzumab infusion (pre-dose) on Days 1 and 8 of Cycle 1, Day 22 of Cycle 2, and Day 1 of Cycle 3 were somewhat prolonged compared to baseline. Elotuzumab infusion did not appreciably prolong the QTc interval further.

CA204011:

At all timepoints when ECG measurements were made, there was no trend in QTcF or Δ QTcF at both dose levels. Most mean Δ QTcF changes over time did not exceed 5 msec. A direct comparison of Δ QTcF during Cycle 1, Days 1 and 8, where there was no impact of differing dosing regimens between the groups, showed that higher elotuzumab concentrations after 20 mg/kg treatment were associated with smaller and negative changes in Δ QTcF. Changes in QTcF were larger after treatment with 10 mg/kg but were associated with large variability and lability.

The sponsor's results for primary analysis are displayed in the following Table 4 and Table 5.

**Table 4: QTcF Interval Summary Statistics by Dose, Day and Time Within Day
(Sponsor's Results for Study CA204004)**

Cycle	Day	Time	Mean QTcF (msec) (SD)	Mean ΔQTcF ^a (msec) (SD)
1	1	-1.0 hour ^b	404.21 (28.51)	-
		0 Hour (predose)	418.89 (31.43)	-
		Baseline	410.52 (28.46)	-
		end-of-infusion	416.27 (30.59)	5.75 (19.36)
		30 minutes post infusion	414.78 (27.40)	7.23 (17.02)
		2 hours post infusion	416.30 (27.17)	8.76 (18.38)
8	8	-1.0 hour ^b	422.82 (30.20)	12.30 (20.14)
		Baseline, 0 Hour (predose)	428.93 (25.19)	18.41 (12.30)
2	22	-1.0 hour ^b	419.94 (21.93)	12.99 (18.46)
		0 Hour (predose)	436.23 (24.58)	29.27 (22.94)
		end-of-infusion	435.29 (23.87)	28.33 (23.14)
		2 hours post infusion	430.73 (21.13)	23.77 (20.36)
3	1	-1.0 hour ^b	408.40 (22.04)	-2.21 (24.15)
		0 Hour (predose)	419.59 (25.79)	14.91 (13.83)

Source: Table S.7.10, Table S.7.11

^a Mean delta QTcF was calculated by subtracting the baseline ECG (which was defined to be the average of the measurements obtained between the two time points: -1.0 and 0 H prior to the first dose of elotuzumab on Cycle 1 Day 1) from the post elotuzumab infusion value

^b prior to medication

Source: sponsor's clinical study report CA204004, Table 8.10.1-1, page 160

**Table 5: QTcF Interval Summary Statistics by Dose, Day and Time Within Day - All Treated Subjects with Baseline and at Least One On-Treatment ECG Measurement
(Sponsor's Results for Study CA204011)**

Day	Time	2.0 mg/kg			1.0 mg/kg			Total		
		Mean QTcF, msec (SD)	Mean ΔQTcF, msec (SD)	N	Mean QTcF, msec (SD)	Mean ΔQTcF, msec (SD)	N	Mean QTcF, msec (SD)	Mean ΔQTcF, msec (SD)	N
Cycle 1 Day 1	Predose ^a	424.95 (18.002)	NA	15	414.80 (13.603)	NA	16	419.71 (16.441)	NA	31
	30 min post EOI	427.67 (17.676)	2.72 (12.017)	15	423.11 (25.869)	8.31 (23.567)	16	425.32 (22.040)	5.61 (18.793)	31
	2 hr post EOI	419.89 (17.397)	-5.68 (15.706)	14	425.19 (26.763)	10.39 (23.091)	16	422.72 (22.658)	2.89 (21.281)	30
	2 hr post EOI	418.30 (21.797)	-6.65 (15.167)	15	413.37 (20.125)	-1.43 (11.274)	16	415.75 (20.748)	-3.95 (13.339)	31
Cycle 1 Day 8	2 hr post EOI	418.70 (23.768)	-6.25 (14.536)	15	424.78 (20.218)	9.98 (13.500)	16	421.84 (21.853)	2.13 (16.051)	31
	Predose	NA	NA	NA	419.30 (17.695)	4.50 (13.605)	16	419.30 (17.695)	4.50 (13.605)	16
Cycle 3, Day 1	Predose	421.39 (25.325)	-3.55 (15.004)	15	412.86 (20.095)	-1.94 (16.028)	16	416.99 (22.804)	-2.72 (15.302)	31
	30 min post EOI	418.60 (25.212)	-6.96 (12.805)	14	423.85 (17.529)	8.66 (13.316)	15	421.31 (21.351)	1.12 (15.097)	29
	2 hr post EOI	420.44 (25.493)	-5.13 (13.769)	14	421.63 (19.662)	6.45 (15.274)	15	421.06 (22.258)	0.86 (15.470)	29
	Predose	NA	NA	NA	415.53 (18.141)	0.73 (19.312)	16	415.53 (18.141)	0.73 (19.312)	16

Source: Table S.7.10 and Table S.7.15

Abbreviations: QTcF = corrected QT interval, Fridericia formula; EOI = end of infusion; NA = not applicable.

Source: sponsor's clinical study report CA204011, Table 8.8.1.1-1, page 88

Reviewer's Comments: Please the reviewer's analysis in section 5.2.

4.2.7.2.2 Assay Sensitivity

Not Applicable

4.2.7.2.3 Categorical Analysis

CA204004:

A formal categorical analysis was not done for this ECG substudy due to the small number of participating subjects.

- Overall, no subject had an uncorrected QT interval or a QTcF interval > 480 ms during the study. No subject had a Δ QTcF > 60 ms; 5 subjects had Δ QTcF values \geq 30 ms.
- Few subjects had a PR interval > 200 ms or a QRS interval > 110 ms during the study. No subject had a Δ PR or Δ QRS > 25% compared to baseline.

CA204011:

Few subjects had QTcF intervals or Δ QTcF that exceeded the pre-specified ranges considered borderline or prolonged. No subject had a QTcF interval >480 ms or a Δ QTcF >60 ms. Five subjects (2 subjects in the 20 mg/kg cohort and 3 subjects in the 10 mg/kg cohort) had a QTcF between 450 to 480 ms. Three subjects in the 10 mg/kg cohort had a Δ QTcF between 30 to 60 ms.

4.2.7.3 Safety Analysis

CA204004:

The safety profile showed that elotuzumab treatment in subjects with relapsed or refractory myeloma was well-tolerated; demonstrating that elotuzumab can be safely administered in combination with Ld.

- No subject that participated in the ECG substudy had an AE that was thought to be potentially related to an abnormal ECG finding. One subject that participated in the ECG substudy had an SAE of Grade 3 syncope during Cycle 13. No ECG was recorded closely preceding or after the event. The event was considered unrelated to study drug by the investigator. During the ECG substudy, the subject had QTc intervals that were all < 470 ms.
- No event was determined to be associated with an abnormal ECG finding potentially related to proarrhythmia.
- A total of 210 (33.1%) deaths occurred (during treatment and during follow-up after study therapy), 94 subjects (29.6%) in the E-Ld group and 116 subjects (36.6%) in the Ld group. The primary cause of death in either treatment group was disease. A total of 11 deaths occurred due to study drug toxicity, 5 subjects (1.6%) treated with E-Ld and 6 (1.9%) subjects treated with Ld.

- Serious adverse events (regardless of relationship) of any grade were reported for 208 subjects (65.4%) treated with E-Ld and for 179 subjects (56.5%) treated with Ld. SAEs of infection of any grade were reported in 31.1% of E-Ld subjects and 25.2% of Ld subjects.
- Treatment-emergent AEs leading to discontinuation of at least 1 study medication, regardless of causality, occurred in similar proportions of subjects in both treatment groups (26.1% in the E-Ld group and 26.8% in Ld group).

CA204011:

The safety profile of elotuzumab treatment in subjects with smoldering myeloma was acceptable, demonstrating that elotuzumab 20 mg/kg or elotuzumab 10 mg/kg can be safely administered as monotherapy.

- Elotuzumab was not associated with clinically meaningful dose or concentration-dependent changes in ECG intervals after administration of 10 or 20 mg/kg. No subject had an AE that was considered related to ECG findings.
- No deaths were reported in this study.
- SAEs regardless of causality were reported in 6 subjects in each cohort (40.0%, in the 20 mg/kg cohort and 37.5% in the 10 mg/kg cohort). Pneumonia was the only SAE reported in more than 1 subject (1 subject [6.7%] in the 20 mg/kg cohort and 1 subject [6.3%] in the 10 mg/kg cohort).
- Adverse events leading to discontinuation of study drug, regardless of causality, were reported in 5 of 31 treated subjects (4 of 15, 26.7%, in the 20 mg/kg cohort and 1 of 16, 6.3%, in 10 mg/kg cohort).
- Three (20.0%) of 15 subjects in the 20 mg/kg cohort and 1 (6.3%) of 16 subjects in the 10 mg/kg cohort experienced 1 or more infusion reactions. No subject discontinued study treatment due to an infusion reaction.
- Two subjects in the 10 mg/kg cohort had second primary malignancies: 1 subject with renal cell carcinoma and 1 subject with prostate cancer.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The elotuzumab PK results are presented in Table 6 and Table 7. As demonstrated on Cycle 3 Day 1, both regimen achieved similar therapeutic exposure at the steady state.

Table 6. Summary Statistics of Elotuzumab Concentration by Visit (20 mg/kg, Study 204011).

Treatment Group: Elo-20mg/kg

Visit	Planned Collection Timepoint	N	Concentration (ug/mL)						
			Mean	SD	Geo. Mean	Median	%CV	Min	Max
CYCLE 1 DAY 1	PREDOSE	15							
	30MIN	15	450.560	84.3166	443.810	433.453	18.7	344.21	667.53
	2H	14	434.127	76.4066	427.495	438.820	17.6	293.72	537.57
CYCLE 1 DAY 8	PREDOSE	15	175.720	102.3296	154.993	172.676	58.2	55.72	504.96
	2H	14	593.127	189.2881	554.233	631.985	31.9	171.58	870.51
CYCLE 2 DAY 1	PREDOSE	15	106.494	53.2115	85.162	128.402	50.0	6.95	189.08
CYCLE 3 DAY 1	PREDOSE	14	83.416	62.1128	44.464	87.963	74.5	0.53	201.78
	30MIN	14	532.668	143.2201	514.410	524.416	26.9	313.56	830.66
	2H	14	508.985	126.7734	493.137	533.232	24.9	302.13	739.92
CYCLE 4 DAY 1	PREDOSE	14	75.440	69.6093	31.502	57.160	92.3	0.52	209.28
CYCLE 6 DAY 1	PREDOSE	13	84.276	77.9887	31.238	57.425	92.5	0.10	250.24
CYCLE 9 DAY 1	PREDOSE	10	91.821	73.4883	57.414	68.376	80.0	5.50	226.26
CYCLE 12 DAY 1	PREDOSE	10	93.083	72.0487	50.579	69.333	77.4	0.63	224.83
CYCLE 15 DAY 1	PREDOSE	9	79.925	59.3364	50.840	88.311	74.2	4.43	186.94
CYCLE 18 DAY 1	PREDOSE	8	85.383	47.4767	73.030	77.669	55.6	30.95	145.42
END OF TREATMENT	OFF TREATMENT	3	4.174	6.2986	1.027	0.998	150.9	0.10	11.43
30 DAY FOLLOW-UP POST END OF TREATMENT	OFF TREATMENT	4	16.246	20.3307	1.712	11.288	125.1	0.10	42.31

Table 7. Summary Statistics of Elotuzumab Concentration by Visit (10 mg/kg, Study 204011).

Treatment Group: Elo-10mg/kg

Visit	Planned Collection Timepoint	N	Concentration (ug/mL)						
			Mean	SD	Geo. Mean	Median	%CV	Min	Max
CYCLE 1 DAY 1	PREDOSE	16							
	30MIN	16	223.117	47.5465	219.367	216.777	21.3	160.84	382.84
	2H	16	213.500	36.8341	210.740	213.444	17.3	168.35	311.87
CYCLE 1 DAY 8	PREDOSE	16	79.977	18.0933	78.043	81.752	22.6	51.58	122.62
	2H	16	320.023	57.8694	315.503	296.953	18.1	247.53	453.73
CYCLE 1 DAY 15	PREDOSE	16	141.968	40.1964	136.936	132.443	28.3	90.93	216.65
CYCLE 2 DAY 1	PREDOSE	16	225.017	66.4587	216.185	200.897	29.5	142.81	344.29
CYCLE 2 DAY 15	PREDOSE	16	263.272	106.3259	246.956	227.706	40.4	148.64	565.34
CYCLE 3 DAY 1	PREDOSE	15	292.228	118.3831	274.887	253.712	40.5	153.58	640.14
	30MIN	15	492.829	118.9015	480.652	443.833	24.1	333.74	773.02
	2H	15	536.609	155.3717	518.035	503.945	29.0	354.75	903.30
CYCLE 3 DAY 15	PREDOSE	16	229.256	142.3622	199.751	188.440	62.1	87.96	682.69
CYCLE 4 DAY 1	PREDOSE	14	208.487	131.1039	176.985	192.627	62.9	63.28	574.17
CYCLE 6 DAY 1	PREDOSE	14	173.032	110.0308	143.395	160.114	63.6	47.03	407.29
CYCLE 9 DAY 1	PREDOSE	12	146.715	92.8128	117.281	123.785	63.3	15.75	340.08
CYCLE 12 DAY 1	PREDOSE	10	152.630	93.5236	129.675	129.547	61.3	60.43	345.25
CYCLE 15 DAY 1	PREDOSE	5	91.644	57.8196	75.924	75.585	63.1	26.98	171.94
END OF TREATMENT	OFF TREATMENT	3	29.998	35.6606	8.686	19.904	118.9	0.47	69.62

4.2.7.4.2 Exposure-Response Analysis

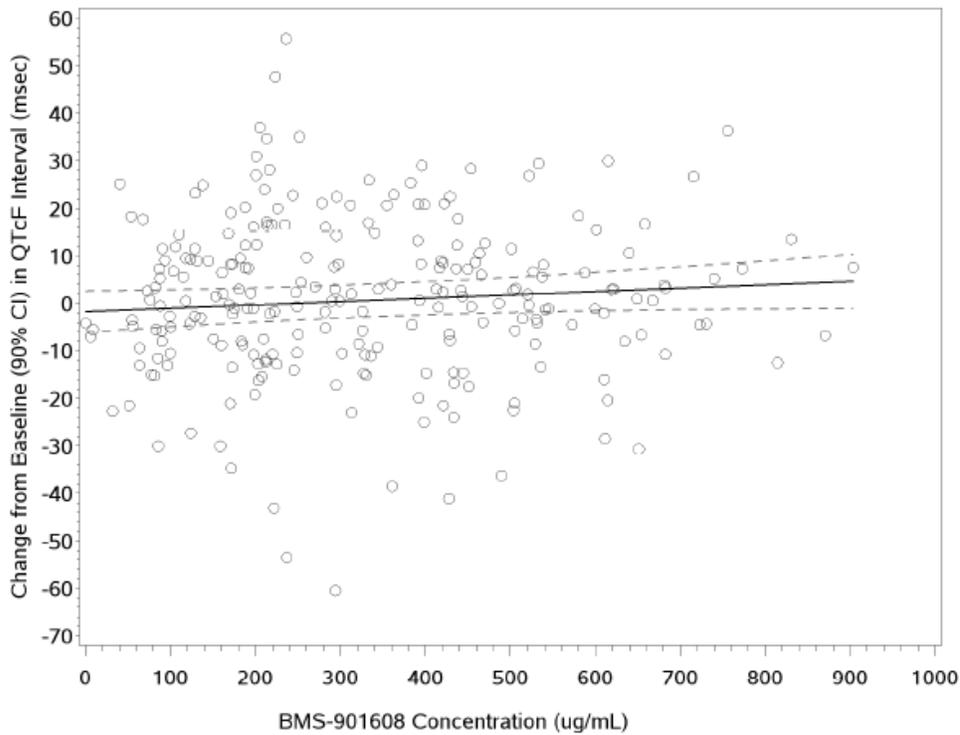
General linear mixed models were considered to model the potential increase of QTcF change from baseline (ms) with plasma concentration (ug/mL) (data matched by time). The compound-symmetry variance-covariance matrix was used to model the correlation among the repeated measures from the same subject. The model with both the random intercept and random slope was not appropriate because the variance-covariance (G)

matrix of the random effects was not positive definite. The model with only the random intercepts (but fixed slope) was not appropriate because the Hessian of the likelihood function was not positive definite. The model with only random slopes (but fixed intercept) was not function did not converge. The final model contains only the fixed effects, which appears appropriate given that the corresponding residuals showed randomness with no systemic pattern. The final fitted model is:

$$\text{QTcF change from baseline (ms)} = -1.7532 + 0.0071 * \text{Plasma Concentration (ug/mL)}$$

The 90% confidence interval of the slope coefficient (0.0071) includes zero, and therefore there is no strong evidence that QTcF increases with plasma concentration in this study (Figure 3). Moreover, the upper limit of the 90% CI for mean change in QTcF was less than 10 msec over the range of observed elotuzumab concentrations.

Figure 3. Concentration-QTcF Relationship Modeling of all ECG Evaluable Subjects.



Parameter	Estimate	SE	90% Confidence Interval		p-value
Intercept	-1.7532	2.6264	-6.2110	2.7046	0.5095
Slope	0.0071	0.0048	-0.0009	0.0150	0.1424

Model: Fixed coefficients repeated measures linear model, where the concentration is the explanatory variable. The bold solid line represents the estimated population average and dashed lines represent corresponding 2-sided 90% confidence interval for the true population average.

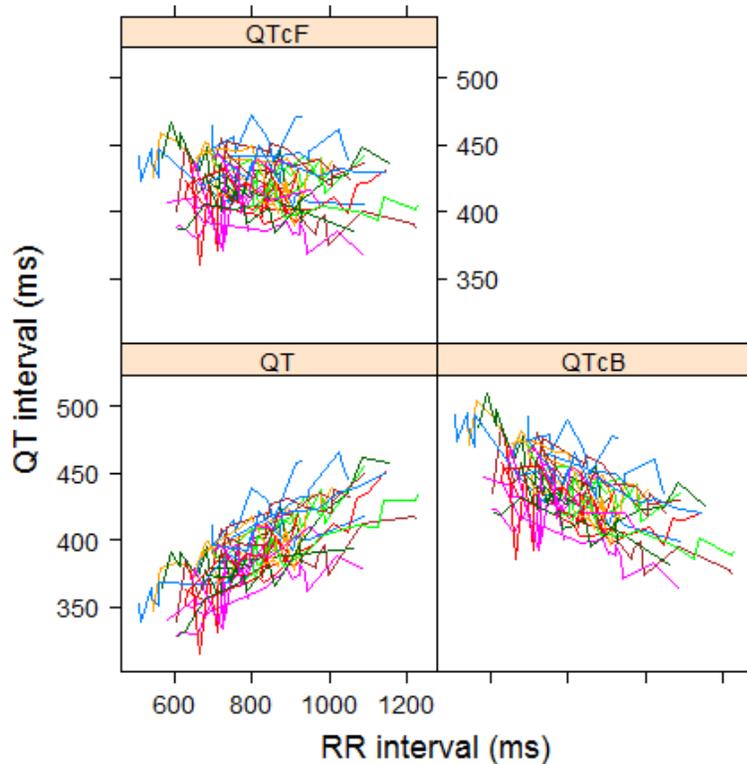
Reviewer's Analysis: A plot of ΔQTc vs. drug concentrations is presented in Figure 7. The sponsor's analysis is consistent with the reviewer's analysis.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 4. This statistical reviewer used QTcF for the primary statistical analysis.

Figure 4: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for E-Ld and Elotuzumab

The primary endpoint is the mean change from baseline in QTcF (Δ QTcF). The descriptive statistics are listed in the following tables.

Large QTc prolongation effect was observed after premedication and prior to elotuzumab infusion in study CA204004, but elotuzumab infusion did not further prolong QTc. For study CA204011, the largest mean change from baseline in QTcF (Δ QTcF) was 10.4 ms with a 90% CI of 0.3 ms to 20.5 ms. The value occurred at 2 hours after end of infusion in the elotuzumab 10-mg/kg IV group and was associated with large variation.

Table 8: Analysis Results of Δ QTcF for E-Ld (Study CA204004)

Cycle	Day	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)
1	1	-1 Hour	9	404.2 (28.5)		
		0 Hour (predose)	10	418.9 (31.4)		
		Baseline	10	410.5 (28.5)		
		EOI	10	416.3 (30.6)	5.7 (19.4)	(-5.5, 17.0)
		0.5 Hour Post EOI	9	414.8 (27.4)	7.2 (17.0)	(-3.3, 17.8)
		2 Hour Post EOI	9	416.3 (27.2)	8.8 (18.4)	(-2.6, 20.1)
	8	-1 Hour	10	422.8 (30.2)	12.3 (20.1)	(0.6, 24.0)
		0 Hour (predose)	10	428.9 (25.2)	18.4 (12.3)	(11.3, 25.5)
2	22	-1 Hour	7	419.9 (21.9)	13.0 (18.5)	(-0.6, 26.5)
		0 Hour (predose)	7	436.2 (24.6)	29.3 (22.9)	(12.4, 46.1)
		EOI	7	435.3 (23.9)	28.3 (23.1)	(11.3, 45.3)
		2 Hour Post EOI	7	430.7 (21.1)	23.8 (20.4)	(8.8, 38.7)
3	1	-1 Hour	9	408.4 (22.0)	-2.2 (24.1)	(-17.2, 12.8)
		0 Hour (predose)	8	419.6 (25.8)	14.9 (13.8)	(5.6, 24.2)

**Table 9: Analysis Results of Δ QTcF for Treatment Group =
Elotuzumab 10 mg/kg IV (Study CA204011)**

Cycle	Day	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)
1	1	Predose	16	414.8 (13.6)		
		0.5 Hour Post EOI	16	423.1 (25.9)	8.3 (23.6)	(-2.0, 18.6)
		2 Hour Post EOI	16	425.2 (26.8)	10.4 (23.1)	(0.3, 20.5)
	8	Predose	16	413.4 (20.1)	-1.4 (11.3)	(-6.4, 3.5)

Cycle	Day	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)
		2 Hour Post EOI	16	424.8 (20.2)	10.0 (13.5)	(4.1, 15.9)
	15	Predose	16	419.3 (17.7)	4.5 (13.6)	(-1.5, 10.5)
3	1	Predose	16	412.9 (20.1)	-1.9 (16.0)	(-9.0, 5.1)
		0.5 Hour Post EOI	15	423.8 (17.5)	8.7 (13.3)	(2.6, 14.7)
		2 Hour Post EOI	15	421.6 (19.7)	6.4 (15.3)	(-0.5, 13.4)
	15	Predose	16	415.5 (18.1)	0.7 (19.3)	(-7.7, 9.2)

**Table 10: Analysis Results of Δ QTcF for Treatment Group =
Elotuzumab 20 mg/kg IV (Study CA204011)**

Cycle	Day	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)
1	1	Predose	15	424.9 (18.0)		
		0.5 Hour Post EOI	15	427.7 (17.7)	2.7 (12.0)	(-2.7, 8.2)
		2 Hour Post EOI	14	419.9 (17.4)	-5.7 (15.7)	(-13.1, 1.8)
	8	Predose	15	418.3 (21.8)	-6.6 (15.2)	(-13.5, 0.3)
		2 Hour Post EOI	15	418.7 (23.8)	-6.2 (14.5)	(-12.9, 0.4)
3	1	Predose	15	421.4 (25.3)	-3.6 (15.0)	(-10.4, 3.3)
		0.5 Hour Post EOI	14	418.6 (25.2)	-7.0 (12.8)	(-13.0, -0.9)
		2 Hour Post EOI	14	420.4 (25.5)	-5.1 (13.8)	(-11.6, 1.4)

**Table 11: Analysis Results of Δ QTcF for Elotuzumab
10 mg/kg IV and 20 mg/kg IV Combined (Study CA204011)**

Cycle	Day	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)
1	1	Predose	31	419.7 (16.4)		

Cycle	Day	Time	N	QTcF (ms) (SD)	Δ QTcF (ms) (SD)	Δ QTcF 90% CI (ms)
		0.5 Hour Post EOI	31	425.3 (22.0)	5.6 (18.8)	(-0.1, 11.3)
		2 Hour Post EOI	30	422.7 (22.7)	2.9 (21.3)	(-3.7, 9.5)
	8	Predose	31	415.8 (20.7)	-4.0 (13.3)	(-8.0, 0.1)
		2 Hour Post EOI	31	421.8 (21.9)	2.1 (16.1)	(-2.8, 7.0)
	15	Predose	16	419.3 (17.7)	4.5 (13.6)	(-1.5, 10.5)
3	1	Predose	31	417.0 (22.8)	-2.7 (15.3)	(-7.4, 1.9)
		0.5 Hour Post EOI	29	421.3 (21.4)	1.1 (15.1)	(-3.7, 5.9)
		2 Hour Post EOI	29	421.1 (22.3)	0.9 (15.5)	(-4.0, 5.7)
	15	Predose	16	415.5 (18.1)	0.7 (19.3)	(-7.7, 9.2)

5.2.1.2 Assay Sensitivity Analysis

Not Applicable.

5.2.1.3 Graph of Δ QTcF Over Time

The following figures display the time profile of Δ QTcF for different treatment groups in the two studies.

Figure 5: Mean and 90% CI Δ QTcF Timecourse (Study CA204004)

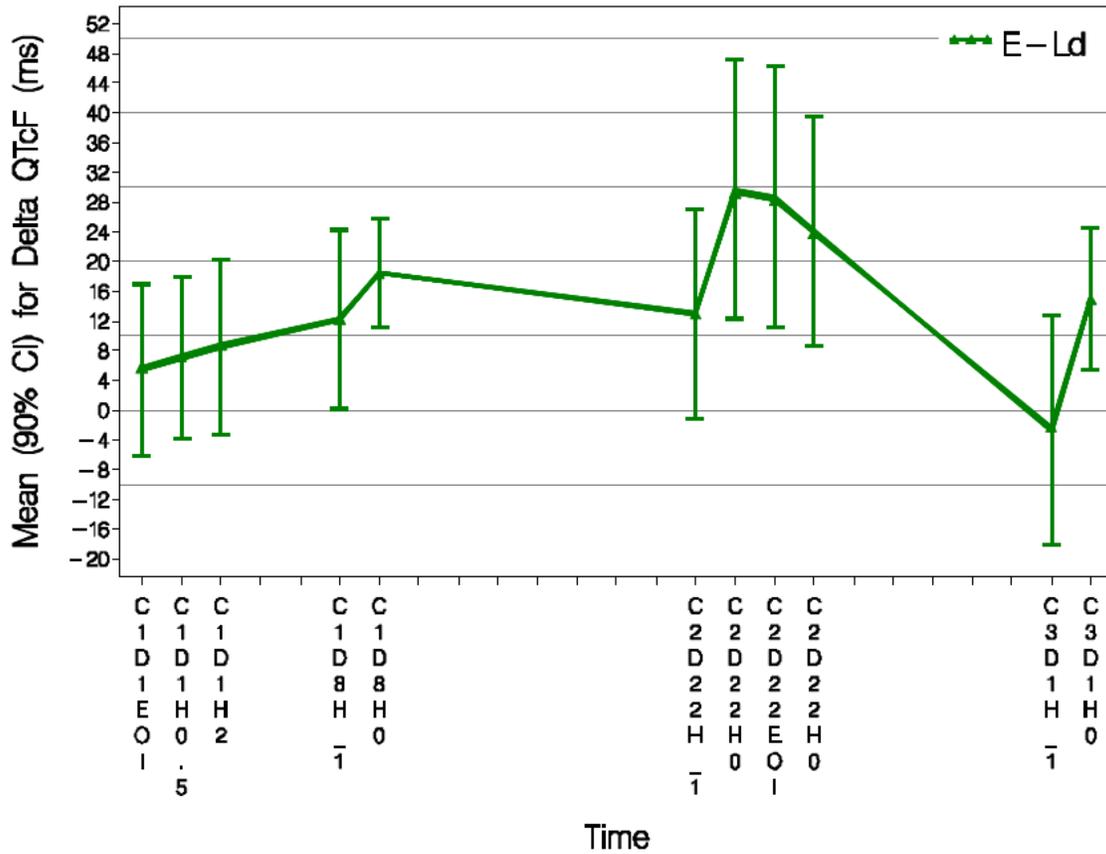
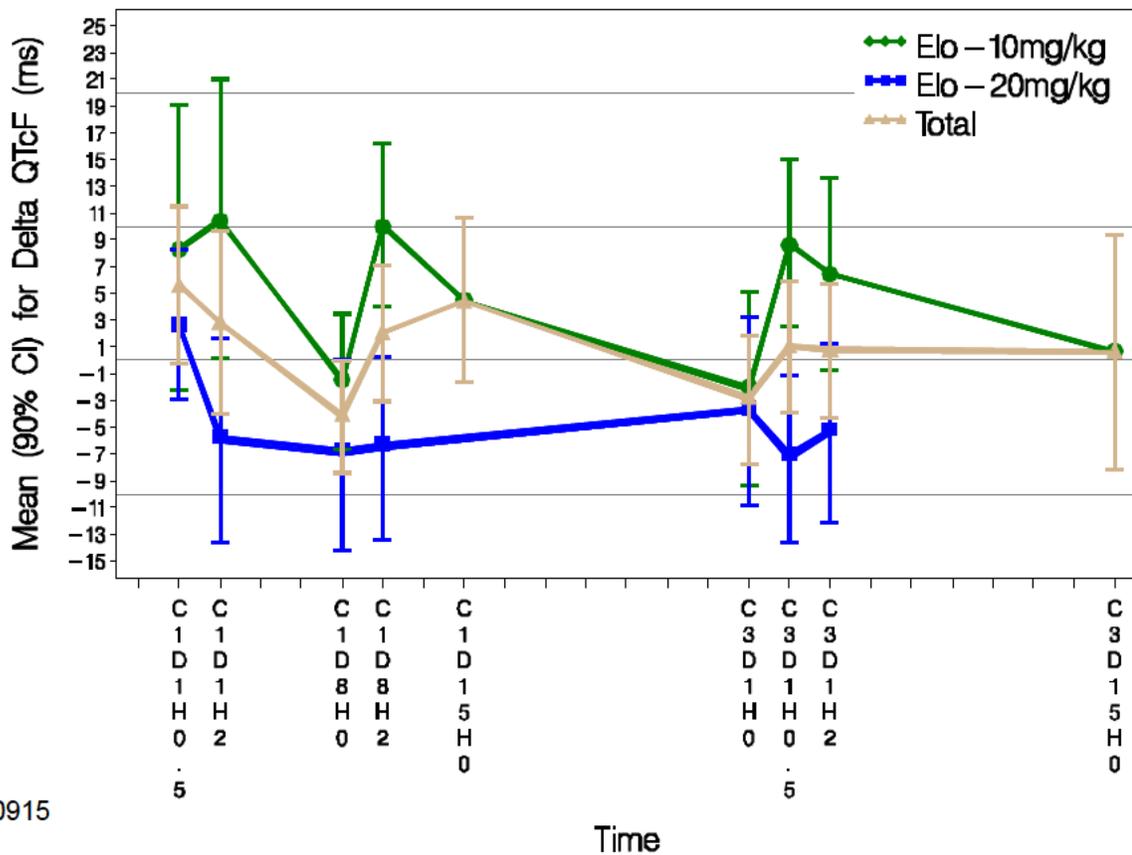


Figure 6: Mean and 90% CI Δ QTcF Timecourse (Study CA204011)



5.2.1.4 Categorical Analysis

Table 12 and Table 13 list the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 12: Categorical Analysis for QTcF (Study CA204004)

Treatment Group	Total N		QTcF \leq 450 ms		450<QTcF \leq 480 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	10	10	9 (90.0%)	9 (90.0%)	1 (10.0%)	1 (10.0%)
Post Baseline	10	93	6 (60.0%)	82 (88.2%)	4 (40.0%)	11 (11.8%)

Table 13: Categorical Analysis for QTcF (Study CA204011)

Treatment Group	Total N		QTcF \leq 450 ms		450<QTcF \leq 480 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	31	31	30 (96.8%)	30 (96.8%)	1 (3.2%)	1 (3.2%)
Elo-10mg/kg	16	142	13 (81.3%)	137 (96.5%)	3 (18.8%)	5 (3.5%)
Elo-20mg/kg	15	102	13 (86.7%)	95 (93.1%)	2 (13.3%)	7 (6.9%)

Table 14 and Table 15 list the categorical analysis results for Δ QTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 14: Categorical Analysis of Δ QTcF (Study CA204004)

Treatment Group	Total N		Δ QTcF \leq 30 ms		30< Δ QTcF \leq 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Post Baseline	10	93	6 (60.0%)	75 (80.6%)	4 (40.0%)	18 (19.4%)

Table 15: Categorical Analysis of Δ QTcF (Study CA204011)

Treatment Group	Total N		Δ QTcF \leq 30 ms		30< Δ QTcF \leq 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Elo-10mg/kg	16	142	13 (81.3%)	135 (95.1%)	3 (18.8%)	7 (4.9%)
Elo-20mg/kg	15	102	15 (100%)	102 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The primary endpoint is the mean change from baseline in HR (Δ HR). The point estimates and the 90% confidence intervals are presented in Table 16 and Table 17. An HR increasing effect was observed in study CA204011.

The outlier analysis results for HR are presented in Table 18 and Table 19.

Table 16: Analysis Results of Δ HR for E-Ld (Study CA204004)

Cycle	Day	Time	N	HR (bpm) (SD)	Δ HR (bpm) (SD)	Δ HR 90% CI (bpm)
1	1	-1 Hour	9	76.4 (10.5)		
		0 Hour (predose)	10	75.0 (8.6)		
		Baseline	10	74.5 (10.3)		
		EOI	10	75.9 (10.2)	1.4 (10.3)	(-4.6, 7.4)
		0.5 Hour Post EOI	9	73.6 (8.0)	0.5 (9.9)	(-5.6, 6.6)
		2 Hour Post EOI	9	80.1 (12.2)	7.0 (14.9)	(-2.2, 16.2)
	8	-1 Hour	10	75.2 (6.9)	0.7 (11.0)	(-5.7, 7.1)
		0 Hour (predose)	10	68.4 (5.3)	-6.1 (12.0)	(-13.1, 0.8)
2	22	-1 Hour	7	69.2 (7.5)	-4.2 (15.1)	(-15.3, 6.9)
		0 Hour (predose)	7	66.7 (5.5)	-6.7 (14.9)	(-17.6, 4.2)
		EOI	7	65.3 (11.1)	-8.1 (17.1)	(-20.6, 4.4)
		2 Hour Post EOI	7	69.2 (8.5)	-4.2 (15.2)	(-15.4, 7.0)
3	1	-1 Hour	9	69.5 (10.6)	-5.5 (12.2)	(-13.0, 2.1)
		0 Hour (predose)	8	69.6 (13.7)	-4.8 (17.6)	(-16.5, 7.0)

Table 17: Analysis Results of Δ HR for Elotuzumab (10mg/kg IV and 20 mg/kg IV) (Study CA204011)

Cycle	Day	Time	Elo-10mg/kg		Elo-20mg/kg		Total	
			N	Δ HR 90% CI (bpm)	N	Δ HR 90% CI (bpm)	N	Δ HR 90% CI (bpm)
1	1	Predose	16		15		31	
		0.5 Hour Post EOI	16	19.9 (16.5, 23.4)	15	13.9 (10.1, 17.6)	31	17.0 (14.4, 19.6)
		2 Hour Post EOI	16	18.5 (14.2, 22.9)	14	17.2 (13.8, 20.6)	30	17.9 (15.2, 20.6)

			Elo-10mg/kg		Elo-20mg/kg		Total	
Cycle	Day	Time	N	Δ HR 90% CI (bpm)	N	Δ HR 90% CI (bpm)	N	Δ HR 90% CI (bpm)
	8	Predose	16	-0.1 (-3.9, 3.7)	15	-2.3 (-5.4, 0.7)	31	-1.2 (-3.5, 1.2)
		2 Hour Post EOI	16	12.9 (8.2, 17.6)	15	7.1 (4.4, 9.8)	31	10.1 (7.3, 12.9)
	15	Predose	16	-0.2 (-3.0, 2.6)	.		16	-0.2 (-3.0, 2.6)
3	1	Predose	16	1.8 (-2.5, 6.1)	15	-5.9 (-9.7, -2.1)	31	-1.9 (-4.9, 1.0)
		0.5 Hour Post EOI	15	11.1 (6.0, 16.2)	14	4.3 (0.5, 8.1)	29	7.8 (4.5, 11.0)
		2 Hour Post EOI	15	11.5 (6.5, 16.5)	14	5.1 (0.9, 9.4)	29	8.4 (5.1, 11.7)
	15	Predose	16	-1.4 (-5.3, 2.6)	.		16	-1.4 (-5.3, 2.6)

Table 18: Categorical Analysis for HR (Study CA204004)

	Total N	HR≤100 bpm	HR>100 bpm	HR>45 bpm	HR≤45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	10	10 (100%)	0 (0.0%)	10 (100%)	0 (0.0%)
Post Baseline	10	9 (90.0%)	1 (10.0%)	10 (100%)	0 (0.0%)

Table 19: Categorical Analysis for HR (Study CA204011)

	Total N	HR≤100 bpm	HR>100 bpm	HR>45 bpm	HR≤45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	31	31 (100%)	0 (0.0%)	31 (100%)	0 (0.0%)
Elo-10mg/kg	16	14 (87.5%)	2 (12.5%)	16 (100%)	0 (0.0%)
Elo-20mg/kg	15	13 (86.7%)	2 (13.3%)	15 (100%)	0 (0.0%)

5.2.3 PR Analysis

The primary endpoint is the mean change from baseline in PR (Δ PR). The point estimates and the 90% confidence intervals are presented in Table 20 and Table 21. The largest mean change from baseline in PR was 6.5 ms and there was no trend for Δ PR.

The outlier analysis results for PR are presented in Table 22 and Table 23.

Table 20: Analysis Results of Δ PR for E-Ld (Study CA204004)

Cycle	Day	Time	N	PR (ms) (SD)	Δ PR (ms) (SD)	Δ PR 90% CI (ms)
1	1	-1 Hour	9	162.7 (23.7)		
		0 Hour (predose)	10	165.3 (25.1)		
		Baseline	10	163.1 (23.8)		
		EOI	10	166.9 (22.1)	3.8 (10.2)	(-2.1, 9.7)
		0.5 Hour Post EOI	9	163.1 (20.9)	4.6 (9.3)	(-1.1, 10.4)
		2 Hour Post EOI	9	161.0 (23.1)	2.5 (7.7)	(-2.2, 7.3)
8		-1 Hour	10	161.7 (23.6)	-1.4 (7.9)	(-6.0, 3.1)
		0 Hour (predose)	10	163.5 (23.0)	0.4 (7.8)	(-4.1, 5.0)
2	22	-1 Hour	7	156.4 (14.3)	-6.8 (10.8)	(-14.7, 1.2)
		0 Hour (predose)	7	164.8 (14.6)	1.7 (10.1)	(-5.7, 9.2)
		EOI	7	161.4 (19.4)	-1.7 (9.7)	(-8.8, 5.4)
		2 Hour Post EOI	7	163.2 (20.6)	0.1 (3.6)	(-2.5, 2.8)
3	1	-1 Hour	9	163.1 (17.5)	-2.8 (7.4)	(-7.4, 1.8)
		0 Hour (predose)	8	168.3 (22.9)	4.9 (10.2)	(-1.9, 11.8)

Table 21: Analysis Results of Δ PR for Elotuzumab (10mg/kg IV and 20 mg/kg IV) (Study CA204011)

Cycle	Day	Time	Elo-10mg/kg		Elo-20mg/kg		Total	
			N	Δ PR 90% CI (ms)	N	Δ PR 90% CI (ms)	N	Δ PR 90% CI (ms)
1	1	Predose	16		15		31	
		0.5 Hour Post EOI	16	-1.5 (-7.3, 4.3)	15	-6.0 (-10.8, -1.2)	31	-3.8 (-7.4, -0.1)
		2 Hour Post EOI	16	1.3 (-3.9, 6.6)	14	-3.4 (-7.9, 1.2)	30	-0.9 (-4.3, 2.5)
	8	Predose	16	0.7 (-3.0, 4.3)	15	6.5 (-2.8, 15.9)	31	3.6 (-1.3, 8.5)
		2 Hour Post EOI	16	-1.9 (-6.4, 2.6)	15	-4.1 (-10.2, 2.1)	31	-3.0 (-6.6, 0.6)

			Elo-10mg/kg		Elo-20mg/kg		Total	
Cycle	Day	Time	N	Δ PR 90% CI (ms)	N	Δ PR 90% CI (ms)	N	Δ PR 90% CI (ms)
	15	Predose	16	-0.5 (-4.2, 3.2)	.		16	-0.5 (-4.2, 3.2)
3	1	Predose	16	-0.2 (-3.9, 3.6)	15	3.4 (-0.8, 7.5)	31	1.6 (-1.1, 4.3)
		0.5 Hour Post EOI	15	0.3 (-5.3, 6.0)	14	-3.0 (-11.0, 5.0)	29	-1.3 (-6.0, 3.3)
		2 Hour Post EOI	15	-2.1 (-8.6, 4.5)	14	-5.3 (-11.5, 1.0)	29	-3.7 (-8.0, 0.6)
	15	Predose	16	-0.8 (-5.6, 3.9)	.		16	-0.8 (-5.6, 3.9)

Table 22: Categorical Analysis for PR (Study CA204004)

Treatment Group	Total N		PR \leq 200 ms		PR $>$ 200 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	10	10	9 (90.0%)	9 (90.0%)	1 (10.0%)	1 (10.0%)
Post Baseline	10	93	8 (80.0%)	88 (94.6%)	2 (20.0%)	5 (5.4%)

Table 23: Categorical Analysis for PR (Study CA204011)

Treatment Group	Total N		PR \leq 200 ms		PR $>$ 200 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	30	30	25 (83.3%)	25 (83.3%)	5 (16.7%)	5 (16.7%)
Elo-10mg/kg	15	133	14 (93.3%)	128 (96.2%)	1 (6.7%)	5 (3.8%)
Elo-20mg/kg	15	102	9 (60.0%)	84 (82.4%)	6 (40.0%)	18 (17.6%)

5.2.4 QRS Analysis

The primary endpoint is the mean change from baseline in QRS (Δ QRS). The point estimates and the 90% confidence intervals are presented in Table 24 and Table 25. The largest mean change from baseline in QRS was 3.9 ms and there was no trend for Δ QRS.

The outlier analysis results for QRS are presented in Table 26 and Table 27.

Table 24: Analysis Results of Δ QRS for E-Ld (Study CA204004)

Cycle	Day	Time	N	QRS (ms) (SD)	Δ QRS (ms) (SD)	Δ QRS 90% CI (ms)	
1	1	-1 Hour	9	93.3 (11.0)			
		0 Hour (predose)	10	91.7 (11.2)			
		Baseline	10	92.2 (11.1)			
			EOI	10	91.5 (9.7)	-0.7 (5.1)	(-3.7, 2.3)
			0.5 Hour Post EOI	9	90.2 (8.4)	-2.2 (6.5)	(-6.2, 1.9)
			2 Hour Post EOI	9	92.1 (6.1)	-0.3 (6.7)	(-4.4, 3.8)
		8	-1 Hour	10	91.4 (7.9)	-0.8 (8.5)	(-5.8, 4.1)
2	22	0 Hour (predose)	10	91.7 (7.1)	-0.5 (7.5)	(-4.9, 3.9)	
		-1 Hour	7	90.5 (8.8)	-2.3 (9.5)	(-9.2, 4.6)	
		EOI	7	91.2 (8.0)	-1.5 (8.6)	(-7.8, 4.8)	
		2 Hour Post EOI	7	89.4 (7.3)	-3.4 (8.5)	(-9.6, 2.9)	
3	1	-1 Hour	9	90.7 (8.2)	-2.2 (7.2)	(-6.7, 2.2)	
		0 Hour (predose)	8	91.3 (6.8)	-1.1 (9.8)	(-7.6, 5.5)	

Table 25: Analysis Results of Δ QRS for Elotuzumab (10mg/kg IV and 20 mg/kg IV) (Study CA204011)

Cycle	Day	Time	Elo-10mg/kg		Elo-20mg/kg		Total		
			N	Δ QRS 90% CI (ms)	N	Δ QRS 90% CI (ms)	N	Δ QRS 90% CI (ms)	
1	1	Predose	16		15		31		
		0.5 Hour Post EOI	16	-1.2 (-5.4, 3.0)	15	-0.4 (-2.4, 1.6)	31	-0.8 (-3.1, 1.5)	
		2 Hour Post EOI	16	-1.4 (-5.4, 2.7)	14	-1.9 (-4.4, 0.6)	30	-1.6 (-4.0, 0.7)	
		8	Predose	16	0.3 (-3.4, 4.0)	15	-0.2 (-2.8, 2.5)	31	0.1 (-2.1, 2.3)
			2 Hour Post EOI	16	0.9 (-2.7, 4.6)	15	-0.4 (-3.3, 2.6)	31	0.3 (-2.0, 2.6)
		15	Predose	16	3.9 (0.9, 6.8)	.		16	3.9 (0.9, 6.8)
3	1	Predose	16	-2.6 (-6.9, 1.6)	15	2.1 (-0.9, 5.1)	31	-0.3 (-2.9, 2.3)	

			Elo-10mg/kg		Elo-20mg/kg		Total	
Cycle	Day	Time	N	Δ QRS 90% CI (ms)	N	Δ QRS 90% CI (ms)	N	Δ QRS 90% CI (ms)
		0.5 Hour Post EOI	15	-1.3 (-5.7, 3.2)	14	-0.7 (-3.3, 1.8)	29	-1.0 (-3.5, 1.5)
		2 Hour Post EOI	15	-1.9 (-6.4, 2.6)	14	0.1 (-2.1, 2.3)	29	-0.9 (-3.4, 1.5)
	15	Predose	16	-4.5 (-8.5, -0.5)	.		16	-4.5 (-8.5, -0.5)

Table 26: Categorical Analysis for QRS (CA204004)

Treatment Group	Total N		QRS \leq 110 ms		QRS $>$ 110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	10	10	10 (100%)	10 (100%)	0 (0.0%)	0 (0.0%)
Post Baseline	10	93	10 (100%)	93 (100%)	0 (0.0%)	0 (0.0%)

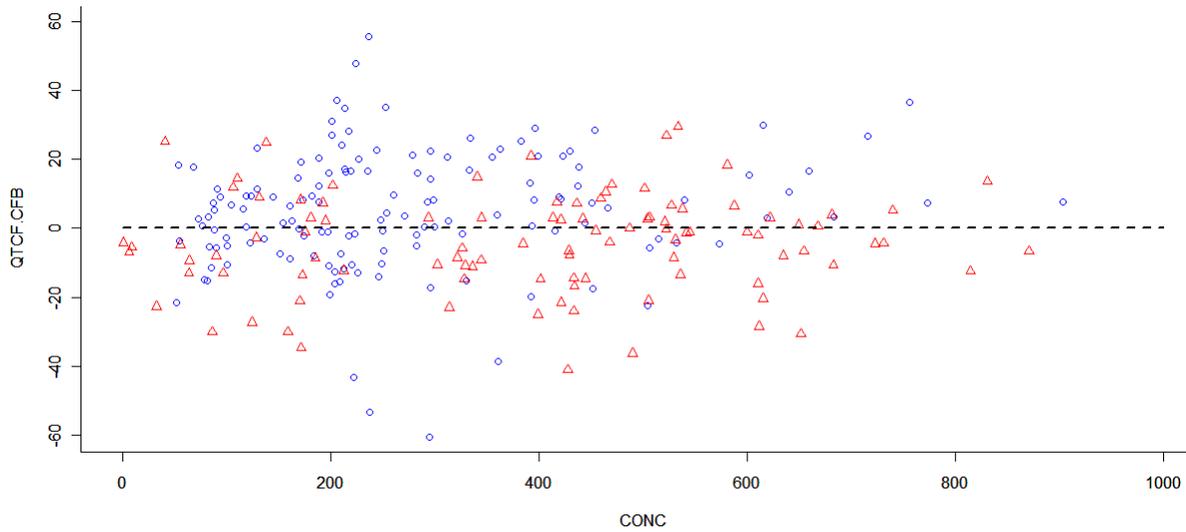
Table 27: Categorical Analysis for QRS (CA204011)

Treatment Group	Total N		QRS \leq 110 ms		QRS $>$ 110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	31	31	27 (87.1%)	27 (87.1%)	4 (12.9%)	4 (12.9%)
Elo-10mg/kg	16	142	12 (75.0%)	125 (88.0%)	4 (25.0%)	17 (12.0%)
Elo-20mg/kg	15	102	13 (86.7%)	94 (92.2%)	2 (13.3%)	8 (7.8%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between Δ QTcF and elotuzumab concentrations is visualized in Figure 7 with no evident exposure-response relationship.

Figure 7: Δ QTcF vs. Elotuzumab concentration. Blue circles indicate the 10 mg/kg dose and red triangles indicate the 20 mg/kg dose.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in either study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There was no clinically relevant effect on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Table 1: Highlights of Clinical Pharmacology and Cardiac Safety

<p>Therapeutic dose</p>	<p>Elotuzumab with lenalidomide and dexamethasone (Ld): 10 mg/kg administered intravenously every week for the first two cycles and every 2 weeks thereafter until disease progression or unacceptable toxicity.</p> <p style="text-align: right;">(b) (4)</p>	
<p>Maximum Tolerated Dose</p>	<p>Dose escalation up to 20 mg/kg was achieved without reaching a MTD.</p>	
<p>Principal Adverse Events</p>	<p>The clinical data across 11 completed/ongoing trials of elotuzumab administered in subjects with relapsed/refractory MM demonstrates a favorable benefit/risk profile.</p> <p>AEs were reported in the majority of subjects in Study CA204004 (99.4% vs. 99.1% respectively) in the E-Ld and Ld groups. The most frequently reported non-hematologic AEs ($\geq 30\%$) in the E Ld and Ld groups were fatigue, diarrhea, pyrexia, constipation, and cough. Elotuzumab administration did not add any relevant risk to the safety profile of Ld treatment. Grade 3-4 AEs in CA204004 were more frequent on the E-Ld group (77.7%) than the Ld group (65.6%). The most frequently reported non-hematologic Grade 3/4 AEs ($\geq 5\%$) were pneumonia, fatigue, hyperglycemia, cataract, deep vein thrombosis, and diarrhea.</p> <p>In CA204009, 100% and 96% of subjects experienced an AE in the E-Bd and Bd treatment group, respectively. The most frequently reported non-hematologic AEs ($\geq 30\%$) in the E-Bd and Bd groups arms were diarrhea, constipation, cough, peripheral neuropathy and pyrexia. Grade 3/4 AEs were more frequent in the E-Bd group (68%) in CA204009 compared to the Bd group (60%). The most frequently reported non-hematologic Grade 3/4 AEs ($\geq 5\%$) were diarrhea, pneumonia, hyperglycemia, hypokalemia, paraesthesia and peripheral neuropathy.</p> <p>In both CA204004 and CA204009, discontinuation due to study drug toxicity (all study drugs) was similar between the elotuzumab and control groups (Ld and Bd).</p>	
<p>Maximum Dose Tested</p>	<p>Single Dose</p>	<p>20 mg/kg</p>
	<p>Multiple Dose</p>	<p>20 mg/kg</p>
<p>Exposures Achieved at Maximum Tested Dose</p>	<p>Single Dose</p>	<p>At 10 mg/kg (Elotuzumab Monotherapy) from Study HuLuc63-1701, Geo. Mean (%CV) Cmax: 334.1 $\mu\text{g/mL}$ (19.7%) Geo. Mean (%CV) AUC(TAU): 34214.5 $\mu\text{g}\cdot\text{h/mL}$(84.0%)</p> <p>At 10 mg/kg (Elotuzumab in combination with Ld) from Study CA204007, Geo. Mean (%CV) Cmax: 217 $\mu\text{g/mL}$ (24%) Geo. Mean (%CV) AUC(TAU): 39559 $\mu\text{g}\cdot\text{h/mL}$ (84.0%)</p>
	<p>Multiple Dose</p>	<p>At 10 mg/kg (Elotuzumab Monotherapy) , Predicted Geo. Mean (%CV) Cmax,ss: 357 $\mu\text{g/mL}$ (32.1%) Predicted Geo. Mean (%CV) AUCss: 2710 $\mu\text{g}\cdot\text{day/mL}$ (50.2%)</p>

		<p>At 10 mg/kg (Elotuzumab in combination with Ld) , Predicted Geo. Mean (%CV) C_{max,ss}: 405 µg/mL(33.1%) Predicted Geo. Mean (%CV) AUC_{ss}: 3790 µg*day/mL (42.5%)</p> <p>At 10 mg/kg (Elotuzumab in combination with Bd) , Predicted Geo. Mean (%CV) C_{max,ss}: 444 µg/mL (40.8%) Predicted Geo. Mean (%CV) AUC_{ss}: 4300 µg*day/mL (50.4%)</p>
Range of Linear PK	Based on HuLuc63-1701 study, elotuzumab exhibits nonlinear pharmacokinetics with clearance of elotuzumab decreasing from 19.2 to 5.3 mL/day/kg with an increase in dose from 0.5 to 20 mg/kg, suggesting target-mediated clearance, resulting in greater than proportional increases in Area under the concentration-time curve (AUC).	
Accumulation at Steady State	Population PK based simulations indicate that following administration of elotuzumab at 10 mg/kg in combination with Ld or Bd, an AUC accumulation ratio of 7.42 and 9.41, respectively.	
Metabolites	The metabolic pathway of elotuzumab has not been characterized. As a humanized IgG1 monoclonal antibody, elotuzumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.	
Absorption	Absolute/Relative Bioavailability	Not applicable, as elotuzumab is dosed intravenously.
	T_{max}	<p>Median (range) for 10 mg/kg from Study HuLuc63-1701: 5.5 hours (1.5-5.7 hours)</p> <p>Median (range) for metabolites: Not applicable</p>
Distribution	V_d/F or V_d	Mean (%CV) for V _{ss} for 10 mg/kg from Study HuLuc63-1701 = 2.96 L (12.4 %)
	% bound	Not applicable
Elimination	Route	As a humanized IgG1 monoclonal antibody, elotuzumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.
	Terminal t_{1/2}	<p>Mean (%CV): Terminal Half-lives are not applicable for drugs with non-linear PK.</p> <p>Population PK based simulations indicate that following administration of elotuzumab at 10 mg/kg in combination with Ld or Bd, values the mean effective half-life of elotuzumab were 33.5 and 43.2 days, respectively.</p> <p>Mean (%CV) for metabolites: Not applicable</p>
	CL/F or CL	<p>Mean (%CV) for 10 mg/kg from Study HuLuc63-1701: 19.8 mL/h (43.4%)</p> <p>Mean (%CV) for metabolites: Not applicable</p>
Intrinsic Factors	Age	No clinically significant impact of age on the PK of elotuzumab as determined via population PK analysis (PPK). Patients with age ≥ 65 years had approximately 5% lower mean C _{max,ss} and AUC _{ss} compared to patients with age < 65 years.
	Sex	No clinically significant impact of sex on the PK of elotuzumab as determined via PPK. Males had approximately 10% lower C _{max,ss} and AUC _{ss} compared to females.
	Race	No clinically significant impact of race on the PK of

		<p>elotuzumab as determined via PPK. Lower individual estimates of CL in Asians and higher in Blacks compared to Whites reflected differences in body weight between races as the distributions of weight-normalized CL values were similar. Population PK analysis and simulations showed that the differences in exposure between Asian and non-Asian subjects did not exceed 15% for all exposure measures.</p>
	Hepatic & Renal Impairment	<p>The effect of renal impairment on the pharmacokinetics of elotuzumab was evaluated in a renal impairment study in patients with normal renal function (CrCl > 90 mL/min; n = 8), severe renal impairment not requiring dialysis (CrCl < 30 mL/min; n = 8), or end-stage renal disease requiring dialysis (CrCl < 30 mL/min; n = 8). No clinically important differences in the pharmacokinetics of elotuzumab were found between patients with severe renal impairment (with and without dialysis) and patients with normal renal function. In addition, renal function (measured by eGFR) did not have clinically significant impact the PK of elotuzumab in the PPK analysis.</p> <p>No formal hepatic impairment studies were performed. However, hepatic function (based on NCI-ODWG criteria) did not have clinically significant impact the PK of elotuzumab in the PPK analysis.</p>
Extrinsic Factors	Drug Interactions	<p>No formal drug-drug interaction studies have been conducted with nivolumab. Elotuzumab is considered to have low potential to affect pharmacokinetics of other drugs based on the lack of effect on cytokines in peripheral circulation.</p> <p>The effect of other drugs on the PK of elotuzumab has not been formally investigated. However, it is unlikely that other drugs will have an impact on the PK of elotuzumab given elotuzumab is a IgG1 mAb, which is likely eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism.</p>
	Food Effects	Not applicable, as elotuzumab is dosed intravenously.
Expected High Clinical Exposure Scenario	<p>High clinical exposures are not expected to exceed PK exposures produced by the elotuzumab 10 mg/kg dosing regimen given that:</p> <ul style="list-style-type: none"> • elotuzumab is administered intravenously in the clinic (low likelihood of administration of incorrect dose) • drug interactions are not anticipated, as the expected route of elimination of IgGs (like elotuzumab) is through non-specific catabolic degradation and target-mediated elimination • the effect of intrinsic and extrinsic factors on clearance and volume of distribution of elotuzumab (other than body weight) is < 20% 	
Preclinical Cardiac Safety	<p>In vitro hERG study: Not applicable Monkey study: No cardiac findings</p>	
Clinical Cardiac Safety	<p>The potential effect of elotuzumab on QTc interval prolongation was evaluated in 31 subjects in a Phase 2 study (CA204011) of elotuzumab monotherapy (10 mg/kg (N = 15) and 20 mg/kg (N = 16)). QTc interval prolongation was also assessed in additional 10 subjects in a Phase 3 sub-study (CA204004) of elotuzumab in combination with Ld. No changes in mean QT interval were detected in elotuzumab-treated patients based on Fridericia correction method.</p>	

	<p>After careful examination of events of seizure/convulsion, syncope/presyncope, QTc prolongation and tachycardia, no event was determined to be associated with an abnormal ECG finding potentially related to proarrhythmia. Overall, elotuzumab does not have QTc prolongation potential in the studied dose range.</p>
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUSTIN C EARP
10/08/2015

JIANG LIU
10/08/2015

HUIFANG CHEN
10/08/2015

QIANYU DANG
10/08/2015

MICHAEL Y LI
10/08/2015

NORMAN L STOCKBRIDGE
10/09/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761035

Application Type: New BLA

Name of Drug/Dosage Form: Empliciti™ (elotuzumab) for injection

Applicant: Bristol-Myers Squibb Company

Receipt Date: June 29, 2015

Goal Date: February 29, 2016 (Action Date: December 1, 2015)

1. Regulatory History and Applicant's Main Proposals

Bristol-Myers Squibb (BMS) has submitted a Biologics License Application (BLA) for elotuzumab. The proposed indication is elotuzumab for the treatment of patients with multiple myeloma who have received one or more prior therapies in combination with lenalidomide and dexamethasone (b) (4).

Orphan drug designation for elotuzumab was granted on September 1, 2011 for the treatment of multiple myeloma.

Breakthrough Therapy Designation was granted on May 12, 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. Rolling review was granted on May 20, 2015.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: No boxed warning or recent major changes.

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: Year to be completed closer to approval

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES**
S 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *Minor edits made to label to reflect standard language*

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: Sponsor highlighted "Bristol-Myers Squibb" and the phone number

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: To be updated upon approval

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

N/A

Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *No RMCs*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment: *Additional comment is noted below "none"*

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: *Under 6.1*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

NATASHA L KORMANIK
10/01/2015

PATRICIA N GARVEY
10/05/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
BLA# 761035	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: EMPLICITI (proposed proprietary name; pending) Established/Proper Name: elotuzumab Dosage Form: Injection Strengths: 300 and 400 mg		
Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable):		
Date of Application: June 27, 2015; Date of Receipt: June 29, 2015 Date clock started after UN: N/A		
PDUFA Goal Date: February 29, 2015		Action Goal Date (if different): December 1, 2015
Filing Date: August 28, 2015		Date of Filing Meeting: August 10, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(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) 		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR
<ul style="list-style-type: none"><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i>	<input type="checkbox"/> QIDP
<ul style="list-style-type: none"><i>The product is a Qualified Infectious Disease Product (QIDP)</i>	<input type="checkbox"/> Tropical Disease Priority Review Voucher
<ul style="list-style-type: none"><i>A Tropical Disease Priority Review Voucher was submitted</i>	<input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.)
	<input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.)
	<input type="checkbox"/> Device coated/impregnated/combined with drug
	<input type="checkbox"/> Device coated/impregnated/combined with biologic
	<input type="checkbox"/> Separate products requiring cross-labeling
	<input type="checkbox"/> Drug/Biologic
	<input type="checkbox"/> Possible combination based on cross-labeling of separate products
	<input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation	<input type="checkbox"/> PMC response
<input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i>	<input type="checkbox"/> PMR response:
<input checked="" type="checkbox"/> Rolling Review	<input type="checkbox"/> FDAAA [505(o)]
<input checked="" type="checkbox"/> Orphan Designation	<input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)
<input type="checkbox"/> Rx-to-OTC switch, Full	<input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)
<input type="checkbox"/> Rx-to-OTC switch, Partial	<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
<input type="checkbox"/> Direct-to-OTC	
Other:	

Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 100043

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in tracking system?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Will contact Document Room to update
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>				

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Priority, BTD, Orphan Designation
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Submitted 5/27/15
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>) <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> N/A <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Granted orphan designation on 9/1/11	
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Some cut off pages; IR sent

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		No pediatric data and has orphan designation

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Submitted 6/29/15, not required, but did provide PLLR format
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7/7/15
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No formal consult per K. Wright
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No formal consult per K. Wright
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Confirmed at Filing Meeting
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 1/25/11 (CMC); 2/15/11; and 10/17/12	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/9/15 and 4/20/15 (CMC)	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 10, 2015

BACKGROUND: Bristol-Myers Squibb (BMS) has submitted a Biologics License Application (BLA) for elotuzumab. The proposed indication is elotuzumab for the treatment of patients with multiple myeloma who have received one or more prior therapies in combination with lenalidomide and dexamethasone (b) (4)

Orphan drug designation for elotuzumab was granted on September 1, 2011 for the treatment of multiple myeloma.

Breakthrough Therapy Designation was granted on May 12, 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. Rolling review was granted on May 20, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Natasha Kormanik	Y
	CPMS/TL:	Theresa Carioti (CPMS) Patricia Garvey (TL)	Y
Cross-Discipline Team Leader (CDTL)	Albert Deisseroth		Y
Division Director/Deputy	Ann Farrell		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Nicole Gormley	Y
	TL:	Albert Deisseroth	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Olanrewaju Okusanya	Y
	TL:	Gene Williams	Y
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	Chia-Wen Ko	N
	TL:	Lei Nie	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Michael Manning	Y
	TL:	Christopher Sheth	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Linan Ha (Sarah Kennett- present at meeting for Linan Ha)	N
	RBPM:	Andrew Shiber	N
• Drug Substance	Reviewer:	Rachel Novak	Y
• Drug Product	Reviewer:	Rachel Novak	Y
• Process	Reviewer:	Rachel Novak	Y
• Microbiology	Reviewer:	Maria Jose Lopez-Barragan Natalia Pripuzova	Y
• Facility	Reviewer:	Rachel Novak	Y
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:	Rachel Novak	Y
• Labeling (BLAs only)	Reviewer:	Jibril Abdus-Samad	Y
• Other (e.g., Branch Chiefs, EA Reviewer)	Patricia Hughes		Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Morgan Walker (not consulted until 8/11/15)	N/A
	TL:	Barbara Fuller	N/A
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nisha Patel	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Michelle Rutledge	Y

	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Mona Patel	Y
	TL:	Naomi Redd	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		

Other reviewers/disciplines			
<ul style="list-style-type: none"> Discipline <p><small>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</small></p>	Reviewer:		
	TL:		
Other attendees	Kevin Wright, OSE RPM		Y
	Theresa Carioti, DHP CPMS		Y
	Mara Miller, DHP TL		Y
	Robert Kane, DHP Deputy Director for Safety		Y
	<small>*For additional lines, right click here and select "insert rows below"</small>		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
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described in published literature):	
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: P/T will sent out an IR for cut off submission in P/T file</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments: TCON with Sponsor on 8/11/15 to discuss issues</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="text"/> <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The application did not raise significant safety or efficacy issues
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: IR to be sent out with review issues</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments: Working on dates</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments: No items identified</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	<p>N/A</p>
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):
September 28, 2015 (Sponsor Meeting)

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74

<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

NATASHA L KORMANIK
08/24/2015

PATRICIA N GARVEY
08/24/2015