CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761097Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 127100

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Laura Simpson, Ph.D.
Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Simpson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Cemiplimab (REGN2810)."

We also refer to the telecon between representatives of your firm and the FDA on November 29, 2017. The purpose of the meeting was to discuss the content and format of the cemiplimab BLA 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.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Missiratch Biable, M.S., R.A.C. (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Guidance
Teleconference Date and Time:	November 29, 2017, 1:00 – 2:00 PM EST
Application Number:	IND 127100
Product Name:	Cemiplimab (REGN2810)
Indication:	Metastatic cutaneous squamous cell carcinoma (mCSCC)
Sponsor/Applicant Name:	Regeneron Pharmaceuticals, Inc.
Meeting Chair:	Steven Lemery
Meeting Recorder:	Missiratch Biable

FDA ATTENDEES

Division of Oncology Products 2
Steven Lemery, M.D., M.H.S., Associate Director, DOP2
Denise Casey, M.D., M.S., Medical Officer
Diana Bradford, M.D., Medical Officer
Missiratch Biable, M.S., Senior Regulatory Health Project Manager
Stacie Woods, Pharm.D., Regulatory Health Project Manager

Division of Oncology Products 1
Jeongmi Kim, Medical Officer Contractor at DOP1

Office of Biostatistics
Pallavi Mishra-Kalyani, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology
Jiang Liu, Ph.D., Pharmacometrics Team Leader

Office of Product Quality, Office of Biological Products
Qing (Joanna) Zhou, Ph.D., Product Quality Team Leader
Willie Wilson,, Ph.D., DS Product Quality Reviewer
Jens Fricke, Ph.D., DP Product Quality Reviewer

SPONSOR ATTENDEES
Regeneron Pharmaceuticals
Israel Lowy, M.D., Ph.D., Clinical Sciences, Oncology

Matthew Fury, M.D., Ph.D., Clinical Sciences, Oncology
Robert Charnas, Ph.D., Program Direction
Frank Seebach, M.D., Regulatory Affairs
Laura Simpson, Ph.D., Regulatory Affairs
Usama Aslam, Pharm. D., Regulatory Affairs
Deba Saha, Ph.D., Regulatory CMC
Jennifer McNay, Industrial Operations and Product Supply
Anne Pirozzi, Ph.D., CMC Regulatory Sciences
Rajesh Ahuja, Ph.D., Validation
Bo Gao, Ph.D., Biostatistics
Anne Paccaly, PharmD, Ph.D., Clinical Pharmacology
Emmanuel Okoye, M.D., MPH, Risk Management

Sanofi
Sunil Gupta, M.D., Global Regulatory Affairs
Karl Hsu, M.D., Clinical Development

BACKGROUND

On September 29, 2017, Regeneron Pharmaceuticals, Inc. (Regeneron) submitted a Type B meeting request to discuss the content and format of a cemiplimab (proposed non-proprietary name) BLA 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.

Regeneron submitted the meeting package on October 27, 2017.

Regulatory history

A pre-BLA meeting was held on July 26, 2017, to obtain agreement between Regeneron and the FDA on the content and presentation of data to support the filing of the planned BLA for cemiplimab (REGN2810) for the following proposed indications:

- "REGN2810 is indicated for the treatment of adults with metastatic cutaneous squamous cell carcinoma (CSCC)", and

- "REGN2810 is indicated for the treatment of adults with locally advanced and unresectable cutaneous squamous cell carcinoma."

A separate CMC only pre-BLA meeting was held on July 27, 2017, to discuss the quality components of the proposed BLA.

During these pre-submission meetings, FDA was not able to reach a final agreement with Regeneron on the contents of a complete application for a BLA for REGN2810 under the PDUFA V program because top-line summary safety and efficacy data in support of the BLA were not available. FDA recommended that Regeneron submit the data from patients with CSCC

enrolled in R2810-ONC-1423 *and* R2810-ONC-1540 as soon as the results are available to obtain final agreement on the proposed content and format of the complete application. These data have not been submitted prior to this meeting.

On September 6, 2017, REGN2810 (cemiplimab) was granted Breakthrough Therapy Designation based on demonstration of durable objective responses in Study R2810-ONC-1423 (1423) for the treatment of adults with metastatic cutaneous squamous cell carcinoma (CSCC) and adults with locally advanced and unresectable CSCC.

Clinical

The data proposed to be used to support a marketing application for REGN2810 are from Study 1423, a dose-finding and safety study in advanced solid tumors and from Study 1540, a non-randomized, two-cohort, multi-center study of REGN2810 in patients with advanced CSCC.

Study 1540 currently includes three cohorts of patients: metastatic CSCC treated with REGN2810 3 mg/kg every two weeks (Group 1), locally advanced CSCC treated with REGN2810 3 mg/kg every two weeks (Group 2), and patients with advanced CSCC treated with REGN2810 350 mg flat dose every three weeks. Regeneron plans to include safety data from all three groups and efficacy data from Groups 1 and 2 in the BLA.

According to the briefing document submitted prior to the preBLA meeting held on July 26, 2017, the investigator-assessed ORR was 46% in 26 patients across expansion cohorts 7 and 8 in Study 1423. Duration of response ranged from approximately two to 15 months with the majority of responses ongoing at data-cutoff. No updated results for Study 1423 and no efficacy data from Study 1540 were included in the briefing document submitted on October 27, 2017, in preparation for the present meeting.

To date, ~75 patients with metastatic (mCSCC) and ~33 patients with locally advanced (laCSCC) have received REGN2810 at 3 mg/kg Q2W. At the time of the cutoff date for submission, it is anticipated that 25 patients with CSCC will have initiated REGN2810 therapy at the 350 mg Q3W dose level, with 16 and 7 patients reaching 80% and > 95% of steady state exposure, respectively. At the time of completion of the ongoing 1540 study, it is expected that up to 53 CSCC patients will have received REGN2810 350 mg Q3W.

Preliminary Comments were sent on November 21, 2017.

SPONSOR QUESTION AND FDA RESPONSE

Clinical

1. Does the agency agree with the inclusion and presentation of the safety data for the 350 mg dose cohort?

FDA Response:
FDA agrees with the proposal to include Group 3 from Study 1540 as part of the safety data for the BLA. Specifically, Regeneron's plan to pool the safety data for Groups 1, 2 and 3 (i.e., data from all patients in Study 1540 receiving at least one dose of either 350 mg Q3W or 3 mg/kg Q2W cemiplimab) in the Summary of Clinical Safety (SCS) with subgroup safety analyses by dose included as an addendum to the SCS is acceptable.

Discussion During the teleconference:
There was no discussion.

2. Does agency agree with this approach to submitting safety data from other studies pertaining to patients treated previously with idelalisib?

FDA Response:
FDA agrees with Regeneron's proposal to include case narratives describing all SAEs experienced by patients previously treated with idelalisib or other PI3K inhibitors. Include an attribution analysis for each case and a discussion of the mechanism(s) of action underlying these toxicities in patients who have been exposed to PI3K inhibitors prior to cemiplimab.

Discussion During the teleconference:
There was no discussion.

3. Does FDA agree with this process for identifying and selecting possible irAEs to be included in the Integrated Summary of Safety?

FDA Response:
Yes. FDA acknowledges the additional information provided in the briefing document, as compared to the initial meeting request, regarding the criteria used by the investigators at Level 2 and the team of four Regeneron physicians at Level 3 to distinguish which adverse events captured in the MeDRA query are likely to be immune-mediated. Regeneron's approach for generation of a master list of preferred terms for irAEs to identify all possible irAEs for the analysis of irAEs in the Integrated Summary of Safety (ISS) appears acceptable. The proposed composite PTs for analyzing the incidence rates of specific types of irAEs are also acceptable.

Discussion During the teleconference:
There was no discussion.

4. Events identified by either methods ("IRR Diagnoses" or "IRR Symptoms") will be considered IRRs in the sensitivity analysis of IRRs in the Integrated Summary of Safety. Does FDA agree with this approach?

FDA Response:
Yes, FDA agrees with Regeneron's plan for conducting a sensitivity analysis for IRRs for the ISS by combining PTs describing IRR diagnoses (as listed in Appendix 3) with PTs

describing IRR symptoms (as listed in Appendix 4) and the categorization of these events that occur on the day of or the day after the cemiplimab infusion as IRRs.

FDA acknowledges that the interim CSRs for Studies 1423 and 1540 will still consider all AEs that occur during the cemiplimab infusion or within two hours after the infusion is completed as infusion-related reactions (IRRs).

Discussion During the teleconference:
There was no discussion.

5. Does the Agency agree with the planned analyses as presented?

FDA Response:
Yes. FDA agrees with the proposed ORR efficacy analyses including:

a. centrally reviewed ORR results for patients with mCSCC from Studies 1423 and 1540.

b. centrally reviewed ORR results for patients with laCSCC with sufficient follow-up from Studies 1423 and 1540.

c. a supportive pooled analysis of the ORR results from patients with mCSCC and patients with laCSCC

Please also include patients treated at the 350 mg Q3W flat dose of cemiplimab in the efficacy analyses.

Regeneron's Response received via email on November 27, 2017:
We would like to discuss the Agency's comment "Please also include patients treated at the 350 mg Q3W flat dose of cemiplimab in the efficacy analyses" as there will be very limited efficacy data from this cohort for the BLA submission.

Discussion During the teleconference:
Regeneron stated that the first patient in the flat dosing cohort was dosed in July of 2017 and 7 to 9 patients have received this dose and have undergone a single scan. Furthermore, no patient has had a confirmatory scan at this time. Regeneron stated that they could provide investigator response information separately; however, it would not be integrated into the efficacy results. FDA agreed with this approach. (b) (4)

FDA stated that this would not preclude approval of the flat dose; however, this would be determined based on data in the application regarding the appropriate dosing regimen (e.g., based on PK data).

Clinical Pharmacology

6. Does the Agency agree that the data from the patients administered 350 mg Q3W could be sufficient to support approval of this dosing regimen? The data include:

   - Integration of PK comparability of the 3 mg/kg Q2W and 350 mg Q3W assessed by modeling and simulation,
   - Observed drug concentration data from approximately 25 patients with mCSCC receiving cemiplimab 350 mg Q3W, and
   - Safety data from the patients receiving 350 mg Q3W

   FDA Response:
   Submit all available data with appropriate justifications to support the flat 350 mg Q3W dose. The appropriate dosage regimen for cemiplimab in patients with mCSCC will be determined during the review of the BLA.

   Discussion During the teleconference:
   There was no discussion.

7. Does the agency agree that the population PK approach outlined above is sufficient to support the cemiplimab BLA submission?

   FDA Response:
   No. Modify the population PK analysis report to provide the model parameter estimates for the entire dataset used (~480 patients) and for the clinically relevant population. The clinically relevant PK information will be determined during the review of the BLA.

   Regeneron's Response received via email on November 27, 2017:
   We think there may have been a misinterpretation of the approach to be taken.

   Discussion During the teleconference:
   Regeneron clarified that the population PK analysis will provide the model parameter estimates for the entire dataset used (~480 patients) and for the clinically relevant population.

   FDA acknowledged Regeneron's response.

8. From the data outlined above, the primary exposure-response analysis plan by the Sponsor will be empirical in nature. Does the agency agree that for CSCC patients a descriptive exposure-response approach is sufficient to support the cemiplimab BLA submission?

   FDA Response:
   The approach appears reasonable; however, the adequacy of the exposure-response analysis will be determined during the review of the BLA.

Discussion During the teleconference:
There was no discussion.

Chemistry, Manufacturing, and Controls

9. Does the Agency agree with the planned data package, including the validation strategy, to support registration of both the 250 mg and 350 mg cemiplimab presentations?

FDA Response:
The planned validation and stability data package presented in Table 2 of the meeting briefing document appears reasonable to support the registration of both the 250 mg and 350 mg cemiplimab presentations. (b) (4)

Regeneron's Response received via email on November 27, 2017:
We would like to confirm the data expected to be included in the validation package for the 250 mg and 350 mg vial presentations.

Discussion During the teleconference:
In the original BLA, Regeneron is proposing to include the process validation protocol including the sampling plan and additional information as specified in FDA's initial response to this question.

(b) (4)

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an

assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

FDA acknowledges receipt of Regeneron's Agreed Initial Pediatric Study Plan submitted on March 10, 2017, and also refers to our March 24, 2017, letter confirming our agreement. This fulfills Regeneron's requirements at this stage of development to reach an Agreed Initial Pediatric Study Plan with the Agency as required by FDASIA for products that would trigger PREA at the time of BLA submission."

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

ISSUES REQUIRING FURTHER DISCUSSION
N/A

ACTION ITEMS
N/A

ATTACHMENTS AND HANDOUTS
N/A

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/s/

MISSIRATCH BIABLE
12/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 127100

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Laura Simpson, Ph.D.
Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Simpson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for REGN2810.

We also refer to the meeting between representatives of your firm and the FDA on July 26, 2017. The purpose of the meeting was to discuss and reach agreement on the content and presentation of data for the planned Biologics License Application (BLA) for REGN2810 for the following proposed indications:

> REGN2810 is indicated for the treatment of adults with metastatic cutaneous squamous cell carcinoma; and
>
> REGN2810 is indicated for the treatment of adults with locally advanced cutaneous squamous cell carcinoma who are not amenable to curative surgery.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Anuja Patel, M.P.H. Senior Regulatory Health Project Manager at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Norma Griffin
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA (clinical)
Meeting Date and Time:	Wednesday, July 26, 2017 9:30 A.M. to 11:00 A.M., EST
Meeting Location:	White Oak Campus; 10903 New Hampshire Avenue Building 22, Room 1421 Silver Spring, Maryland
Application Number:	IND 127100
Product Name:	REGN2810
(Proposed) Indications:	REGN2810 is indicated for the treatment of adults with metastatic cutaneous squamous cell carcinoma; and REGN2810 is indicated for the treatment of adults with locally advanced cutaneous squamous cell carcinoma who are not amenable to curative surgery.
Sponsor/Applicant Name:	Regeneron Pharmaceuticals, Inc.
Meeting Chair:	Suzanne Demko
Meeting Recorder:	Norma Griffin

FDA Meeting Attendees

Division of Oncology Products 2
Steven Lemery, M.D., H.H.S., Associate Director, DOP2
Suzanne Demko, P.A.-C., Clinical Team Leader
Denise Casey, M.D., M.S., Medical Officer
Diana Bradford, M.D., M.S., Medical Officer
Norma Griffin (covering for Anuja Patel), Lead Regulatory Health Project Manager
Shubhangi (Gina) Mehta, Regulatory Health Project Manager

Division of Hematology and Oncology Toxicology
Whitney Helms, Ph.D., Pharmacology/Toxicology Team Leader

Office of Biostatistics
Kun He, Ph.D., Statistical Associate Division Director
Manasi Sheth-Chandra, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Brian Furmanski, Ph.D., Clinical Pharmacology Reviewer
Giang Ho, Clinical Pharmacology Reviewer

Office of Product Quality, Office of Biological Products
Marjorie Shapiro, Ph.D., Product Quality Team Leader
Antonina Aydanian Ph.D., Product Quality Reviewer

Office of Surveillance and Epidemiology
Elizabeth Everhart, MSN, ACNP

SPONSOR ATTENDEES

Regeneron Pharmaceuticals
Israel Lowy, M.D., Ph.D., Clinical Sciences, Oncology
Matthew Fury, M.D., Ph.D., Clinical Sciences, Oncology
Robert Charnas, Ph.D., Program Direction
Frank Seebach, M.D., Regulatory Affairs
Laura Simpson, Ph.D., Regulatory Affairs
Usama Aslam, Pharm.D., Clinical Fellow-Regulatory Affairs
Bo Gao, Ph.D., Biostatistics
Dale LeSueur, M.S., Statistical Programming
Anne Paccaly, PharmD, Ph.D., Clinical Pharmacology
Romana Hosain, M.D., Risk Management
Emmanuel Okoye, M.D., MPH, Risk Management

Sanofi
Karl Hsu, M.D. Clinical Development
Sunil Gupta, M.D., Regulatory Affairs

BACKGROUND

The objective of the pre-BLA meeting to be held on July 26, 2017, is to obtain agreement between Regeneron and the FDA on the content and presentation of data to support the filing of the planned BLA for REGN2810 for the proposed indications cited below.

As this meeting is also a pre-submission meeting for a new molecular entity, the forthcoming applications will be subject to "the Program" under PDUFA V. Therefore, the purpose of this meeting is also to reach agreement between Regeneron and the FDA on the contents of a complete application, including preliminary discussions regarding the need for risk evaluation and mitigation strategies (REMS) or other risk management actions.

Proposed Indications

Regeneron seeks approval for the following two indications under one BLA submission:

> "REGN2810 is indicated for the treatment of adults with metastatic cutaneous squamous cell carcinoma (CSCC)", and
>
> "REGN2810 is indicated for the treatment of adults with locally advanced and unresectable cutaneous squamous cell carcinoma."

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 cutaneous squamous cell carcinoma (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 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 stated that the eligibility criteria should require that the most recent biopsy of the lesion be reviewed centrally by an independent dermatopathologist to assure that the lesions are CSCC without the presence of other malignant components.

- FDA agreed that a primary endpoint of confirmed objective response rate (ORR) 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.

- FDA recommended that objective response and duration of response data be independently reviewed for the efficacy analyses to reduce potential reader bias and measurement variability. For patients with locally advanced disease, FDA recommended independent review of all radiology, photography, and biopsy results by a blinded central review committee in order to determine the overall response for each patient based on an integration of these assessment modalities for the proposed composite endpoint.

- FDA stated that Regeneron must provide a detailed, study-specific response guideline in the protocol submitted to the IND. This response assessment criterion should address issues of measurement of scar, fibrosis, ulceration, protuberance formation, and palpable subcutaneous components that may not be visible or evident in photography. The procedures for choosing baseline target and non-target lesions and the methods for obtaining serial measurements using color photography should be well-described. The guideline should outline the methods for obtaining tumor biopsies, the time points for biopsy assessments and the number and location of the biopsies that will be taken depending on the size of the target lesion. The criteria should include definitions of complete response (CR), partial response (PR), stable disease (SD), and progression based on the alternative response assessment.

- FDA recommended that the modified response criteria include a provision that all patients considered to have a complete response will be biopsied with central pathologic review to confirm absence of tumor; otherwise response assessment will be considered as PR.

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 cutaneous squamous cell carcinoma (CSCC).

On October 17, 2016, a CMC meeting was held to gain agreement with FDA on the

(b) (4)

Regeneron requested Preliminary Breakthrough Therapy Designation Request (BTDR) Advice on December 16, 2016. On December 30, 2016, FDA requested additional information on the CSCC cohorts that were provided in the BTDR. On January 17, 2017, Regeneron provided the requested information and a teleconference with FDA was held on January 25, 2017. During this 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 will review the subtypes of metastatic cutaneous squamous cell carcinoma (CSCC) and locally advanced CSCC separately given the different natural histories and prognostic factors associated with the different 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.

Regeneron requested additional Preliminary BTDR Advice on June 7, 2017, 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 followed-responders longer in order to provide data that the responses were sufficiently durable. FDA stated that six months of follow-up for durability following onset of response would provide a stronger justification for the breakthrough request when presented to the Office of Hematology and Oncology and the Medical Policy Council. FDA requested that the updated data cutoff be from June, 2017. FDA clarified for Regeneron that four months was the minimum, but that given that it is now June, it did not seem unfeasible to get an updated analysis such that most patients would have six months of follow-up; and that this data would be more convincing in terms of clinical benefit. FDA further stated that no new scans would need to be performed and that the only data that needed to be submitted with the June data cut-off was response and response duration data. FDA requested that Regeneron submit a Swimmer Plot and updated data through June 8, 2017, with the forthcoming Request for Breakthrough Therapy Designation.

On July 18, 2017, FDA requested via electronic mail (e-mail) that Regeneron submit a detailed listing of Table of Contents for the planned BLA submission as one was not included in the meeting package. Regeneron submitted their response via email on July 18, 2017, and followed with a formal submission on July 19, 2017.

FDA acknowledges Regeneron's July 18, 2017, amendment containing a Breakthrough Therapy Designation Request which is currently under review.

Chemistry, Manufacturing and Control (CMC)

A separate CMC only pre-BLA meeting is scheduled between Regeneron and the FDA on July 27, 2017. The purpose of meeting is to obtain FDA's concurrence on specific CMC information to be included in the upcoming BLA and the CMC plans outlined in the meeting briefing document including:

- Designation of trade secrets within Module 3,
- Inclusion of risk-based, generic comparability protocols within Module 3 of the BLA,
- (b) (4)
- The proposed stability data that will be provided at the time of the submission and, via simple stability updates, during the BLA review to establish the initial commercial shelf-life,
- FDA's expectations around the presence of proteinaceous particulate matter in the final drug product, and,
- The proposed contents and organization of the Module 3.2 Body of Data for the submission.

Nonclinical

In vitro and in vivo studies have been conducted to characterize the activity and toxicity of RGN2810, including binding studies, tissue cross-reactivity studies, tumor xenograft studies using mice genetically engineered to express a human/mouse PD-1 chimeric receptor, and a 28-day repeat-dose toxicology study in cynomolgus monkeys that included cardiovascular and neurotoxicity safety parameters, as well as an evaluation of local tolerability. These studies were submitted under cross-referenced IND 123950. Regeneron stated that reproductive and developmental toxicology studies have not been conducted.

Clinical

Disease Background
CSCC is the second most common human cancer in the United States, with up to 420,000 individuals diagnosed each year in the United States. Precise incidence 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 poor prognosis in CSCC include tumor size > 2 cm, tumor depth > 2 mm, perineural invasion, host immunosuppression, and recurrent lesions. The standard of care is complete surgical resection. For the small percentage of patients who develop locoregionally recurrent or unresectable disease, treatment options are limited. Radiation-based therapy 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. Patients with recurrent disease with lymph node involvement or distant metastases have a poor prognosis. Ten-year survival rates are less than 20 percent for patients with regional lymph-node involvement and less than 10 percent for patients with distant metastases. There are no FDA-approved systemic therapies for advanced CSCC. There have been single-arm studies of several systemic therapies which often contained heterogeneous groups of patients with different stages of disease; none of these studies demonstrated a therapeutic advantage.

REGN2810 is a humanized monoclonal antibody directed against PD-1. Clinical experience with this drug is derived from six clinical trials conducted under U.S. INDs and two additional ex-U.S. studies. The data proposed to be used to support a marketing application for REGN2810 are from Study 1423, a dose-finding and safety study in advanced solid tumors and Study 1540 (Study 1540), a non-randomized, two-cohort, multi-center study of REGN2810 in patients with advanced CSCC.

Regeneron seeks FDA guidance on two proposed pathways for approval of REGN2810 in patients with advanced CSCC:

1. Accelerated approval based on the ORR and duration of response data from patients treated in Study 1423

2. Regular approval based on the results from the metastatic CSCC cohort in the ongoing Study 1540 supported by the additional patients with metastatic disease from Study 1423. For this pathway, Regeneron proposes to seek approval based on the results in metastatic CSCC and then subsequently extend the indication to locally advanced CSCC when the locally-advanced CSCC arm of the trial (planned enrollment=76) is fully accrued and has at least 6 months follow-up.

Efficacy Summary
According to the briefing document, 27 patients with advanced CSCC have enrolled in Study 1423 including 11 patients with metastatic CSCC and 16 patients with locally advanced CSCC. Regeneron reports that investigator-assessed ORR was 46% in 26 patients across expansion cohorts 7 and 8. Based on the reported results in Table 17 in the briefing document, FDA calculates a centrally reviewed ORR of 55% for the 11 patients with metastatic CSCC and 31% for the 16 patients with locally advanced disease. Duration of response ranged from approximately two to 15 months with the majority of responses ongoing at data-cutoff. No efficacy data was provided for Study 1540.

Safety Summary
The exposure and safety information in the briefing document is based on a data cut-off date of January 20, 2017. As of this cutoff, 353 patients were exposed to REGN2810 including 300 at the 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 related to REGN2810 (however, this patient may

have had a pre-existing predisposition to paraneoplastic limbic encephalitis). 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 occurred in 34% of patients, and 5% of patients had serious immune-mediated adverse reactions (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. For Study 1540, 53 patients had a median exposure time of 9.4 weeks as of the data cut-off. There were four deaths, two due to PD and two patients died in their sleep due to unknown reasons. Nine percent of patients experienced at least one SAE. Forty-five percent experienced imARs including one SAE of pneumonitis and 4% of patients experienced $\geq$ Grade 3 AST, arthritis, and pneumonitis. Aside from the relatively increased proportion of patients with skin-related AEs, the safety profile in patients with CSCC does not appear to differ from that seen in other patients.

DISCUSSION OF SPONSOR QUESTIONS AND FDA RESPONSES

GENERAL COMMENTS

FDA will not be able to reach agreement with Regeneron on the contents of a complete application for a BLA for REGN2810 under the PDUFA V program, because the pre-BLA meeting for discussion of quality components has not been held. We acknowledge that a separate pre-BLA meeting to discuss quality components is scheduled for July 27, 2017. During this meeting, FDA and Regeneron will need to reach agreement on all discipline information necessary to allow the BLA to be considered complete, and to reach agreement on submission of late components, if any are planned.

Please note that the FDA renumbered the questions from the meeting package to facilitate discussion.

Clinical Questions

1. Does the Agency agree that the efficacy data, composed of the response rate and the duration of response, as proposed are sufficient to support a BLA filing? (Please note, the safety data to be provided to support a BLA filing is the subject of question 5 and 6)

   FDA Response: FDA agrees that demonstration of an ORR of clinically meaningful magnitude and duration could support a BLA filing for REGN2810 for the treatment of patients with metastatic CSCC, or for the treatment of patients with unresectable laCSCC. As previously stated, efficacy in patients with metastatic disease will be evaluated independently from efficacy in patients with laCSCC because the two conditions have different prognoses and a different treatment effect may be observed in patients with metastatic disease as compared to patients with locally advanced disease. Therefore, it will be essential to have an adequate sample size in both populations in order to demonstrate clinical benefit.

FDA acknowledges that the confirmed, centrally reviewed ORR of 55% (6/11 patients including one patient from the dose-escalation portion of Study 1423) in patients with metastatic CSCC is suggestive of a clinically important anti-tumor effect of REGN2810. However, FDA requests that Regeneron rely on the ORR and DOR results from the additional 58 patients who have enrolled in Group 1 of Study 1540 as of April 2017. (b) (4)

With regard to the group of patients with locally advanced CSCC, whether or not both indications are sought in a marketing application will depend on the continued enrollment and results of Study 1540. FDA does not object to filing an application based on a single indication (i.e., metastatic CSCC) while the data in patients with locally advanced disease is maturing.

If REGN2810 receives Breakthrough Designation, Regeneron may request a rolling review (e.g. early submission of CMC and Nonclinical data) to facilitate expedited review of the complete application.

Regeneron's 7/25/2017 Email Response: Regeneron would like to discuss response to Question 1.

- The natural history/prognosis of patients with unresectable and locally advanced CSCC
- Treatment effect in patients with unresectable and locally advanced CSCC

Discussion During 7/26/2017 Meeting: Regeneron provided data from a prospective cohort study in 36 patients that showed that patients with unresectable and locally advanced CSCC appear to have a poor prognosis comparable with metastatic disease. FDA acknowledged Regeneron's position and FDA stated that the Agency would consider this data and Regeneron's own data in the BLA. With the enrollment of more patients and with more follow-up, Regeneron expects the observed response rate in patients with locally advanced disease (LAD) to be similar to that seen in patients with metastatic disease.

FDA asked whether Regeneron could provide a package that includes patients with LAD in the original BLA. Regeneron planned to provide data from 58 (from Study 1540) plus 17 (from Study 1423) patients with metastatic disease in the BLA. Regeneron would also be able to provide data from 11 patients with LAD who were enrolled in Study 1423. Regeneron argued that response assessment in these 11 patients would not be in isolation given that responses were observed in patients with metastatic disease. FDA stated that the Agency could consider this approach during the review of the BLA. FDA also stated that Regeneron could also provide data (e.g., with photographs) of improvement in skin disease in patients with metastatic disease to support an action in patients with LAD.

Although Regeneron did not plan for an interim analysis in Study 1540 to assess for ORR in patients with locally advanced disease, Regeneron asked whether they could perform an interim assessment of the data from patients with LAD with sufficient follow-up. Regeneron stated that 29 patients with LAD have been dosed by March 31st, 2017, in Study 1540. FDA did not object to an approach where Regeneron could conduct an interim analysis of the single arm study as long as they provided a rationale as to the specific date and the selected number of patients. FDA requested that Regeneron submit a proposal before conducting the analysis of the centrally reviewed data. Regeneron proposed selecting a date that would correspond to the metastatic analysis. FDA suggested for the LAD cohort that Regeneron select the number of patients who will have had their responses followed for at least six months (e.g., patients who have initiated treatment nine months prior to the cut-off date).

FDA stated that a plan for an interim look should be pre-specified; however, FDA stated that an alpha penalty would not be necessary for the single-arm study.

Questions 2 and 3 is for Accelerated approval based on the CSCC patients from R2810-ONC-1423:

2. Does the Agency agree the data from the Phase 1 expansion cohorts could support an accelerated approval?

FDA Response: See FDA response #1. While FDA agrees that advanced CSCC is a serious and life-threatening condition with no available therapy, (b) (4)

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 2 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 2.

3. Does the Agency agree that complete data from the metastatic cohort (Group 1) and locally advanced and unresectable cohort (Group 2) from R2810-ONC-1540 can provide confirmatory evidence to convert the accelerated approval into a regular approval for metastatic and locally advanced and unresectable CSCC, respectively?

FDA Response: See FDA response #1 and #2.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 3 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 3.

Question 4 is for Regular approval: submission with complete metastatic data set from Cohort 1 in R2810-ONC-1540:

4. Should the Agency disagree with the accelerated approval approach described above, does the Agency agree that complete data from the metastatic cohort (Group 1) from R2810-ONC-1540 are sufficient for regular approval of REGN2810 for the treatment of CSCC in patients with metastatic disease (b) (4)

FDA Response: FDA agrees that the complete data from Group 1 in Study 1540 in addition to data from Study 1423 could support a marketing authorization for REGN2810 for the treatment of CSCC in patients with metastatic disease if the effect size on independently assessed ORR and duration of response is of sufficient magnitude. Whether the data will support regular approval or accelerated approval will depend on the results observed. Regeneron will need to provide justification for the proposed effect size and duration of effect to be considered evidence of direct benefit or likely to predict clinical benefit based on a lower limit of the confidence interval observed around the response rate.

The patient population treated and the safety profile of the drug will also considered for regulatory decision making. (b) (4)

Regeneron's 7/25/2017 Email Response: Regeneron would like to discuss response to Question 4.

- Clarify the regrouping of the Phase 1 cohorts with CSCC by the Phase 2 definition of metastatic.
- Clarify proposal for duration of follow-up to be provided in the BLA.

Discussion During 7/26/2017 Meeting: Refer to Slide 9 in Regeneron's slide presentation. FDA agreed with Regeneron's proposal.

5. Does the Agency agree that the patient exposure to REGN2810, including the primary and supportive safety data sets, are adequate to support a BLA filing for:

   a. Accelerated approval based on the CSCC patients from R2810-ONC-1423?

      FDA Response: No, see FDA response #1 and #2.

   b. Regular approval based on the metastatic cohort (Group 1) from R2810-ONC-1540 as described in question 4 above?

FDA Response: FDA agrees that the 94 patients exposed to REGN2810 for at least six months, if not discontinued earlier, in Study 1540 in combination with the exposure data from supportive safety populations including the 27 patients with advanced CSCC and 367 patients with various other solid tumors treated at doses of REGN2810 ranging from 1-10 mg/kg or a flat dose of REGN2810 in Study 1423 comprise an adequate safety database to support filing a BLA.

Regeneron's 7/25/2017 Email Response: Regeneron would like to discuss response to Question 5. Clarify the safety data to be included for studies other than R2810-ONC-1540 and R2810-ONC-1423.

Discussion During 7/26/2017 Meeting: FDA agreed with Regeneron's proposal regarding the safety database and regarding submission of narratives and case report forms. FDA stated that additional CRFs or narratives should be submitted during the review of the BLA upon request.

6. Does the Agency agree with the proposed pooling strategy for safety for:

   a. Accelerated approval based on the CSCC patients from the Phase 1, R2810-ONC-1423 study?

      FDA Response: No, see FDA response #1 and #2.

   b. Regular approval based on the metastatic cohort (Group 1) from R2810-ONC-1540 as described in question 4 above?

      FDA Response: The proposed pooling strategy for safety that includes pooling a.) all patients with CSCC across Studies 1423 and 1540; b.) all patients from Study 1423 with various solid tumors (with the exception of those with hepatocellular carcinoma and glioblastoma) treated with single-agent REGN2810 with patients from Study 1540; and, c.) all patients with various solid tumors in Study 1423 treated with single agent or combination therapy with patients in Study 1540 is acceptable. FDA also agrees with the proposed presentation of data by disease subtypes for the metastatic and locally advanced populations of CSCC and in total. FDA recommends including side-by-side comparison tables in the Summary of Clinical Safety.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 6 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 6.

7. Does the Agency agree that a REMS for REGN2810 is not necessary?

FDA Response: FDA agrees that a REMS is unlikely to be necessary for REGN2810; however, final determination will be made during the BLA review.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 7 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 7.

8. Does the Agency agree that the proposed data set evaluating the QT prolongation potential of REGN2810 is adequate to support a BLA filing?

FDA Response: Inclusion of a data set evaluating the QT prolongation potential of REGN2810 in a BLA is not required as monoclonal antibodies such as REGN2810, in general, are not expected to prolong QT intervals.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 8 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 8.

Clinical Pharmacology Questions

9. Does the Agency agree with the proposed content and format of Module 2.7.2?

FDA Response: The proposed content and format appears acceptable.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 9 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 9.

10. Does the Agency agree that the population PK and exposure-response (E-R) analyses are adequate to support a BLA filing?

FDA Response: The proposed population PK and exposure-response (E-R) analyses appear acceptable.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 10 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 10.

11. Does the Agency agree that a flat dose of 350 mg Q3W of REGN2810 can be supported and approved based on the PK modeling of observed data with 3 mg/kg Q2W dosing and simulation of exposures with 350 mg Q3W dosing?

FDA Response: Discussion of the approvability of the 350 mg Q3W flat dose of REGN2810 based on the PK modeling is premature. The adequacy of the dosage regimen for REGN2810 will be determined upon review of the BLA.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 11 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 11.

Statistical Questions

12. Does the Agency agree with the proposed statistical analysis plan for:

    a. Accelerated approval based on the CSCC patients from the Phase 1, R2810-ONC-1423 study?

       FDA Response: No. Please see FDA Responses to Questions 1 and 2.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 12 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 12.

13. Does the Agency agree with proposed electronic data submission plan?

FDA Response: FDA recommends that Regeneron submit a well-documented Data Define file, Clinical Study Report (CSR), Statistical Analysis Plan, and Case Report Forms (CRFs) along with the datasets and coding documentation.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 13 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 13.

Regulatory Questions

14. Does the Agency agree that the proposed efficacy and safety data could warrant a priority review?

FDA Response: FDA agrees that advanced CSCC is a serious condition and that REGN2810 may provide a significant improvement in safety or effectiveness when compared to the systemic therapies that are currently employed. Regeneron may submit a request for priority review in the BLA application that contains justification as to how REGN2810 meets the criteria for receiving a priority review. A final determination on whether FDA will grant priority review will be made after the submission of the BLA.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 14 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 14.

15. Assuming breakthrough designation, does the Agency agree with the proposed schedule for a rolling submission for:

a. Accelerated approval based on the CSCC patients from the Phase 1, R2810-ONC-1423 study?

Submission 1 **October 2017**	**Submission 2** **December 2017**
• Module 2.4 Nonclinical Overview • Module 2.6 Pharmacology, Pharmacokinetics, Toxicology Written and Tabulated Summaries • Module 4 Nonclinical Study Reports	• Module 1 Administrative • Module 2.3 Quality Overall Summary • Module 2.5 Clinical Overview • Module 2.7 Clinical Summaries • Module 5 Clinical Study Reports • Module 3 Quality

FDA Response: No, see FDA response #1 and #2.

b. Regular approval based on the metastatic cohort (Group 1) from R2810-ONC-1540 as described in question 4 above?

Submission 1 October 2017	**Submission 2 December 2017**	**Submission 3 March 2018**
• Module 2.4 Nonclinical Overview • Module 2.6 Pharmacology, Pharmacokinetics, Toxicology Written and Tabulated Summaries • Module 4 Nonclinical Study Reports	• Module 2.3 Quality Overall Summary • Module 3 Quality	• Module 1 Administrative • Module 2.5 Clinical Overview • Module 2.7 Clinical Summaries • Module 5 Clinical Study Reports

FDA Response: FDA agrees with the proposed timeline; however, the decision regarding whether to grant accelerated versus regular approval will be made during the review of the BLA.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 15 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 15.

16. Does the Agency agree that the efficacy and safety data can support the treatment of patients with metastatic and locally advanced (b) (4) CSCC as labelled indications with both the accelerated and regular approval approach?

FDA Response: FDA agrees that the proposed package described in the table above that includes Study 1540 can facilitate FDAs review of the BLA. FDA will determine the indication and type of approval during the BLA review.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 16 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 16.

17. Does the Agency agree with the Sponsor's proposed list of studies to be considered "covered clinical studies" for the purposes of providing financial disclosure and summary level clinical site data for BIMO requirements?

FDA Response: FDA agrees that the studies listed in Table 1 of the briefing document should be considered "covered clinical studies" with regard to documentation of financial disclosures and providing summary level clinical site data for BIMO requirements.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's response for Question 17 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Question 17.

Additional FDA Clinical Comments:

18. Provide clarification in the BLA regarding the regrouping of cohorts based on the Study 1540 definitions of metastatic and locally advanced CSCC (see Primary Efficacy table in Section 9 on page 15 of the meeting briefing document). State the reasons why individual patients were classified differently and whether or not the regrouping had an effect on the overall response rates for each cohort.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 18 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Comment 18.

19. Provide clarification regarding the response criteria used to assess locally advanced CSCC during Study 1423 (i.e., were the criteria consistent with the criteria used for Study 1540?).

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 19 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Comment 19.

20. Different sections of the briefing document state different numbers of patients with advanced CSCC treated in Study 1423. Please confirm that a total of 27 patients have been treated with at least one dose of REGN2810 as of the last data cut-off and that this total number includes 11 patients with metastatic disease (one patient with metastatic disease treated at 1 mg/kg during dose-escalation plus 10 patients with metastatic CSCC treated with the 3 mg/kg dose in cohort 7) and 16 patients with locally advanced CSCC treated with 3 mg/kg (cohort 8). Considering all patients treated and referring to Table 17 in the briefing document, FDA calculates an independently reviewed ORR of 55% for the 11 patients with metastatic CSCC and 31% for the 16 patients with locally advanced CSCC. Please confirm or provide Regeneron's alternative calculations for centrally-reviewed ORRs in both cohorts.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 20 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Comment 20.

21. If Regeneron plans to potentially seek an indication for the treatment of locally advanced CSCC, describe the plans for submitting photographic data contributing to the response assessment for patients with locally advanced CSCC in the BLA.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 21 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Comment 21.

22. Submit for FDA review a detailed list of analyses to be included in the Summary of Clinical Efficacy (SCE) in the BLA. With regard to the content of the SCE:

    a. The primary analysis of efficacy should include all patients in the intent to treat populations of Studies 1423 and 1540 with the stage of disease for which Regeneron intends to include in the indication statement(s) in product labeling (e.g., metastatic CSCC or locally advanced CSCC or both). Efficacy for patients with locally advanced CSCC and those with metastatic CSCC will be analyzed separately.

    Regeneron's 7/25/2017 Email Response: Regeneron would like to discuss Clinical Comment 22.a. Primary analysis of efficacy for the proposed labelled indication

    Discussion During 7/26/2017 Meeting: FDA agreed that for patients in the metastatic disease population, Regeneron could submit a pooled analysis of response rate.

    b. The ORR, duration of response, and complete response (CR) rate assessments included in the efficacy analysis must be conducted by an independent review committee.

    c. Include a summary table of responders that includes for each patient: prior treatment for CSCC, location and extent of disease at study entry, centrally reviewed best overall response, time to onset of response from initiation of REGN2810, duration of response, and whether or not the response was ongoing at data cutoff.

d. Include a benefit:risk assessment of REGN2810 based on the results of Studies 1423 and 1540 for the intended treatment population.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Clinical Comments 22.b – 22.d and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Clinical Comments 22.b – 22.d.

23. Please confirm that Regeneron will provide case report forms and patient narratives for all patients treated in Studies 1423 and 1540 who experienced REGN2810-related deaths, SAEs, AEs leading to discontinuation or adverse events of special interest (AESI) (e.g., imARs and infusion reactions) in the original BLA submission as well as in the safety update.

- **Regeneron's 7/25/2017 Email Response:** Regeneron would like to discuss Clinical Comment 23. Definitions of IRRs

Discussion During 7/26/2017 Meeting: FDA requested that Regeneron provide a justification regarding the proposed definition of infusion reaction which specified a 2-hour period from the end of the study drug infusion. FDA also recommended that Regeneron perform a sensitivity analysis at day one to ensure that the adverse reaction of infusion reaction would be adequately described in labeling.

24. Regeneron's proposed MedDRA query of preferred terms that will be used to capture events potentially related to immune-mediate reactions appears reasonable, however, the proposed case definition for classifying adverse events as imARs requires further detail. Include in the case definition for imARs specific criteria used to distinguish these events from non-immune adverse events with similar symptoms and/or laboratory abnormalities including but not limited to: onset and duration of the event, whether or not immunosuppressive treatments or hormone replacement therapies were administered, the presence of other concurrent endocrinologic findings and whether or not there is a clear alternative etiology or biopsy findings consistent with an immune-related event. Analyses of imARs should include the overall incidences and severities of the events, treatment(s) administered (dose and duration of corticosteroid use, need for additional immunomodulatory agents), additional interventions (e.g., biopsies, procedures), onset and duration of events, if there was resolution, requirement for dose modification or discontinuation, and whether or not there were other concurrent endocrinologic conditions.

Regeneron's 7/25/2017 Email Response: Regeneron would like to discuss Clinical Comment 24 - Definitions of imARs.

Discussion During 7/26/2017 Meeting: FDA agreed Regeneron's approach is acceptable.

25. The proposed case definition for classifying adverse events as infusion-related reactions (IRRs) requires further detail. Include in the case definition for IRR a time-frame for identifying all AEs thought to be potentially related to REGN2810 infusion (i.e., 24-48 hours following infusion). The MedDRA query of preferred terms used to capture AEs commonly observed as infusion-reactions should include (but is not limited to) fever, rigors, flushing, cutaneous reactions, hypotension, dyspnea, wheezing, back pain, and abdominal pain. Analyses of IRRs should include the incidence rate by treatment cycle, interventions for management of infusion reactions, including medications administered, alterations of infusion rate, etc., and the incidences of IRRs in patients with previous infusion reactions (i.e., re-challenge).

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 25 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Comment 25.

Additional FDA Clinical Pharmacology Comments:

26. Address the following questions in the Summary of Clinical Pharmacology:

    a. What is the basis for selecting the doses and dosing regimen used in the registration trials to support the marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

    b. What are the exposure-response relationships for efficacy, safety and biomarkers?

    c. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of the drug? What dose modifications are recommended?

    d. What is the impact of immunogenicity on exposure, efficacy, and safety?

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 26 and no further discussion was needed.

Discussion During 7/26/2017: Although no discussion was held regarding this question, FDA recommended that Regeneron provide all available data, including PK and safety data, in order to provide support for the use of the flat dose of REGN2810.

27. Apply the following advice in preparing the clinical pharmacology sections of the original BLA submission:

    a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

    b. Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

    c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. Each subject's unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

    d. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

    e. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; and the reasons for dose modifications in the datasets.

    Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 27 and no further discussion was needed.

    Discussion During 7/26/2017: There was no discussion for Comment 27.

28. Submit the following for the population pharmacokinetic analysis reports:

    a. Standard model diagnostic plots.

    b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.

    c. Model parameter names and units in tables.

    d. Summary of the report describing the clinical application of modeling results.

    e. Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 28 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Comment 28.

29. Submit the following information and data to support the population pharmacokinetic analysis:

    a. SAS transport files (*.xpt) for all datasets used for model development and validation.

    b. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

    c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 29 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Comment 29.

30. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population.

    Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

Regeneron's 7/25/2017 Email Response: Regeneron acknowledged FDA's Comment 30 and no further discussion was needed.

Discussion During 7/26/2017: There was no discussion for Comment 30.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- There are no agreements for late submission of clinical, clinical pharmacology, or non-clinical application components.

- Since a chemistry pre-submission meeting is to be held on July 27, 2017, FDA cannot agree at this time on the contents of a complete application for a BLA for REGN2810 under the PDUFA V program. Please refer to the meeting minutes for the July 27, 2017, CMC meeting for additional discussion.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

FDA acknowledges receipt of Regeneron's Agreed Initial Pediatric Study Plan submitted on March 10, 2017, and also refers to our March 24, 2017, letter confirming our agreement. This fulfills Regeneron's requirements at this stage of development to reach an Agreed Initial Pediatric Study Plan with the Agency as required by FDASIA for products that would trigger PREA at the time of BLA submission.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

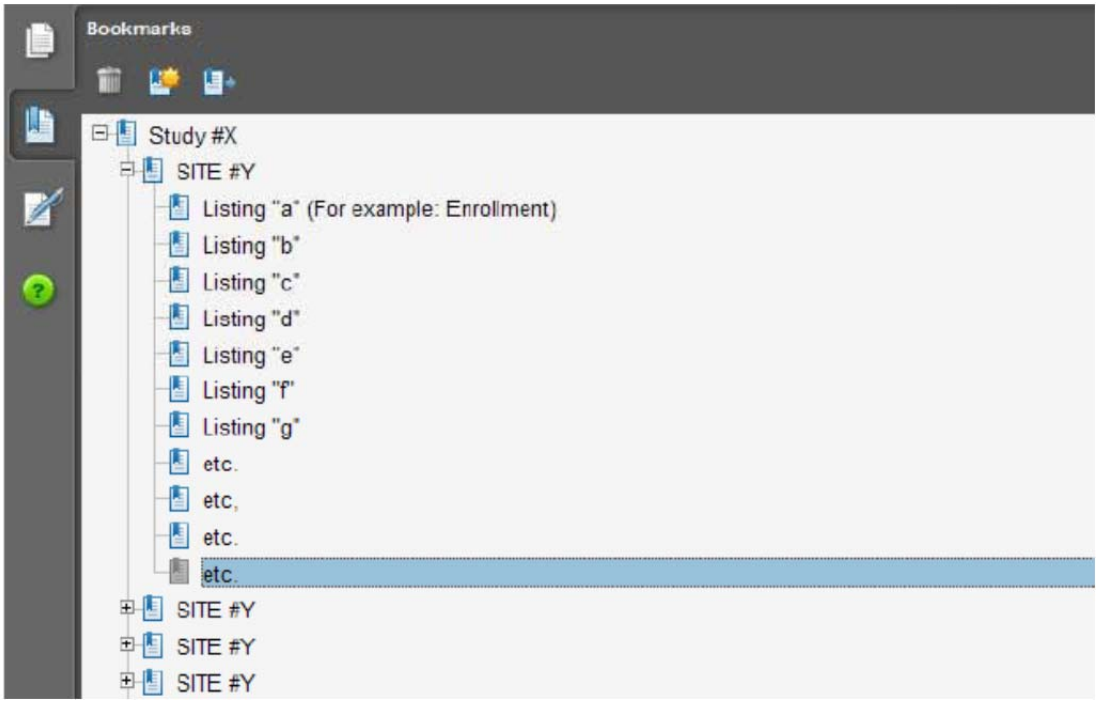
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

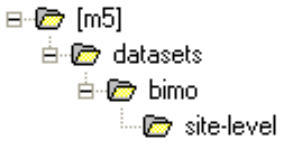
Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ATTACHMENTS

- Regeneron Slide Presentation – "REGN2810 (anti-PD-1 mAb) Metastatic and Locally Advanced and Unresectable Cutaneous Squamous Cell Carcinoma (CSCC)"
- Meeting Attendance List

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/s/

NORMA S GRIFFIN
07/31/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 127100

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Laura Simpson, Ph.D.
Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Simpson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for REGN2810.

(b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-Phase 3

Meeting Date and Time: August 1, 2016, 2:00 P.M. to 3:00 P.M., EST

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 127100
Product Name: REGN2810
Indication: (b) (4)

Sponsor/Applicant Name: Regeneron Pharmaceuticals, Inc.

Meeting Chair: Suzanne Demko
Meeting Recorder: Anuja Patel

FDA ATTENDEES

Center for Drug Evaluation and Research, Division of Oncology Products 2 (DOP 2)
Patricia Keegan, Director
Suzanne Demko, Clinical Team Leader
Denise Casey, Clinical Reviewer
Monica Hughes, Chief, Project Management Staff
Anuja Patel, Senior Regulatory Health Project Manager
Idara Udoh, Senior Regulatory Health Project Manager
Whitney Helms, Nonclinical Team Leader

Office of Biostatistics (OB), Division of Biometrics V (DBV)
Kun He, Statistical Team Leader
Pallavi Mishra-Kalyani, Statistical Reviewer

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(b) (4)

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) **within 60 days of this meeting**. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov.

For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Tracked and clean version of the protocol formally to the IND with a request for FDA feedback	Sponsor	TBD
FDA Feedback on Protocol	FDA	Within 60 days of receipt or sooner

ATTACHMENTS AND HANDOUTS

Slides presented during August 1, 2016 meeting are attached for reference.

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/s/

ANUJA PATEL
08/09/2016