APPLICATION NUMBER:

761097Orig1s000

OTHER REVIEW(S)
Date: September 27, 2018

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)

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: Ruth Lidoshore, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Concurrence with Submitted: Medication Guide (MG)

Drug Name (established name): LIBTAYO (cemiplimab-rwlc)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761097

Applicant: Regeneron Pharmaceuticals, Inc.
INTRODUCTION

On February 28, 2018, Regeneron Pharmaceuticals, Inc. submitted for the Agency’s review an original Biologics License Application (BLA) 761097 for LIBTAYO (cemiplimab-rwlc) injection. The proposed indication for LIBTAYO (cemiplimab-rwlc) is for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery.

On September 26, 2018 the Applicant submitted updated labeling to include the proper name with four letter suffix: cemiplimab-rwlc. On September 26, 2018, the Division of Oncology Products 2 (DOP2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant’s updated Medication Guide (MG) for LIBTAYO (cemiplimab-rwlc) injection.

This memorandum documents the DMPP review and concurrence with the Applicant’s proposed MG for LIBTAYO (cemiplimab-rwlc) injection.

MATERIAL REVIEWED

• LIBTAYO (cemiplimab-rwlc) injection MG received on September 26, 2018, and received by DMPP on September 27, 2018.

• LIBTAYO (cemiplimab-rwlc) injection Prescribing Information (PI) received on September 26, 2018, and received by DMPP on September 27, 2018.

• DMPP review of draft LIBTAYO (cemiplimab) injection MG dated August 7, 2018.

CONCLUSIONS

We find the Applicant’s proposed MG is acceptable as submitted.

RECOMMENDATIONS

• Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RUTH I LIDOSHORE
09/27/2018

BARBARA A FULLER
09/27/2018
**MEMORANDUM**

**REVIEW OF REVISED LABEL AND LABELING**

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)

**Date of This Memorandum:** September 27, 2018  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** BLA 761097  
**Product Name and Strength:** Libtayo (cemiplimab-rwlc) Injection, 250 mg/5 mL and 350 mg/7 mL  
**Applicant/Sponsor Name:** Regeneron Pharmaceuticals, Inc.  
**FDA Received Date:** September 26, 2018  
**OSE RCM #:** 2017-2591-1  
**DMEPA Safety Evaluator:** Colleen Little, PharmD  
**DMEPA Team Leader:** Sevan Kolejian, PharmD, MBA

Reference ID: 4326833
1 PURPOSE OF MEMORANDUM
Regeneron Pharmaceuticals submitted revised container labels and carton labeling on September 26, 2018 to display the established name, cemiplimab-rwlc.

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Libtayo (Appendix A) to determine if it is acceptable from a medication error perspective.

2 CONCLUSION
We previously reviewed the Libtayo container labels and carton labeling on July 19, 2018. The only changes proposed by Regeneron in the September 26, 2018 submission are enumerated below along with our conclusions.

1. The FDA-designated nonproprietary name suffix, -rwlc, has been added to the core established name, cemiplimab. The labels and labeling are now marked with the correct established name in every place that the established name is used. We find these revisions acceptable.

2. On the PDP of the container labels and carton labeling, the dosage form ‘injection’ is moved under the established name and appears on a separate line. OBP finds this acceptable and other changes to comply with the relevant labeling regulations, USP standards, and CDER labeling practices and guidances. We have no safety concerns with this change and find the revision acceptable.

3. Carton labeling has been revised to add a bar code on the side panel. This is acceptable from a medication error perspective.

Thus, we find that the revised Libtayo container labels and carton labeling submitted on September 26, 2018 are acceptable from a medication error perspective. This review concurs with the conclusions of the Office of Biotechnology Products (OBP), which also finds that the revised container labels and carton labeling are acceptable.

We have no further revisions to request for these labels. These labels are acceptable for FDA approval.

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3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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\(^a\) See FDA Letter designating the suffix for this BLA sent on September 21, 2018.

\(^b\) See OBP/Scott Dallas Labels and Labeling Review dated September 27, 2018.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

COLLEEN L LITTLE
09/27/2018

SEVAN H KOLEJIAN
09/27/2018
Date of This Review: September 18, 2018
Responsible OND Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: BLA 761097
Product Name and Strength: Libtayo (cemiplimab-rwlc) Injection, 50 mg/mL
Product Type: Single Ingredient Product
Applicant/Sponsor Name: Regeneron Pharmaceuticals, Inc.
OSE RCM #: 2018-872
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Deputy Director: Danielle Harris, PharmD, BCPS
1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffix for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761097.

1.1 Regulatory History

Regeneron Pharmaceuticals, Inc. was notified of the Agency’s intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an Advice Letter\(^a\).

2 Assessment of the Nonproprietary Name

cemiplimab-rwlc

FDA generated a four-letter suffix, -rwlc. This suffix was evaluated using the principles described in the applicable guidance\(^b\).

We determined that the FDA-generated suffix -rwlc, is not too similar to any other products’ suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

3 Communication of DMEPA’s Analysis

These findings were shared with OPDP. In email correspondence dated September 18, 2018, OPDP did not identify any concerns that would render this suffix unacceptable. DMEPA also communicated our findings to the Division of Oncology Products 2 (DOP2) via e-mail on September 18, 2018.

4 Conclusion

We find the suffix -rwlc acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to cemiplimab-rwlc.

4.1 Recommendation for Regeneron Pharmaceuticals, Inc.

We find the nonproprietary name, cemiplimab-rwlc, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, cemiplimab-rwlc will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of this suffix will be re-evaluated when you respond to the deficiencies. If we find the suffix unacceptable upon our re-evaluation, we would inform you of our finding.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TINGTING N GAO
09/18/2018

DANIELLE M HARRIS
09/18/2018
**CDER Breakthrough Therapy Designation Determination Review Template**

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<th>IND/NDA/BLA #</th>
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<tr>
<td>Product</td>
<td>REGN2810</td>
</tr>
<tr>
<td>Indication</td>
<td>Metastatic and locally advanced and unresectable cutaneous squamous cell carcinoma (CSCC)</td>
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<tr>
<td>Drug Class/Mechanism of Action</td>
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<td>OHOP/DOP2</td>
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<tr>
<td>Breakthrough Therapy Request Goal Date (within 60 days of receipt)</td>
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</tbody>
</table>

Note: This document should be uploaded into CDER’s electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

   The proposed indication for REGN2810 is for the treatment of patients with metastatic and locally advanced and unresectable cutaneous squamous cell carcinoma (CSCC).

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold? □YES □NO

   If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No”, proceed with below:

3. Consideration of Breakthrough Therapy Criteria:
   a. Is the condition serious/life-threatening?)? □YES □NO

   If 3a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

      □YES the BTDR is adequate and sufficiently complete to permit a substantive review
      □Undetermined
      □NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

---

i. Only animal/nonclinical data submitted as evidence

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)

v. No or minimal clinically meaningful improvement as compared to available therapy2 historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

N/A.

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

Disease Background

CSCC is the second most common human cancer in the United States, with an estimated annual incidence of 700,000 cases.1 While most cases are localized tumors amenable to curative resection, approximately 4% of patients will develop nodal metastases, and an estimated 2% of patients will die from their disease.1,2 High-risk patients are those who have recurrent disease or are at high risk for recurrence, lymph node metastases or distant metastases. Precise

Reference ID: 4148311

incidences of overall disease, high-risk disease and survival outcomes are not available because these cancers are grouped with other nonmelanoma skin cancers (NMSC) in the Surveillance, Epidemiology, and End Results (SEER) database. Factors associated with recurrence and poor prognosis in CSCC include tumor size > 2 cm, tumor depth > 2 mm (Breslow thickness), perineural invasion, host immunosuppression, poorly differentiated histology and location on the ear, temple or lip. Ten-year survival rates are less than 20 percent for patients with regional lymph-node involvement, and for those patients who develop distant metastases, the median survival time is less than two years.

The standard of care for locoregional CSCC is complete surgical resection with a minimum margin of 5 mm for low risk tumors and 10 mm for high risk tumors. If there is nodal involvement, a regional lymph node dissection is recommended, and adjuvant radiation therapy is utilized in most cases. Treatment options are limited for the small subset of patients with CSCC who develop local recurrences, unresectable disease, or distant metastatic disease. Radiation as the definitive treatment may be considered in some patients with unresectable locally advanced disease based on the durable response rates and disease free survival described in retrospective studies.

There are no FDA-approved systemic therapies for patients with locally advanced and unresectable or metastatic CSCC. Additionally, there are case reports of various EGFR inhibitors and single arm, prospective studies of cetuximab and gefitinib in patients with high-risk CSCC that have reported objective responses; in one of the largest clinical studies of cetuximab in 36 patients with advanced CSCC, the median overall survival was 8.1 months.

REGN2810
REGN2810 is a humanized monoclonal antibody directed against PD-1 that works through blockade of T-cell inhibition leading to augmentation of the host immune response in the tumor environment. Drugs in class that have been approved for other cancer indications include nivolumab, pembrolizumab, atezolizumab and avelumab. There are also multiple PD-1 and PD-L1 inhibitors currently in development for various indications. As of January 2017, almost 400 patients with various malignancies have been exposed to REGN2810. Clinical experience is derived from six clinical trials conducted under U.S. INDs and two additional ex-U.S. studies. The data to support this BTDR is from Study 1423, a dose-finding and safety study in patients with advanced solid tumors including CSCC. Specifically, the 1423 trial includes two expansion cohorts for the evaluation of REGN2810 in patients with either locally advanced and unresectable CSCC (cohort 7) or patients with metastatic CSCC (cohort 8).

Relevant Regulatory History
The initial IND (IND 123950) for REGN2810 was submitted to the Division of Oncology Products 1 (DOP 1) on December 22, 2014. The IND included the clinical protocol for Study R2810-ONC-1423 entitled, “A First-in-Human (FIH) Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death-1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies in Patients with Advanced Malignancies.” The study may proceed letter was issued on January 21, 2015.

On September 10, 2015, a pre-IND meeting was held with DOP2 to discuss the development program for REGN2810 in CSCC. The following key points were made:

- FDA agreed to the enrollment of patients without a requirement for prior systemic therapy as long as Regeneron agreed to provide analyses of confirmed objective response rates (ORR) based on subgroups defined by extent of prior therapy (no prior systemic therapy or having received any prior systemic therapy).
- FDA agreed to the enrollment of patients with metastatic CSCC without a requirement for prior radiation therapy; however, in patients with locally advanced CSCC, FDA recommended that an individualized benefit:risk
assessment be performed by a multidisciplinary team consisting of a medical oncologist with expertise in cutaneous malignancies or a dermato-oncologist and a radiation oncologist prior to enrollment in the proposed study. FDA also stated that the case report form (CRF) for patients with locally advanced CSCC should capture the reasons for enrollment in the study including why the patient with locally advanced CSCC was not a candidate for surgical resection or for radiation therapy.

- FDA recommended that pre-specified subgroup analyses of patients with locally advanced and metastatic disease be outlined in the statistical analysis plan. FDA also stated that since a different treatment effect may be observed in patients with metastatic disease as compared to patients with locally advanced disease, it will be essential to have an adequate sample size to demonstrate direct clinical benefit in both populations.

- FDA agreed that a primary endpoint of ORR (as determined by independent review) may be acceptable provided ORR is shown to be clinically meaningful in magnitude and duration, with an acceptable safety profile for REGN2810 in this patient population. For patients with locally advanced CSCC, a (generally) non-life-threatening disease, Regeneron must provide justification that the observed reduction in tumor size provides clearly defined, direct clinical benefit.

On December 7, 2015, IND 127100 was submitted and contained the protocol for Study R2810-ONC-1540 (1540), an open-label, non-randomized, multicenter study of REGN2810 administered at a dose of 3 mg/kg every two weeks to two groups of patients with advanced CSCC.

On December 16, 2017, Regeneron requested Preliminary Breakthrough Therapy Designation Request (BTDR) Advice and described preliminary results from 25 patients with CSCC treated with REGN2810. During the teleconference, FDA stated that while the data from 25 patients dosed may be adequate for a breakthrough request in a rare disease, the determination of breakthrough designation will depend on the magnitude of the treatment effect in an analysis that includes all patients who have received at least one dose or partial dose of the study drug. Additionally, for this disease, FDA stated that the results for the subtypes of metastatic CSCC and locally advanced CSCC will be reviewed separately given the different natural histories and prognostic factors associated with the different disease stages. FDA recommended that the sponsor seek a second preliminary breakthrough designation request discussion after all patients included in the dataset have been followed for a minimum of four months after the onset of response, that there be an independent review of all responses, and that available medical photographs be submitted for patients enrolled in the study if an improvement in disfiguring lesions is considered to be of clinical benefit in this disease.

On June 7, 2017, Regeneron requested additional Preliminary BTDR Advice, and a teleconference was held with the FDA on June 27, 2017, to review the updated data on the same 25 patient cohort. During the teleconference, FDA stated that although the data appeared consistent with what could merit a BTD, it would be helpful if Regeneron provide six months of followup for durability following onset of response as it was already June and an updated analysis did not seem unfeasible. This could provide a stronger justification for the breakthrough designation request.

On July 18, 2017, Regeneron submitted a formal request for BTD determination for REGN2810.

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Regeneron considers durable objective response rate to be a clinically meaningful endpoint supporting the BTDR. ORR and duration of response (DOR) according to RECIST v1.1 was measured in Study 1423, and these results
are provided to support the BTDR. In the ongoing Study 1540, ORR will be measured using a composite endpoint that measures radiographic response according to RECIST in addition to medical photography and tissue evaluation of target lesions. Regeneron will also submit photographic data from Study 1540 as supportive evidence of clinical benefit in the potential marketing application.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).
- A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).
- An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.

DOP2 agrees that demonstration of a meaningful effect size on durable ORR according to centrally reviewed RECIST or a modified RECIST guideline (that considers digital photographic assessments and tissue analysis in addition to radiographic measures) would be clinically meaningful in patients with metastatic or locally advanced and unresectable CSCC and could support an application for marketing approval. Given that some patients with CSCC suffer from disfiguring lesions, clear photographic evidence of substantial improvement in such lesions would be acceptable as supportive evidence of clinical benefit.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.
- In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.

The standard of care for patients with CSCC is local treatment via surgical resection or in some cases radiotherapy. The REGN2810 development program is intended for patients that do not have local control options. There are no FDA-approved therapies and no known curative treatments for patients with inoperable and locally advanced or metastatic CSCC. The most common systemic regimens that are used off-label to treat this advanced subset of patients are cisplatin-based chemotherapy and EGFR inhibitors. The following table summarizes agents that have been or are currently being evaluated in clinical studies in patients with CSCC with advanced disease. The RECIST guideline was used for assessing ORR and DOR in these studies. The REGN2810 development program utilizes RECIST and additionally incorporates photographic and histologic results into the overall response evaluations. The table does not include topical agents, cytotoxic chemotherapeutics or drugs being evaluated in refractory all-comer cancer populations.

Reference ID: 4148311
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<th>Mechanism of Action</th>
<th>Sponsor or reference</th>
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<td>Cetuximab</td>
<td>EGFR TKI</td>
<td>Maubec et. al. 2011</td>
<td>Completed. 36 patients with unresectable CSCC (three patients with metastatic disease). ORR per RECIST was 28%. DOR not reported. Median OS 8.1 months.</td>
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<td>Gefitinib</td>
<td>EGFR TKI</td>
<td>Lewis et. al. 2012</td>
<td>Completed. 22 patients with aggressive or recurrent local CSCC. Patients with distant metastases excluded. Neoadjuvant gefitinib for 2 cycles followed by standard of care local control. ORR [%].</td>
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<td>Panitumumab</td>
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<td>Foote et. al. 2014</td>
<td>Completed. 16 patients with incurable advanced CSCC (two patients had metastatic disease). ORR per RECIST was 31% (95 CI: 11-59). DOR not reported. Median OS 11 months.</td>
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TKI: tyrosine kinase inhibitor, MAB: monoclonal antibody

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

No other drugs have received breakthrough therapy designation for this indication.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The data supporting the BTDR for REGN2810 comes from one trial: Study 1423. This is an ongoing, first-in-human, multicenter, dose-finding and activity-estimating study of REGN2810 administered intravenously as a single-agent or in combination with cyclophosphamide or radiation (depending on the expansion cohort) every three weeks in patients with various advanced solid tumors. Specifically, the efficacy results to date from patients treated in expansion cohorts 7 (metastatic CSCC) and 8 (locally advanced and unresectable CSCC) are being submitted to support the BTDR. The patients in these cohorts received single agent REGN2810 and no concomitant radiation.

An analysis of centrally reviewed ORR and DOR was performed using data from the first 25 patients with metastatic (n=11) or locally advanced and unresectable (n=14) CSCC treated in Study 1423 who received at least one infusion of REGN2810 as of December 14, 2016. The data cut off date for the response rate analysis was June 12, 2017. The centrally reviewed ORR was 44% (11/25) in this combined group of patients with either locally advanced or metastatic CSCC. Note that in January 2017, 11 of the 25 patients had investigator-assessed objective responses; however, upon central review, one patient (ID [redacted]) withdrew consent and had not had a confirmatory scan and was considered to have a best response of stable disease (SD). At the time of the June cut off date, however, four additional patients had scans centrally reviewed, and another patient in cohort 8 (ID [redacted])...
was noted to have a partial response. Therefore, there are still currently 11 responders from the first 25 patients with CSCC enrolled in Study 1423.

The following swimmer’s plot and summary table, copied from the briefing document, show the investigator and centrally-reviewed ORR and DOR results for the 11 patients who were considered to be responders in January 2017 and the additional patients who had their scans centrally reviewed after January 2017. Among 11 patients who had an objective response, nine have maintained the response as of the June 2017 data cutoff. Two patients have since progressed, one with brain metastasis and one with new nodal disease. The median duration of response has not been reached. Six patients (55% of the responder subgroup) have ongoing responses of at least seven months at data cutoff.

Figure 1: Swimmer's Plot

Expansion Cohort 7 M1 CSCC and Expansion Cohort 8 MO CSCC and Dose Escalation Patient with CSCC

![Swimmer's Plot](image)

Reference ID: 4148311
Table 1: Study 1423 ORR and DOR results for patients with CSCC

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<th>Row</th>
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</tr>
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</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; NE, not evaluable; uPR, unconfirmed partial response

a As presented to FDA on 25 January 2017
b This subject completed 48 weeks of treatment, followed by approximately 24 weeks of post-treatment follow-up, on October 26, 2016. This was his End of Study visit, because protocol events end with the completion of this follow-up period. Personal communication from the investigator on 5 May 2017, the patient continues to do well and has had no evidence of disease according to routine assessments since completing the study.
c After 25 January 2017, the investigator changed best response to SD, based on local re-review.
d This subject met criteria for unconfirmed partial response at his first response assessment (week 8). He became non-compliant after 3 additional treatments and the second response assessment (week 16) was not done. He was lost to follow up until the third scheduled response assessment (week 24), at which point his overall response assessment was stable disease due to increase in tumor during the period of non-compliance. He then resumed treatment and partial response was observed at the fourth (week 32) and fifth (week 40) response assessments. Duration of response is therefore calculated from week 32 as per RECIST 1.1. Photographs are shown in Figure 6.
e Patient withdrew consent during Cycle 2. Because a confirmatory scan was not obtained, his best response is SD per RECIST 1.1. Photographs are shown in Figure 1.

DOP2 additionally reviewed the ORR and DOR results separately for the subgroups of patients with locally advanced CSCC and patients with metastatic CSCC. Six of 11 patients (55%) with metastatic disease and five of the 14 patients (36%) with locally advanced disease from Study 1423 had a centrally reviewed objective response to REGN2810. The ORR in patients with metastatic disease is particularly encouraging. The higher response rate in patients with metastatic disease as compared to those patients with locally advanced disease is likely due to the small sample sizes and not a difference in the biologic antitumor effect of REGN2810 in these patients.

Finally, Regeneron also submitted photographic data to depict some of the more dramatic responses noted in patients with baseline disfiguring tumors. One example from the briefing document is copied below:
b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

- *Safety data: Provide a brief explanation of the drug’s safety profile, elaborating if it affects the Division’s recommendation.*

Patients with metastatic and locally advanced unresectable CSCC represent a population with an unmet medical need. There are no known curative therapies and no available treatments for these subsets of high-risk CSCC. DOP2 considers the objective response and duration of response data from patients with advanced CSCC treated with REGN2810 in Study 1423 to be preliminary evidence of a substantial improvement over the published results of off-label use of cytotoxic chemotherapy regimens and EGFR inhibitors.7,8

DOP2 also took into consideration that Regeneron’s development program from REGN2810 in CSCC includes an ongoing trial (Study 1540) intended to support a marketing application for REGN2810 in patients with advanced CSCC. Study 1540 is an open-label, non-randomized, multicenter study of REGN2810 administered at a dose of 3 mg/kg every two weeks to patients with metastatic CSCC (Group 1) or locally advanced and unresectable CSCC (Group 2). This trial is enrolling well with 58 patients with metastatic disease and over 30 patients with locally advanced disease treated as of April 2017. Regeneron recently met with DOP2 to discuss plans for submitting an application for REGN2810 for the treatment of patients with CSCC in Q1 2018.
The summary safety data provided in the BTDR and the recently submitted preBLA Type B meeting briefing materials were also reviewed. As of January 20, 2017, 353 patients were exposed to REGN2810 including 300 at the recommended 3 mg/kg dose in Study 1423, and the median exposure was 14 weeks. There were no dose-limiting toxicities observed during dose-escalation. Regeneron reports one patient experienced fatal hepatic failure that was considered related to REGN2810 and one patient experienced fatal paraneoplastic encephalomyelitis assessed as possibly related to REGN2810. Twenty-three percent of patients experienced serious adverse events (SAEs), and 7% of patients experienced at least one treatment-related SAE. Immune-mediated adverse reactions (imARs) occurred in 34% of patients, and 5% of patients had serious imARs. The types of imARs reported are similar to those associated with other drugs in class. Common treatment emergent adverse events (AEs) that occurred in more than 10% of patients included fatigue, nausea, decreased appetite, anemia, constipation, arthralgia, diarrhea, dyspnea, cough, pyrexia, vomiting, asthenia and back pain. Of the 25 patients with CSCC in Study 1423, Grade 3 or greater AEs included rash, arthralgia, asthenia and liver enzyme elevation. Two patients discontinued for AEs of grade 3 rash and liver enzyme elevation. Two patients died within 30 days of REGN2810 infusion; both were considered unrelated to study drug and due to disease progression. Overall, the safety profile of REGN2810 in patients with CSCC does not appear to differ from that seen in other patients with cancer.

11. Division’s recommendation and rationale (pre-MPC review):

- **GRANT**:

  Provide brief summary of rationale for granting:

  *Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

  There are no systemic therapies approved for patients with metastatic or locally advanced CSCC. DOP2 considers the effect size on response rate of 44% together with the durability of responses (ranging from 2+ to 14.5+ months) to date in patients with advanced CSCC Study 1423 to be preliminary evidence of a substantial improvement over alternative treatment options which include off-label use of cisplatin-based chemotherapy regimens and EGFR inhibitors. DOP2 has also considered the supportive photographic evidence of clinical benefit and the overall development program in CSCC.

- **DENY**:

  Provide brief summary of rationale for denial:

  *Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

12. Division’s next steps and sponsor’s plan for future development:

   a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

      DOP2 will continue to communicate with Regeneron and provide regulatory guidance to facilitate the development program for REGN2810 in advanced CSCC.

   b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:
13. List references, if any:


14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DENISE A CASEY
09/05/2017

SUZANNE G DEMKO
09/05/2017

STEVEN J LEMERY
09/05/2017
Memorandum

Date: August 8, 2018

To: Patricia Keegan, M.D., Director
Division of Oncology Products 2 (DOP2)

Missiratch Biable, Regulatory Project Manager, DOP2

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, M.B.A., Team Leader, OPDP

Subject: OPDP Labeling Comments for Libtayo® (cemiplimab) injection, for intravenous use

BLA: 761097

In response to DOP2’s consult request dated March 1, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, container label, and carton labeling for the original BLA submission for Libtayo® (cemiplimab) injection, for intravenous use (Libtayo).

OPDP’s comments on the proposed labeling are based on the draft PI, Medication Guide received by electronic mail from DOP2 (Missiratch Biable) on July 31, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on August 7, 2018.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 18, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEVIN WRIGHT
08/08/2018
Date: August 7, 2018

To: Patricia Keegan, MD
   Director
   Division of Oncology Products 2 (DOP2)

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: Ruth Lidoshore, PharmD
   Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)

Kevin Wright, PharmD
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): LIBTAYO (cemiplimab)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761097

Applicant: Regeneron Pharmaceuticals, Inc.
1 INTRODUCTION
On February 28, 2018, Regeneron Pharmaceuticals, Inc. submitted for the Agency’s review an original Biologics License Application (BLA) 761097 for LIBTAYO (cemiplimab) injection. The proposed indication for LIBTAYO (cemiplimab) injection is for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery.

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 Oncology Products 2 (DOP2) on April 6, 2018 and March 1, 2018, respectively, for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) for LIBTAYO (cemiplimab) injection.

2 MATERIAL REVIEWED
- Draft LIBTAYO (cemiplimab) injection MG received on February 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 24, 2018 and again on July 31, 2018.
- Draft LIBTAYO (cemiplimab) injection Prescribing Information (PI) received on February 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 24, 2018 and again on July 31, 2018.

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.

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 APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:
- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
• ensured that the MG meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS
The MG 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 MG 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 MG.

Please let us know if you have any questions.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RUTH I LIDOSHORE
08/07/2018

KEVIN WRIGHT
08/07/2018

BARBARA A FULLER
08/07/2018

LASHAWN M GRIFFITHS
08/07/2018
Clinical Inspection Summary

<table>
<thead>
<tr>
<th>Date</th>
<th>7/27/2018</th>
</tr>
</thead>
</table>
| From          | Navid Homayouni, M.D., Medical Officer
               | Susan Thompson, M.D., Team Leader
               | Kassa Ayalew, M.D., M.P.H., Branch Chief
               | Good Clinical Practice Assessment Branch
               | Division of Clinical Compliance Evaluation
               | Office of Scientific Investigations |
| To            | Missiratch Biable, Regulatory Project Manager
               | Denise Casey, M.D., Clinical Reviewer
               | Suzanne Demko, P.A.-C., Cross Discipline Team Leader
               | Division of Oncology Products 2 |
| NDA #         | 761097 |
| Applicant     | Regeneron Pharmaceuticals, Inc. |
| Drug          | Cemiplimab |
| NME           | Yes |
| Therapeutic Classification | Priority |
| Proposed Indication | Treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC), or with locally advanced cutaneous squamous cell carcinoma (laCSCC) who are not candidates for surgery. |
| Consultation Request Date | March 12, 2018 |
| Summary Goal Date | July 28, 2018 |
| Action Goal Date | August 28, 2018 |
| PDUFA Date     | August 28, 2018 |

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study Protocol R2810-ONC-1540 (from now on called Study 1540) was submitted to FDA in support of a proposed indication for BLA 761097. This was a phase 2, nonrandomized, multicenter study of cemiplimab, a fully human monoclonal antibody to programmed death – 1 (PD-1), in patients with advanced cutaneous squamous cell carcinoma. The data for Study 1540 submitted by the Sponsor to the Agency in support of BLA 761097 appear reliable based on available information from the inspections of four domestic clinical sites and the Sponsor.

Four clinical sites, Dr. Michael Migden, M.D. (Site 840001), Dr. Ann Lynn Chang, M.D. (Site 840008), Dr. Leonel F. Hernandez-Aya, M.D. (Site 840013) and Dr. Chrysalyne Schmults, M.D. (Site 840015) and the Sponsor, Regeneron Pharmaceuticals, Inc. were selected for audit.

There were no significant inspectional observations for the clinical investigators, Dr. Ann Lynn Chang, M.D., Dr. Leonel F. Hernandez-Aya, M.D., Dr. Chrysalyne Schmults, M.D., and the Sponsor, Regeneron Pharmaceuticals, Inc., and the final compliance classification for these
inspections is No Action Indicated (NAI).

Although GCP violations were observed during the inspection of the clinical investigator, Dr. Michael Migden, M.D., they were unlikely to substantially impact the determination of efficacy and safety of the clinical trial and the final compliance classification for the inspections is Voluntary Action Indicated (VAI).

II. BACKGROUND

Regeneron Pharmaceuticals, Inc., as sponsor of BLA 761097 seeks priority approval for the use of cemiplimab for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC), or with locally advanced cutaneous squamous cell carcinoma (laCSCC) who are not candidates for surgery. Cemiplimab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with programmed death ligands (PD-L1 and PD-L2), countering PD-1 mediated inhibition of the immune response, including the anti-tumor immune response. Blockade of the programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoint enhances antitumor immune responses and has demonstrated efficacy in patients with various solid tumors.

Study 1540 is an ongoing phase 2, nonrandomized, 3-group, multicenter pivotal study evaluating the efficacy and safety of cemiplimab in patients with advanced CSCC. The screening period was up to 28 days. The first patient was screened on April 7, 2016 and the first patient was enrolled on May 11, 2016. The data cut-off for BLA was October 27, 2017.

The study included the following cohorts:
- Group 1: Patients with mCSCC included patients with both nodal metastatic and distant metastatic disease.
- Group 2: Patients with unresectable, laCSCC who had contraindications to surgery or radiation or had not achieved disease control with these treatments.
- Group 3: Patients with mCSCC (both nodal metastatic and distant metastatic disease) who received a fixed dose during the treatment period.

Study duration was up to 96 weeks of treatment in Groups 1 and 2 (cemiplimab 3 mg/kg administered as an IV infusion over 30 minutes Q2W), up to 54 weeks of treatment in Group 3 (cemiplimab 350 mg administered as an IV infusion over 30 minutes Q3W), and up to 6 months of follow-up.

The primary efficacy endpoint was Objective Response Rate (ORR) based on a centrally reviewed evaluation at each time point at which a response assessment occurred using RECIST 1.1 or the composite response criteria. Composite response was based on photographic assessment of externally visible lesions and assessment of radiologic data according to RECIST 1.1. ORR was determined by the proportion of patients with best overall responses (BORs) of complete response (CR) or partial response (PR) in the full analysis set by group.

Study 1540 was conducted at 31 centers in the United States, Germany, and Australia. As of the data cut-off, a total of 194 patients had been screened and a total of 137 patients had been
enrolled and treated (59 patients in Group 1, 55 patients in Group 2, and 23 patients in Group 3. Group 3 opened after the completion of enrollment to Group 1. Forty-one patients had discontinued study drug prematurely. The most common primary reason for premature treatment discontinuation was disease progression.

GCP inspection was conducted at four clinical investigator (CI) sites and the Sponsor. The CI sites for inspection were chosen primarily based on protocol violations and safety events.

### III. RESULTS (by site):

<table>
<thead>
<tr>
<th>Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.</th>
<th>Protocol #</th>
<th># of Subjects</th>
<th>Inspection Dates</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michael Migden, M.D. Site Number: 840001 MD Anderson Cancer Center 1400 Pressler Street Houston, TX 77030</td>
<td>Study: 1540</td>
<td>Enrolled: 12</td>
<td>June 11-15 and 20, 2018</td>
<td>VAI</td>
</tr>
<tr>
<td>Anne Lynn Chang, M.D. Site Number: 840008 Stanford Cancer Center 450 Broadway Street Redwood City, CA 94063</td>
<td>Study: 1540</td>
<td>Enrolled: 8</td>
<td>June 6-8 and 11-13, 2018</td>
<td>NAI</td>
</tr>
<tr>
<td>Leonel F. Hernandez-Aya, M.D. Site Number: 840013 Washington University 660 S. Euclid Avenue St. Louis, MO 63110</td>
<td>Study: 1540</td>
<td>Enrolled: 8</td>
<td>May 21-25 and 29, 2018</td>
<td>NAI</td>
</tr>
<tr>
<td>Chrysalyne Schmults, M.D. Site Number: 840015 Dana Farber Cancer Institute 1153 Center Street Boston, MA 02130</td>
<td>Study: 1540</td>
<td>Enrolled: 10</td>
<td>June 11 and 13-14, 2018</td>
<td>NAI</td>
</tr>
<tr>
<td>Sponsor: Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591</td>
<td>Study: 1540</td>
<td></td>
<td>June 11-14 and 18, 2018</td>
<td>NAI</td>
</tr>
</tbody>
</table>

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.
1. Michael Migden, M.D. (Site 840001)

The site screened 17 subjects and 12 were randomized and treated. At the time of the inspection, 7 subjects were on study treatment. Two (2) subjects completed the study, 2 discontinued treatment due to severe adverse event or disease progression. One (1) subject died due to disease progression. An audit of all enrolled subject’s records was conducted.

The inspection evaluated all subject informed consent forms. Additionally, the inspection included review of subject medical records, source documents, pharmacy logs, IRB/CI correspondences, subject assessments, monitor logs, primary efficacy endpoint, and Adverse Event (AE) reporting to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and the electronic Case Report Forms (eCRF) and found to be the same.

Inspectional observations were noted and at the conclusion of the inspection, a two-item Form FDA 483 was issued to the CI for the following two observations:

1. Investigational drug disposition records are not adequate with respect to use by subjects.
2. An investigation was not conducted in accordance with the investigational plan.

With respect to the inspectional observation 1, there was an instance of investigational product (IP) dispensation mix up involving two subjects in Group 2 (cemiplimab 3mg/kg) on the same day who received the IP dose prepared and infused using the wrong vial and diluent ordered for the opposite patient. Specifically, per the Interactive Voice Response System (IVRS) IP dispensation form dated ______ for Cycle 1-Day 15, Subject ______ was to be dispensed vial # ______ and diluent # ______. However, the actual IP dose was prepared using vial ______ and diluent # ______ which were ordered for Subject ______. Similarly, per the IVRS IP dispensation form dated ______ for Cycle 1-Day 15, Subject ______ was to be dispensed vial ______ and diluent # ______. The actual IP dose was prepared using vial ______ and diluent # ______ which were ordered for Subject ______. The study team identified the error the next day and appropriate notifications and documentations were made. The inspection found no other instances of drug accountability discrepancies.

In his response to Form FDA 483, Dr. Migden’s written response dated July 9, 2018 acknowledged the inspectional observation 1 and outlined the preventive action plan. The plan included refresher training for the investigational pharmacy staff on the IVRS assignments including discussion about the importance of completing the process to quality check of the drug pulled and transferred against the vial# assignment report generated by the IVRS and transmission of patient specific IVRS assignment via email or a physical copy of IVRS assignment with the IP being delivered to the dispensing area. An additional checking process was also implemented requiring the verifying pharmacist to also review the IVRS assignment (via printed email or paper copy delivered with IP) and check the specific kit/lot # against the actual IP checked out and documented in the institutions iData system.

In regards to the inspectional observation 2, there were protocol deviations with respect to laboratory tests being performed in a manner not consistent with the clinical protocol. The
study used various methods to assure safety such as hematology, and chemistry blood work, PK samples, PTT, PT/INR, and serial ECG’s. Specifically, per the protocol Study Schedule (Screening and Treatment) for Groups 1 and 2 the PTT test was to be conducted on Cycle 1-Day 1, Cycle 2-Day 1, and subsequent Cycles (Day 1 visit). The PT/INR was done on all visits. However, the PTT testing was not conducted on five subjects (Subjects ) until Cycle 2-Day 1, or Cycle 3-Day 1 visit.

As per Dr. Migden’s written response to Form FDA 483 dated July 9, 2018, he acknowledged the protocol deviations and outlined a corrective and preventive action plan that included training and implementing multiple verification checkpoints during the conduct of a clinical investigation to prevent reoccurrences in the future.

Although GCP violations were noted at the clinical site, they do not appear to significantly impact study outcomes. The investigator determined primary efficacy endpoint data were verifiable. While the described protocol deviations with respect to the missed PTT laboratory tests were not reported to the NDA, the overall adverse impact on patient safety was likely low. There was no evidence of under reporting of AEs. The data from Site 840001 appear reliable based on available information.

2. Anne Lynn Chang, M.D. (Site 840008)

The site screened 20 subjects and 8 were randomized and treated. At the time of the inspection, 3 subjects completed the study, 4 subjects discontinued treatment due to either adverse events or disease progression, and 1 subject died due to disease progression. An audit of all enrolled subject’s records was conducted.

The inspection evaluated all subject informed consent forms. Additionally, the inspection included a review of the sites ICFs, IRB approvals, 1572s, study staff qualifications and training, correspondence, drug accountability records, primary efficacy endpoint source documentation, serious adverse events (SAE) reporting, adverse event (AE) reporting and adherence to inclusion and exclusion criteria to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and the eCRF and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 840008 appear reliable based on available information.

3. Leonel F. Hernandez-Aya, M.D. (Site 840013)

The site screened 12 subjects and 8 were randomized and treated. At the time of the inspection, 4 subjects were on study treatment. Two (2) subjects completed the study and 2 discontinued treatment due to disease progression but were still in follow up. An audit of all enrolled subject’s records was conducted.
The inspection evaluated all subject informed consent forms. Additionally, the inspection covered informed consent, protocol adherence, adverse event reporting, Institutional Review Board (IRB) oversight, monitoring, test article accountability, and a data audit of the primary efficacy and safety endpoints. Study source documents and records of the audited subjects were compared to the data listings and the eCRF and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of SAEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 8400013 appear reliable based on available information.

4. Chrysalyne Schmults, M.D. (Site 840015)

The site screened 20 subjects and 10 were randomized and treated. At the time of the inspection, 7 subjects were on study treatment across the three cohorts. One (1) subject discontinued treatment due to disease progression and 2 subjects died due to disease progression. An audit of all enrolled subject’s records was conducted.

The inspection evaluated all subject informed consent forms. Additionally, all subject records were reviewed to verify protocol adherence, subject eligibility, concomitant medications, personnel training and qualifications, primary efficacy endpoints and adverse event detection and reporting. Study source documents and records of the audited subjects were compared to the data listings and the eCRF and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 840015 appear reliable based on available information.

5. Regeneron Pharmaceuticals, Inc. (Sponsor)

The inspection was issued to review the conduct of Study 1540 performed in support of the application. The inspection included a review of the financial disclosures, standard operation procedures and policies, monitoring procedures, safety and adverse event reporting, data collection and handling, electronic records, Trial Master File (TMF) management and security policies.

The inspection found no major regulatory violations or deficiencies that would impact data integrity or subject safety. A form FDA 483, Inspectional Observation was not issued. There was appropriate oversight and management of the clinical trial. There was no evidence of under reporting of AEs.

Overall, the Sponsor appeared to adequately verify that the clinical investigation was conducted in accordance with the investigational plan and that responsibilities of the clinical
investigators were carried out. The data from Regeneron Pharmaceuticals, associated with Study 1540, appear reliable based on available information.

{See appended electronic signature page}

Navid Homayouni, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Susan 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

cc:

Central Doc. Rm.
Review Division /Associate Director/Steven Lemery
Review Division /Medical Team Leader/Suzanne Demko
Review Division/Medical Officer/Denise Casey
Review Division /Project Manager/Missiratch Biable
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Navid Homayouni
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database PM/Dana Walters
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAVID R HOMAYOUNI
07/27/2018

SUSAN D THOMPSON
07/27/2018

KASSA AYALEW
07/27/2018
Date of This Review: July 19, 2018
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: BLA 761097
Product Name and Strength: Libtayo (cemiplimab) Injection, 250 mg/5 mL and 350 mg/7 mL
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Regeneron Pharmaceuticals, Inc.
FDA Received Date: February 28, 2018 and June 18, 2018
OSE RCM #: 2017-2591
DMEPA Safety Evaluator: Colleen Little, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD
1 REASON FOR REVIEW

As part of BLA 761097, this review evaluates the proposed Libtayo prescribing information (PI), container labels, and carton labeling to identify areas of vulnerability that could lead to medication errors.

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.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
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<td>Human Factors Study</td>
<td>C-N/A</td>
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<tr>
<td>ISMP Newsletters</td>
<td>D-N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E-N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 PRESCRIBING INFORMATION

Our review of materials found the proposed Libtayo PI may be improved to promote safe use of this product.

3.2 CONTAINER LABEL AND CARTON LABELING

We reviewed the February 28, 2018 proposed Libtayo container labels and carton labeling and determined that they may be improved to promote safe use of the proposed product.

We noted the use of the package type term, on container labels, carton labeling, and in PI. We consulted the Office of Pharmaceutical Quality (OPQ) via internal email on June, 4, 2018 for the determination of the correct package term type. OPQ confirmed the appropriate package term type is “single-dose vial.”

We provided the following recommendations to OPQ Labeling Reviewer to get OPQ concurrence. In addition to OPQ’s labeling comments, DOP2 communicated our container label
and carton labeling recommendations below to Regeneron Pharmaceuticals, Inc. on June 7, 2018.

A. General Comments (Container labels & Carton Labeling)

1. **Revise the product code in the NDC numbers**

   Injectable products might contain the same product concentration but contain a different total amount of drug in the container because of differences in the fill volume (e.g., 20 mg/2 mL (10 mg/mL), 40 mg/4 mL (10 mg/mL)). When the same product code number is used for all of the different containers, healthcare practitioners have had difficulty distinguishing the difference in total drug content. Each of these injectable products should therefore have a different product code assigned.

2. **Revise the statements to read “Single-Dose Vial- Discard Unused Portion” to display the appropriate package type term.**

3. **Identify the location and header of the lot number and expiration date on the container labels and carton labeling.**

   a. Ensure the lot number and expiration date are clearly differentiated from one another and are not located in close proximity to other numbers where the numbers can be mistaken as the lot number.

---


b. For the expiration date, we recommend using a format such as MMMYYYY (e.g. JAN2019) or MMMDDYYYY (e.g. JAN312019) to minimize confusion and reduce the risk for deteriorated drug medication errors.a

B. Container Labels
   1. Revise the statement “” to “For intravenous infusion after dilution.”

C. Carton Labeling
   1. Revise the statement “” to “For intravenous infusion after dilution.”

   2. Revise the “Carton Statement” from Package Insert, and Medication Guide” to “1 Single-Dose Vial, Prescribing Information, and Medication Guide” to display the appropriate packaging type term and maintain consistency with PI.

   3. Consider revising the storage and handling statement from “Store in the original carton...” to “Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton” to “Do not freeze or shake.” to maintain consistency with PI.

Regeneron Pharmaceuticals, Inc. submitted revised Libtayo container labels and carton labeling on June 18, 2018 in response to our recommendations above and OPQ’s labeling comments.

We found the revised Libtayo container labels and carton labeling acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude the proposed Libtayo PI received on February 28, 2018, may be improved to promote the safe use of the product as described in Section 4.1. The revised Libtayo container labels and carton labeling received on June 18, 2018 are acceptable from a medication error perspective.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. Please see Appendix H for our PI recommendations in track changes.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Libtayo received on February 28, 2018 from Regeneron Pharmaceuticals, Inc.

| Table 2. Relevant Product Information for Libtayo |
|------------------|------------------|
| **Initial Approval Date** | N/A |
| **Active Ingredient** | cemiplimab |
| **Indication** | For the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for (b) (4) |
| **Route of Administration** | Intravenous |
| **Dosage Form** | Injection |
| **Strength** | 250 mg/5mL (50 mg/mL) and 350 mg/7mL (50 mg/mL) |
| **Dose and Frequency** | 350 mg every 3 weeks administered as an intravenous infusion over 30 minutes until symptomatic disease progression or unacceptable toxicity. |
| **How Supplied** | Singe-dose vial |
| **Storage** | Store in a refrigerator at 2°C to 8°C (36°F to 46°F) (b)(4) in the original carton (b)(4) Do not freeze or shake. |
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Libtayo labels and labeling submitted by Regeneron Pharmaceuticals, Inc.

- Container labels received on February 28, 2018
- Carton labeling received on February 28, 2018
- Revised Container labels received on June 18, 2018
- Revised Carton labeling received on June 18, 2018
- Prescribing Information (Image not shown) received on February 28, 2018

G.2 Label and Labeling Images

Container labels received on February 28, 2017

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

COLLEEN L LITTLE
07/19/2018

CHI-MING TU
07/19/2018
CDER Breakthrough Therapy Designation Determination Review Template

<table>
<thead>
<tr>
<th>IND/NDA/BLA #</th>
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</tr>
<tr>
<td>Product</td>
<td>REGN2810</td>
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<tr>
<td>Indication</td>
<td>Metastatic and locally advanced and unresectable cutaneous squamous cell carcinoma (CSCC)</td>
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<td>Drug Class/Mechanism of Action</td>
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<td>ODE/Division</td>
<td>OHOP/DOP2</td>
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<tr>
<td>Breakthrough Therapy Request Goal Date (within 60 days of receipt)</td>
<td>September 17, 2017</td>
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</table>

Note: This document should be uploaded into CDER’s electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

   The proposed indication for REGN2810 is for the treatment of patients with metastatic and locally advanced and unresectable cutaneous squamous cell carcinoma (CSCC).

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

   □ YES  □ NO

   If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No”, proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

   a. Is the condition serious/life-threatening?  

      □ YES  □ NO

   If 3a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

      □ YES the BTDR is adequate and sufficiently complete to permit a substantive review

      □ Undetermined

      □ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)

v. No or minimal clinically meaningful improvement as compared to available therapy\(^2\)/historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

N/A.

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

**Disease Background**

CSCC is the second most common human cancer in the United States, with an estimated annual incidence of 700,000 cases.\(^1\) While most cases are localized tumors amenable to curative resection, approximately 4% of patients will develop nodal metastases, and an estimated 2% of patients will die from their disease.\(^1,2\) High-risk patients are those who have recurrent disease or are at high risk for recurrence, lymph node metastases or distant metastases. Precise

incidences of overall disease, high-risk disease and survival outcomes are not available because these cancers are grouped with other nonmelanoma skin cancers (NMSC) in the Surveillance, Epidemiology, and End Results (SEER) database. Factors associated with recurrence and poor prognosis in CSCC include tumor size > 2 cm, tumor depth > 2 mm (Breslow thickness), perineural invasion, host immunosuppression, poorly differentiated histology and location on the ear, temple or lip. Ten-year survival rates are less than 20 percent for patients with regional lymph-node involvement, and for those patients who develop distant metastases, the median survival time is less than two years.

The standard of care for locoregional CSCC is complete surgical resection with a minimum margin of 5 mm for low risk tumors and 10 mm for high risk tumors. If there is nodal involvement, a regional lymph node dissection is recommended, and adjuvant radiation therapy is utilized in most cases. Treatment options are limited for the small subset of patients with CSCC who develop local recurrences, unresectable disease, or distant metastatic disease. Radiation as the definitive treatment may be considered in some patients with unresectable locally advanced disease based on the durable response rates and disease free survival described in retrospective studies.

There are no FDA-approved systemic therapies for patients with locally advanced and unresectable or metastatic CSCC. Additionally, there are case reports of various EGFR inhibitors and single arm, prospective studies of cetuximab and gefitinib in patients with high-risk CSCC that have reported objective responses. In one of the largest clinical studies of cetuximab in 36 patients with advanced CSCC, the median overall survival was 8.1 months.

REGN2810 is a humanized monoclonal antibody directed against PD-1 that works through blockade of T-cell inhibition leading to augmentation of the host immune response in the tumor environment. Drugs in class that have been approved for other cancer indications include nivolumab, pembrolizumab, atezolizumab and avelumab. There are also multiple PD-1 and PD-L1 inhibitors currently in development for various indications. As of January 2017, almost 400 patients with various malignancies have been exposed to REGN2810. Clinical experience is derived from six clinical trials conducted under U.S. INDs and two additional ex-U.S. studies. The data to support this BTDR is from Study 1423, a dose-finding and safety study in patients with advanced solid tumors including CSCC. Specifically, the 1423 trial includes two expansion cohorts for the evaluation of REGN2810 in patients with either locally advanced and unresectable CSCC (cohort 7) or patients with metastatic CSCC (cohort 8).

Relevant Regulatory History
The initial IND (IND 123950) for REGN2810 was submitted to the Division of Oncology Products 1 (DOP 1) on December 22, 2014. The IND included the clinical protocol for Study R2810-ONC-1423 entitled, “A First-in-Human (FIH) Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death -1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies in Patients with Advanced Malignancies.” The study may proceed letter was issued on January 21, 2015.

On September 10, 2015, a pre-IND meeting was held with DOP2 to discuss the development program for REGN2810 in CSCC. The following key points were made:

- FDA agreed to the enrollment of patients without a requirement for prior systemic therapy as long as Regeneron agreed to provide analyses of confirmed objective response rates (ORR) based on subgroups defined by extent of prior therapy (no prior systemic therapy or having received any prior systemic therapy).
- FDA agreed to the enrollment of patients with metastatic CSCC without a requirement for prior radiation therapy; however, in patients with locally advanced CSCC, FDA recommended that an individualized benefit:risk
assessment be performed by a multidisciplinary team consisting of a medical oncologist with expertise in cutaneous malignancies or a dermato-oncologist and a radiation oncologist prior to enrollment in the proposed study. FDA also stated that the case report form (CRF) for patients with locally advanced CSCC should capture the reasons for enrollment in the study including why the patient with locally advanced CSCC was not a candidate for surgical resection or for radiation therapy.

- FDA recommended that pre-specified subgroup analyses of patients with locally advanced and metastatic disease be outlined in the statistical analysis plan. FDA also stated that since a different treatment effect may be observed in patients with metastatic disease as compared to patients with locally advanced disease, it will be essential to have an adequate sample size to demonstrate direct clinical benefit in both populations.

- FDA agreed that a primary endpoint of ORR (as determined by independent review) may be acceptable provided ORR is shown to be clinically meaningful in magnitude and duration, with an acceptable safety profile for REGN2810 in this patient population. For patients with locally advanced CSCC, a (generally) non-life-threatening disease, Regeneron must provide justification that the observed reduction in tumor size provides clearly defined, direct clinical benefit.

On December 7, 2015, IND 127100 was submitted and contained the protocol for Study R2810-ONC-1540 (1540), an open-label, non-randomized, multicenter study of REGN2810 administered at a dose of 3 mg/kg every two weeks to two groups of patients with advanced CSCC.

On December 16, 2017, Regeneron requested Preliminary Breakthrough Therapy Designation Request (BTDR) Advice and described preliminary results from 25 patients with CSCC treated with REGN2810. During the teleconference, FDA stated that while the data from 25 patients dosed may be adequate for a breakthrough request in a rare disease, the determination of breakthrough designation will depend on the magnitude of the treatment effect in an analysis that includes all patients who have received at least one dose or partial dose of the study drug. Additionally, for this disease, FDA stated that the results for the subtypes of metastatic CSCC and locally advanced CSCC will be reviewed separately given the different natural histories and prognostic factors associated with the different disease stages. FDA recommended that the sponsor seek a second preliminary breakthrough designation request discussion after all patients included in the dataset have been followed for a minimum of four months after the onset of response, that there be an independent review of all responses, and that available medical photographs be submitted for patients enrolled in the study if an improvement in disfiguring lesions is considered to be of clinical benefit in this disease.

On June 7, 2017, Regeneron requested additional Preliminary BTDR Advice, and a teleconference was held with the FDA on June 27, 2017, to review the updated data on the same 25 patient cohort. During the teleconference, FDA stated that although the data appeared consistent with what could merit a BTD, it would be helpful if Regeneron provide six months of followup for durability following onset of response as it was already June and an updated analysis did not seem unfeasible. This could provide a stronger justification for the breakthrough designation request.

On July 18, 2017, Regeneron submitted a formal request for BTD determination for REGN2810.

7. **Information related to endpoints used in the available clinical data:***

   a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

   Regeneron considers durable objective response rate to be a clinically meaningful endpoint supporting the BTDR. ORR and duration of response (DOR) according to RECIST v1.1 was measured in Study 1423, and these results...
are provided to support the BTDR. In the ongoing Study 1540, ORR will be measured using a composite endpoint that measures radiographic response according to RECIST in addition to medical photography and tissue evaluation of target lesions. Regeneron will also submit photographic data from Study 1540 as supportive evidence of clinical benefit in the potential marketing application.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).
- A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).
- An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.

DOP2 agrees that demonstration of a meaningful effect size on durable ORR according to centrally reviewed RECIST or a modified RECIST guideline (that considers digital photographic assessments and tissue analysis in addition to radiographic measures) would be clinically meaningful in patients with metastatic or locally advanced and unresectable CSCC and could support an application for marketing approval. Given that some patients with CSCC suffer from disfiguring lesions, clear photographic evidence of substantial improvement in such lesions would be acceptable as supportive evidence of clinical benefit.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.
- In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.

The standard of care for patients with CSCC is local treatment via surgical resection or in some cases radiotherapy. The REGN2810 development program is intended for patients that do not have local control options. There are no FDA-approved therapies and no known curative treatments for patients with inoperable and locally advanced or metastatic CSCC. The most common systemic regimens that are used off-label to treat this advanced subset of patients are cisplatin-based chemotherapy and EGFR inhibitors. The following table summarizes agents that have been or are currently being evaluated in clinical studies in patients with CSCC with advanced disease. The RECIST guideline was used for assessing ORR and DOR in these studies. The REGN2810 development program utilizes RECIST and additionally incorporates photographic and histologic results into the overall response evaluations. The table does not include topical agents, cytotoxic chemotherapeutics or drugs being evaluated in refractory all-comer cancer populations.
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<thead>
<tr>
<th>Product</th>
<th>Mechanism of Action</th>
<th>Sponsor or reference</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Cetuximab</td>
<td>EGFR TKI</td>
<td>Maubec et. al. 2011</td>
<td>Completed. 36 patients with unresectable CSCC (three patients with metastatic disease). ORR per RECIST was 28%. DOR not reported. Median OS 8.1 months.</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR TKI</td>
<td>Lewis et. al. 2012</td>
<td>Completed. 22 patients with aggressive or recurrent local CSCC. Patients with distant metastases excluded. Neoadjuvant gefitinib for 2 cycles followed by standard of care local control. ORR 31%.</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>MAB to EGFR</td>
<td>Foote et. al. 2014</td>
<td>Completed. 16 patients with incurable advanced CSCC (two patients had metastatic disease). ORR per RECIST was 31% (95 CI: 11-59). DOR not reported. Median OS 11 months.</td>
</tr>
</tbody>
</table>

TKI: tyrosine kinase inhibitor, MAB: monoclonal antibody

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation.  

No other drugs have received breakthrough therapy designation for this indication.

10. Information related to the preliminary clinical evidence:  

a. A table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The data supporting the BTDR for REGN2810 comes from one trial: Study 1423. This is an ongoing, first-in-human, multicenter, dose-finding and activity-estimating study of REGN2810 administered intravenously as a single-agent or in combination with cyclophosphamide or radiation (depending on the expansion cohort) every three weeks in patients with various advanced solid tumors. Specifically, the efficacy results to date from patients treated in expansion cohorts 7 (metastatic CSCC) and 8 (locally advanced and unresectable CSCC) are being submitted to support the BTDR. The patients in these cohorts received single agent REGN2810 and no concomitant radiation.

An analysis of centrally reviewed ORR and DOR was performed using data from the first 25 patients with metastatic (n=11) or locally advanced and unresectable (n=14) CSCC treated in Study 1423 who received at least one infusion of REGN2810 as of December 14, 2016. The data cut off date for the response rate analysis was June 12, 2017. The centrally reviewed ORR was 44% (11/25) in this combined group of patients with either locally advanced or metastatic CSCC. Note that in January 2017, 11 of the 25 patients had investigator-assessed objective responses; however, upon central review, one patient (ID 123456) withdrew consent and had not had a confirmatory scan and was considered to have a best response of stable disease (SD). At the time of the June cut off date, however, four additional patients had scans centrally reviewed, and another patient in cohort 8 (ID 789012)...

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3 Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

4 Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Reference ID: 4148305
was noted to have a partial response. Therefore, there are still currently 11 responders from the first 25 patients with CSCC enrolled in Study 1423.

The following swimmer’s plot and summary table, copied from the briefing document, show the investigator and centrally-reviewed ORR and DOR results for the 11 patients who were considered to be responders in January 2017 and the additional patients who had their scans centrally reviewed after January 2017. Among 11 patients who had an objective response, nine have maintained the response as of the June 2017 data cutoff. Two patients have since progressed, one with brain metastasis and one with new nodal disease. The median duration of response has not been reached. Six patients (55% of the responder subgroup) have ongoing responses of at least seven months at data cutoff.

**Figure 1: Swimmer’s Plot**

Expansion Cohort 7 M1 CSCC and Expansion Cohort 8 M0 CSCC and Dose Escalation Patient with CSCC

- **Partial Response**
- **Stable Disease**
- **Progressive Disease**

Reference ID: 4148305
Table 1: Study 1423 ORR and DOR results for patients with CSCC

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<th>Best Overall Response, per Central Review</th>
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<th>Time to 1st PR assessment by Central Review (months)</th>
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Additional Patients Whose Tumor Assessments Were Sent For Central Review

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</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; NE, not evaluable; uPR, unconfirmed partial response

a As presented to FDA on 25 January 2017
b This subject completed 48 weeks of treatment, followed by approximately 24 weeks of post-treatment follow-up. This was his End-of-Study visit, because protocol events end with the completion of this follow-up period. Personal communication from the investigator on 5 May 2017, the patient continues to do well and has had no evidence of disease according to routine assessments since completing the study.

c After 25 January 2017, the investigator changed best response to SD, based on local re-review.
d This subject met criteria for unconfirmed partial response at his first response assessment (week 8). He became non-compliant after 3 additional treatments and the second response assessment (week 16) was not done. He was lost to follow up until the third scheduled response assessment (week 24), at which point his overall response assessment was stable disease due to increase in tumor during the period of non-compliance. He then resumed treatment and partial response was observed at the fourth (week 32) and fifth (week 40) response assessments.

duration of response is therefore calculated from week 32 as per RECIST 1.1. Photographs are shown in Figure 6.

e Patient withdrew consent during Cycle 2. Because a confirmatory scan was not obtained, his best response is SD per RECIST 1.1. Photographs are shown in Figure 1.

DOP2 additionally reviewed the ORR and DOR results separately for the subgroups of patients with locally advanced CSCC and patients with metastatic CSCC. Six of 11 patients (55%) with metastatic disease and five of the 14 patients (36%) with locally advanced disease from Study 1423 had a centrally reviewed objective response to REGN2810. The ORR in patients with metastatic disease is particularly encouraging. The higher response rate in patients with metastatic disease as compared to those patients with locally advanced disease is likely due to the small sample sizes and not a difference in the biologic antitumor effect of REGN2810 in these patients.

Finally, Regeneron also submitted photographic data to depict some of the more dramatic responses noted in patients with baseline disfiguring tumors. One example from the briefing document is copied below:
b. Include any additional relevant information. Consider the following in your response:

- **Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.**

- **Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.**

- **Safety data: Provide a brief explanation of the drug’s safety profile, elaborating if it affects the Division’s recommendation.**

Patients with metastatic and locally advanced unresectable CSCC represent a population with an unmet medical need. There are no known curative therapies and no available treatments for these subsets of high-risk CSCC. DOP2 considers the objective response and duration of response data from patients with advanced CSCC treated with REGN2810 in Study 1423 to be preliminary evidence of a substantial improvement over the published results of off-label use of cytotoxic chemotherapy regimens and EGFR inhibitors.7,8

DOP2 also took into consideration that Regeneron’s development program from REGN2810 in CSCC includes an ongoing trial (Study 1540) intended to support a marketing application for REGN2810 in patients with advanced CSCC. Study 1540 is an open-label, non-randomized, multicenter study of REGN2810 administered at a dose of 3 mg/kg every two weeks to patients with metastatic CSCC (Group 1) or locally advanced and unresectable CSCC (Group 2). This trial is enrolling well with 58 patients with metastatic disease and over 30 patients with locally advanced disease treated as of April 2017. Regeneron recently met with DOP2 to discuss plans for submitting an application for REGN2810 for the treatment of patients with CSCC in Q1 2018.
The summary safety data provided in the BTDR and the recently submitted preBLA Type B meeting briefing materials were also reviewed. As of January 20, 2017, 353 patients were exposed to REGN2810 including 300 at the recommended 3 mg/kg dose in Study 1423, and the median exposure was 14 weeks. There were no dose-limiting toxicities observed during dose-escalation. Regeneron reports one patient experienced fatal hepatic failure that was considered related to REGN2810 and one patient experienced fatal paraneoplastic encephalomyelitis also assessed as possibly related to REGN2810. Twenty-three percent of patients experienced serious adverse events (SAEs), and 7% of patients experienced at least one treatment-related SAE. Immune-mediated adverse reactions (imARs) occurred in 34% of patients, and 5% of patients had serious imARs. The types of imARs reported are similar to those associated with other drugs in class. Common treatment emergent adverse events (AEs) that occurred in more than 10% of patients included fatigue, nausea, decreased appetite, anemia, constipation, arthralgia, diarrhea, dyspnea, cough, pyrexia, vomiting, asthenia and back pain. Of the 25 patients with CSCC in Study 1423, Grade 3 or greater AEs included rash, arthralgia, asthenia and liver enzyme elevation. Two patients discontinued for AEs of grade 3 rash and liver enzyme elevation. Two patients died within 30 days of REGN2810 infusion; both were considered unrelated to drug and due to disease progression. Overall, the safety profile of REGN2810 in patients with CSCC does not appear to differ from that seen in other patients with cancer.

11. Division’s recommendation and rationale (pre-MPC review):

☐ GRANT:

Provide brief summary of rationale for granting:

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

There are no systemic therapies approved for patients with metastatic or locally advanced CSCC. DOP2 considers the effect size on response rate of 44% together with the durability of responses (ranging from 2+ to 14.5+ months) to date in patients with advanced CSCC Study 1423 to be preliminary evidence of a substantial improvement over alternative treatment options which include off-label use of cisplatin-based chemotherapy regimens and EGFR inhibitors. DOP2 has also considered the supportive photographic evidence of clinical benefit and the overall development program in CSCC.

☐ DENY:

Provide brief summary of rationale for denial:

*Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

12. Division’s next steps and sponsor’s plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

   DOP2 will continue to communicate with Regeneron and provide regulatory guidance to facilitate the development program for REGN2810 in advanced CSCC.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:
13. List references, if any:


14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

\( /s/ \)

DENISE A CASEY
09/19/2017