

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209899Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



NDA 209899

**MEETING MINUTES**

Celgene International II Sàrl  
Attention: Matthew W. Lamb, Pharm.D., R.Ph.  
Vice President, Regulatory Affairs  
86 Morris Avenue  
Summit, NJ 07901

Dear Dr. Lamb:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zeposia (ozanimod) 0.23 mg, 0.46 mg, and 0.92 mg capsules.

We also refer to the meeting between representatives of your firm and FDA on April 3, 2018. The purpose of the meeting was to discuss proposals to address deficiencies described in the February 23, 2018, Refuse to File letter.

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 LCDR Nahleen Lopez at (240) 402-2659.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Deputy Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** A  
**Meeting Category:** Guidance

**Meeting Date and Time:** April 3, 2018 (12:00pm-1:00pm EST)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1421  
Silver Spring, Maryland 20903

**Application Number:** 209899  
**Product Name:** Zeposia (ozanimod)  
**Indication:** Relapsing forms of multiple sclerosis (RMS)  
**Sponsor/Applicant Name:** Celgene International II Sarl

**Meeting Chair:** Dr. Billy Dunn, MD  
**Meeting Recorder:** Fannie Choy, RPh

**FDA ATTENDEES**

Division of Neurology Products  
Billy Dunn, MD, Director  
Eric Bastings, MD, Deputy Director  
Nicholas Kozauer, MD, Associate Director  
John Marler, MD, Clinical Team Leader  
Lois Freed, PhD, Supervisory Pharmacologist  
Richard Siarey, PhD, Nonclinical Reviewer  
Larry Rodichok, MD, Clinical Reviewer  
Fannie Choy, RPh, Project Manager  
Sandy Folkendt, Project Manager

Office of Clinical Pharmacology  
Mehul Mehta, PhD, Director  
Kevin Krudys, PhD, Team Leader  
Hristina Dimova, PhD, Reviewer

Division of Gastroenterology and Inborn Errors Products  
Tara Altepeter, MD, Clinical Team Leader  
Jackye Peretz, PhD, Nonclinical Reviewer

**SPONSOR ATTENDEES**

Jay Backstrom, MD  
Terrie Curran  
Gondi Kumar, PhD  
Susan Meier-Davis, DVM, PhD, DABT  
Maria Palmisano, MD

Chief Medical Officer & Head of Regulatory Affairs  
President, Inflammation & Immunology  
Vice President, Nonclinical Development  
Senior Director, Preclinical Sciences  
Corporate Vice President, Clinical Pharmacology

Jonathan Tran, PharmD  
David Kao, PharmD, MBA  
Penny Ng  
Matthew Lamb, PharmD, RPh

Executive Director, Clinical Pharmacology  
Executive Director, Regulatory Affairs  
Director, Regulatory Affairs  
Vice President, Regulatory Affairs

## 1. BACKGROUND

The purpose of the this Type A meeting is to discuss proposals to address deficiencies described in the February 23, 2018, FDA Refuse to File letter.

FDA sent Preliminary Comments to Celgene on March 30, 2018.

## 2. DISCUSSION

### 2.1. CLINICAL PHARMACOLOGY

**Question 1: Does the Division agree that the 17-month long-term stability (LTS) data along with population PK analysis approach will be adequate to address the clinical pharmacology deficiency outlined in the RTF letter?**

**FDA Preliminary Response to Question 1:**

We agree that the 17-month long-term stability (LTS) data along with a population PK analysis approach might be adequate to address the clinical pharmacology RTF deficiency. You need to provide RPC01-1910 and RPC01-1911 full clinical study reports at the time of the NDA resubmission.

The adequacy of the results from studies RPC01-1904 and RPC01-1906 (b) (4) will be a review issue.

We do not agree with your plan to include the data outside the established LTS in your population PK base model. You should first only include data within the established LTS in your base model. Once the base model is established, you may use a posterior predictive check to compare simulated data from the base model to the observations outside the established LTS (that is, Month 3 and Month 6 data). If the results of the posterior predictive check are acceptable, you may then include data outside the established LTS in your model. Even if you ultimately include data outside the established LTS in your model, you should submit results of final models with and without this data to show the sensitivity of your conclusions to the inclusion of data outside the established LTS.

Adequate characterization of the drug-drug interaction (DDI) potential of ozanimod and the need for dosing adjustments in patients taking concomitant medications, while not a RTF issue, is still of concern.

The ability of your population PK analysis (without the results for RP112273 from the dedicated DDI studies listed in Table 2) to adequately assess DDI potential will be a

review issue. Considerations will include the number of subjects receiving the concomitant medications and the availability of accurate dosing records for both the substrate and perpetrator (for example, timing of administration of both drugs, the dose amount, route of administration, and dosing frequency). In addition, you should demonstrate the ability of the bioanalytical assay(s) to differentiate and quantify RP112273 in the presence of concomitant medications. If population PK is not adequate to determine the DDI, especially for interactions which may raise safety concerns, additional in vivo DDI studies may be needed.

**Meeting Discussion:** Celgene asked what concerns FDA may have with the 17-month LTS and the population PK analysis. FDA clarified that there are no concerns with the approach. The word “might be adequate” were used to allow for unexpected issues arising during the review. Celgene acknowledged that the adequacy of the results from studies RPC01-1904 and RPC01-1906 [REDACTED] (b) (4) will be a review issue and concurs with the FDA’s recommendation of methods to handle LTS data within the population PK analysis. Celgene acknowledged that adequate characterization of the drug-drug interaction (DDI) potential of ozanimod, while not a Refuse-To-File issue, is still of concern to FDA.

Celgene’s assessment of DDI risk is that for RP112273 as a potential victim, RP112273 is not a substrate of drug transporters and RP112273 is formed via MAO-B. Celgene clarified that co-administration of MAO inhibitors with ozanimod will be contraindicated in the labeling and therefore they plan to perform no clinical DDI studies. For RP112273 as a victim, Celgene described plans to conduct a clinical PK DDI study for CYP2C8. No additional DDI studies are planned. Because Celgene does not anticipate completion of the PK DDI study for CYP2C8 before the time of NDA resubmission, FDA encouraged Celgene to submit the results early in the review cycle. If this is not possible, the ozanimod label will reflect data available at the time of the NDA resubmission.

Other concerns about RP112273 as a potential victim are that (a) RP112273 has not been quantified in study RPC01-1902 and hence the effect of itraconazole on RP112273 is not known; (b) that even though the results of study RPC01-1902 show that itraconazole had no significant effect on RP101075 (the metabolite directly preceding RP112273), there were problems with quantification of the RP101075 metabolite such as the failure of the incurred sample reanalysis to meet the acceptance criterion, and (c) cyclosporine, a strong inhibitor of P-gp and BCRP, doubled exposure to RP101988 and RP101075. It is difficult to predict whether the increase in RP101075 would lead to a similar increase in RP112273 exposure.

For RP112273 as a perpetrator, to address whether clinical PK DDI studies for RP112273 as an inhibitor of BCRP are needed, FDA requested that, after the meeting, Celgene re-calculate the ratio of free  $C_{max}$  to  $IC_{50}$  in accordance with the latest FDA guidance released in 2017 and submit it for review. FDA agreed to address the question in these minutes when that information became available [See **Post-Meeting Comment** below].

Regarding the need for a clinical DDI study with serotonergic agents, FDA disagreed with Celgene's conclusion regarding the effect of RP112273 on MAO-B. Serotonin syndrome and hypertensive crisis have occurred even with selective MAO-B inhibitors at higher doses. In addition, FDA stated that not enough data are available to support development of a  $C_{max}$ -based threshold for MAO inhibition similar to that for CYP enzymes and some transporters. Therefore, the recommendation on conducting an in vivo study to assess the inhibition potential of ozanimod will depend on the possibility of concomitant use with MAO-A or MAO-B substrates and the extent of the safety concern for the substrate drug. In addition, FDA stated that if Celgene does not conduct a tyramine pressor effect study, ozanimod labeling will, as with other MAO-B inhibitor drugs, include dietary tyramine restrictions.

Regarding the ability of population PK to address potential DDI for RP112273, Celgene clarified that they will not use population PK analysis to assess DDI potential because they do not have the information FDA specified in their preliminary response.

## 2.2. NONCLINICAL

**Question 2: Does the Division agree that the proposed bridging program will be adequate to address the nonclinical deficiency outlined in the RTF letter?**

**FDA Preliminary Response to Question 2:**

On face, your proposed bridging strategy appears sufficient, except that the report of the PK bridging study in rat (1840-033) provides data in males only. We remind you that all nonclinical study reports submitted to the NDA must be final (not draft) reports.

Meeting Discussion: Based on the Celgene's April 2, 2018, response to the FDA preliminary response, the Division questioned the need for the Celgene's proposed 3-month and 28-day toxicity studies of RP112273 in rat and mouse, respectively. The Division noted that those studies would not be needed if the toxicokinetic (TK) bridging studies with ozanimod demonstrated adequate exposure to the metabolite in the completed pivotal toxicity studies. However, if the bridging studies demonstrated inadequate exposure, the planned studies would not be of adequate duration to assess the chronic toxicity of the metabolite.

The Division also noted that the plasma RP112273 exposures achieved in the mouse and rat carcinogenicity studies are not adequate, in the absence of data indicating higher RP112273 exposures would not be tolerated or feasible to achieve. Therefore, studies (in two species) to assess the carcinogenic potential of RP112273 may be needed, unless additional information can be provided that support the adequacy of the ozanimod doses tested in the completed studies.

**Question 3: Can the Division please confirm that the signature page provided by the pathologist (included in Appendix 15.4) is acceptable?**

**FDA Preliminary Response to Question 3:**

The study pathologist signed the GLP compliance page. This does not substitute for a signed and dated pathology report under GLP. You will need to either provide a signed and dated Pathology Report or a signed statement from the pathologist that there is agreement with the pathology report as written.

**Meeting Discussion:** No discussion.

### 2.3. REGULATORY

**Question 4: Does the Division agree with the proposal for a 30 April 2018 planned data cutoff point for a new safety analyses supporting the NDA?**

**FDA Preliminary Response to Question 4:**

The appropriate date for the data cutoff point for new safety analyses is dependent on when the NDA will be submitted. Based on your projected submission target of no later than January 2019, your proposed date for data cutoff appears acceptable.

**Meeting Discussion:** No discussion.

**Question 5: Beyond agreement with the Division on the plans to address the clinical pharmacology and nonclinical deficiencies in the RTF letter, agreement on a new data cut-off point for the safety database, and agreement to include the requested non-RTF information, does the Division have any other recommendations to support a successful NDA submission?**

**FDA Preliminary Response to Question 5:**

We do not have any further recommendations.

**Meeting Discussion:** No discussion.

### 3. ISSUES REQUIRING FURTHER DISCUSSION

During Discussion on the potential for metabolite RP112273 to inhibit BCRP (Part 4.b of Celgene's Response to Question 1), the Agency requested that Celgene recalculate the  $C_{max}/IC_{50}$  ratio in accordance with the latest FDA guidance released in 2017.

**Post-Meeting Comment:** Celgene has subsequently submitted evidence that the  $I_{gut}/IC_{50}$  ratio for the inhibition of BCRP by RP112273 is 0.017, which is substantially less than the 10-fold threshold identified in the guidance. FDA agrees that there is no need to conduct an in vivo drug interaction study with a BCRP substrate.

**4. ACTION ITEMS**

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
DDI Studies as a perpetrator	FDA	As soon as possible
Redo calculations based on the updated Guidance, “In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies (October 2017)”	Celgene	As soon as possible (submitted by email on April 5, 2018)

**5. ATTACHMENTS AND HANDOUTS**

See attachment.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ERIC P BASTINGS  
04/27/2018



NDA 209899

**REFUSAL TO FILE**

Celgene International II Sàrl  
Attention: Gerlee D. Thomas  
Director, Regulatory Affairs, Receptos Services LLC  
3033 Science Park Road, Suite 300  
San Diego, CA 92121

Dear Ms. Thomas:

Please refer to your New Drug Application (NDA) dated December 22, 2017, received December 26, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Zeposia (ozanimod) 0.23 mg, 0.46 mg, and 0.92 mg capsules.

After a preliminary review, we find your application insufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Clinical Pharmacology

The long-term stability of RP112273, a recently identified predominant and active metabolite of ozanimod, has not yet been established. Retained plasma samples were used to quantify RP112273 in studies RPC01-201 (Part A and B), RPC01-301, RPC01-1904, RPC01-1906 and for most of subjects in study RPC01-1001. The samples were analyzed outside of the long-term stability window (136 days) for RP112273, and more than one year after collection for some of the samples. Long-term stability evaluations for RP112273 are ongoing. Per the Guidance for Industry on Bioanalytical Method Validation (2013)<sup>1</sup>, “Assays of all samples of an analyte in a biological matrix should be completed within the time period for which stability has been demonstrated”. Because of the above issue, the clinical pharmacokinetics of RP112273 have not been adequately characterized. The results of the pharmacokinetic analyses for RP112273 will inform critical assessments related to Zeposia dosing, e.g, the need for dosing adjustments for intrinsic or extrinsic factors that might affect the pharmacokinetic or pharmacodynamics of ozanimod. Without such information, labeling cannot be written to inform drug use in specific populations or patients taking concomitant medications.

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<sup>1</sup><https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>

### Nonclinical

RP112273, an active metabolite with potency at the S1P 1 and 5 receptors similar to that of the parent compound, accounts for the majority ((b) (4)%) of drug-related material in circulation in humans. Therefore, you will need to demonstrate that RP112273 has been assessed in a standard battery of nonclinical studies. To bridge to the existing nonclinical data, you would need to demonstrate adequate plasma RP112273 exposures in males and females, using the same dosing regimens used in the pivotal studies, in all species tested. Based on a preliminary examination, the available TK data are insufficient to allow a determination of the adequacy of the safety assessment for RP112273.

While the issues below are not related to the refusal to file decision for this application, you should address them if the application is resubmitted.

### Nonclinical

1. Methods Validation studies for RP112273 in mouse, rabbit, and monkey plasma cannot be located in the NDA.
2. The in vitro chromosomal aberration assay for RP112273 (AF00PS.341ICH (b) (4)) was submitted as an audited draft report. Only final study reports are to be submitted to an NDA. A final study report for the in vitro assay will need to be provided.
3. We ask that you provide a summary table of all TK data from the pivotal nonclinical (and TK bridging) studies in which the data are expressed in the same units across species and studies.
4. A signed and dated Pathology Report was not provided for the 26-week carcinogenicity study in Tg.rasH2 mouse (AE18BZ.7G8R (b) (4)); only the GLP statement was signed by the Study Pathologist. You will need to submit a signed and dated Pathology Report in order for us to consider the study complete.

### Prescribing Information (PI)

During our preliminary review of your submitted labeling, we identified the following issues that should be addressed if the application is resubmitted:

1. For the Indications and Usage (I/U) section,
  - a) revise the I/U statement to include the age group (i.e., adults) for which the drug is proposed to be indicated
  - b) remove (b) (4) to avoid unnecessary clutter and to enhance clarity of the Indications and Usage statement
  - c) because there is only one proposed indication, remove the subsection number
2. Under subsection 2.2 (Prior to Initiation of Therapy), revise the order of the bulleted information to be the same as the order of the Warnings and Precautions subsections.

3. Place all headings and subheadings in title case and use consistent formatting throughout all sections of the PI; for example, underline all headings and italicize all subheadings.
4. For all cross-references include the section title with the subsection number and place the cross reference in brackets. For example, the cross-reference under subsection 5.7 includes the subsection title rather than the section title should be *[see Use in Specific Populations (8.1)]*.
5. In the Adverse Reactions (ARs) section, relocate the list of most clinically significant ARs (those listed in the Warnings and Precautions section) to between the section 6 heading and subsection 6.1 subheading. Precede the list with the following introductory statement:

“The following serious adverse reactions are described elsewhere in the labeling:”
6. For the Pediatric Use subsection (8.4), we refer you to 21 CFR 201.57(c)(iv)(F) for the required statement if the requirements for a finding of substantial evidence to support a pediatric indication have not been met for any pediatric population. The required statement under these circumstances is: "Safety and effectiveness in pediatric patients have not been established."
7. Delete the Overdosage section (10) because there are no specific signs or symptoms of overdose nor treatment procedures based on data from overdose with ozanimod [see CFR 201.57(c)(11)] and because a statement that there were no adverse symptoms during overdose could imply that the dose administered was safe. Use of dosages that are not included in the Dosage and Administration section must not be implied in other sections of the labeling [see CFR 201.57(c)(3)(ii)].
8. Regarding the Clinical Pharmacology Section of the PI, we refer you to the Guidance for Industry, Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (Dec 2016). In particular, you should
  - a) include a brief introduction under the Pharmacokinetics subsection (12.3)
  - b) include “Effect of Food” subheading and the content to be included under this subheading
  - c) organize the “Elimination” heading followed by two subheadings of *Metabolism* and *Excretion*
  - d) use cross-references to avoid inclusion of clinical recommendations in this section

### Patient Labeling

Your submission does not include patient labeling. To align with approved labeling for other drugs for the treatment of multiple sclerosis, you should propose patient labeling with your resubmission of the NDA.

### Controlled Substance Staff

1. If the application is resubmitted, you should address all potential abuse related adverse events (AEs) for all Phase 1, 2, and 3 clinical studies. Potential abuse-related AEs

include euphoria, dissociative effects, hallucinations, psychosis, changes in mood, impaired cognition, attention, psychomotor effects, inappropriate affect, patient dropouts, overdoses, misuse, lost or unaccounted for medication, and unjustified dose increases. Report separate subgroup analyses for different subpopulations such as healthy volunteers, patients with MS, and patients with other disorders. See also section V.B. of the Abuse guidance 2017 for additional details and recommendations reporting abuse-related AEs.

2. Provide drug accountability data for the whole clinical development program. These data would include discrepancies in amount of the clinical supplies of the study drug dispensed and number of study drug doses lost or otherwise not accounted for, and reasons for missing study drug.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

### **PROPOSED PROPRIETARY NAME**

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at [OSECONSULTS@cderr.fda.gov](mailto:OSECONSULTS@cderr.fda.gov).'

If you have any questions, call LCDR Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely yours,

*{See appended electronic signature page}*

Eric Bastings, MD  
Deputy Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ERIC P BASTINGS  
02/23/2018



IND 109159

**MEETING PRELIMINARY COMMENTS**

Celgene International II Sàrl  
Attention: Gerlee Thomas  
Director, Regulatory Affairs, Receptos Services LLC  
3033 Science Park Road, Suite 300  
San Diego, CA 92121

Dear Ms. Thomas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RPC1063 (ozanimod).

We also refer to your correspondence, dated and received August 31, 2017, requesting a meeting to discuss your plans to submit a New Drug Application (NDA) for ozanimod to treat patients with relapsing forms of multiple sclerosis (RMS).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-2659.

Sincerely,

*{See appended electronic signature page}*

LCDR Nahleen Lopez, PharmD  
Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** November 27, 2017 (2:00-3:00pm EST)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1419  
Silver Spring, Maryland 20903

**Application Number:** 109159  
**Product Name:** RPC1063 (ozanimod)  
**Indication:** Multiple Sclerosis  
**Sponsor/Applicant Name:** Celgene International II Sàrl

**Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 27, 2017, 2:00-3:00pm EST, at FDA White Oak Building 22, Room 1419, between Celgene International II Sàrl and the Division of Neurology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

**1. BACKGROUND**

Celgene International II Sàrl requested a Type B Pre-NDA meeting on August 31, 2017, to discuss plans to submit an NDA for ozanimod for the treatment of patients with relapsing forms of multiple sclerosis (RMS). On March 2, 2017, FDA provided written responses to questions about the format and presentation of data for the NDA submission.

## 2. DISCUSSION

### 2.1. CLINICAL AND SAFETY

**Question 1a: Does the Agency agree that the results of the ozanimod Phase 3 clinical program (Studies RPC01-201B and RPC01-301), supported by the results of the Phase 2 study in RMS (Study RPC01-201A), are sufficient to characterize the efficacy and safety profile of ozanimod and may serve as adequate evidence to support the filing for the registration of ozanimod for the indication of the treatment of patients with RMS?**

*FDA Response to Question 1a:*

With regard to efficacy, based on the information in the meeting package, studies RPC01-201B and RPC01-301 appear to have the potential to support approval of a marketing application for the treatment of patients with relapsing MS. The adequacy of the data from those studies to support approval will be a matter of review. With regard to the safety profile, see the response to Question 1b.

**Question 1b: Does the Agency agree that the extent and duration of subject exposure is sufficient to support registration of ozanimod for the treatment of patients with RMS?**

*FDA Response to Question 1b:*

As described in the meeting package, your database appears to be sufficient for filing in terms of patient exposure. The adequacy of those data to support approval will be a matter of review. We expect that you will report adverse events occurring until 5 half-lives of ozanimod and any of its active metabolites after the last dose.

### 2.2. CLINICAL AND STATISTICAL

**Question 2: Does the Agency agree with the revised structure and content of the data and the proposed change to narratives/case report forms (CRFs) for submission that were previously agreed to in the 02 Mar 2017 Written Responses from FDA?**

*FDA Response to Question 2:*

Yes, regarding the narrative and CRFs. Regarding effectiveness data, we refer you to additional comments below that provide more detail on our recommendations made in Attachment 2 of the March 2, 2017, Written Responses.

### 2.3. NONCLINICAL

**Question 3: Does the Agency agree that the proposed nonclinical package, including the evaluation of major metabolites, is adequate to support the filing for the registration of ozanimod?**

FDA Response to Question 3:

Based on the information provided in your briefing document, we have the following comments on your nonclinical program:

- a) You should ensure that all circulating major human metabolites (i.e.,  $\geq 10\%$  of total circulating drug-related material) have been adequately assessed in the nonclinical studies (see ICH M3(R2), January 2010; ICH M3(R2) Q&A, February 2013). Interspecies comparisons should be made based on plasma exposure data for each major metabolite, not the sum of exposures for parent compound and active metabolites (“total agonist”).
- b) Metabolite RP112273 is stated to account for <sup>(b)(4)</sup>% of total drug-related exposure in humans; therefore, you will need to ensure that adequate exposure to RP112273 was achieved in a full battery of nonclinical studies, including chronic toxicity, reproductive and developmental, and carcinogenicity studies, in two species. We note that most of the plasma exposure data in animals for metabolite RP112273 are estimated (Table 24, footnote b). You will need to provide toxicokinetic data to document that RP112273 has been adequately assessed in the nonclinical studies. (See ICH M3(R2), January 2010 and ICH M3(R2) Q&A, February 2013.)

The adequacy of the data will be a matter of review.

## 2.4. CLINICAL PHARMACOLOGY

**Question 4: Does the Agency agree that the overall proposed clinical pharmacology package, including the additional information planned to be provided early in the NDA review, is acceptable and supports the filing for the registration of ozanimod?**

FDA Response to Question 4:

No. A complete clinical pharmacology package, including all relevant PK and PD studies and population PK and ER analyses is required at the time of submission. We note that multiple dose (steady state) PK evaluation of the major active metabolite RP112273 will be based on study RPC01-1001. You propose to submit an abbreviated clinical study report (CSR) of study RPC01-1001 at the time of NDA submission. Full CSRs (including the bioanalytical and validation reports) for this study and all relevant clinical PK and PD studies are needed at the time of the NDA submission. Please refer to the FDA Response to Question 10, Type C meeting, March 2, 2017.

You will need to address additional clinical pharmacology issues in the NDA submission:

- a) State whether ozanimod was dosed to steady state (based on the half-life of the major metabolite RP112273) in the QT study.
- b) Because in vitro studies show that RP112273 is a MAO-B inhibitor, provide an assessment of the inhibition potential of ozanimod in vivo; otherwise, ozanimod labeling (if approved) will include contraindications similar to those for other MAO-B inhibitor drugs.

- c) Because CYP2C8 is involved in the metabolism of ozanimod, you should discuss the role of this enzyme.
- d) There should be a discussion of the low recovery in the mass balance study ((b)<sub>(4)</sub>% total mean recovery of the administered radioactivity).

**Question 5: Does the Agency agree with Celgene’s proposed timing for the bioanalytical data package for the recently-identified major and active metabolite RP112273?**

*FDA Response to Question 5:*

Include the Validation and Analytical Study Reports for all major metabolites in the CSRs for all relevant PK and PD studies. These reports must be available at the time of the NDA submission.

State whether fresh or retained plasma samples were used to quantify RP112273 in the relevant clinical studies, including RPC01-1001, RPC01-1904, RPC01-1906, RPC01-301, and RPC01-201B). If you used retained plasma samples to quantify RP112273 in the relevant Phase 1 studies, you will need to provide evidence that demonstrates the stability of RP112273 in human plasma at the time of the NDA submission.

## 2.5. REGULATORY

**Question 6a: Based on the safety data and benefit-risk profile for ozanimod presented within the briefing document, Celgene does not believe a Risk Evaluation and Mitigation Strategy (REMS) is needed. Does the Agency agree? If during review of the application, the Agency believes a REMS may be required, can the Agency provide any insight into the timing for notification and subsequent REMS submission?**

*FDA Response to Question 6a:*

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks and, if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

**Question 6b: Does the Agency anticipate an Advisory Committee for this NDA? If yes, can the Agency comment on potential topics for discussion at an Advisory Committee meeting for ozanimod?**

*FDA Response to Question 6b:*

Although we are not aware of any issues at this time that would clearly require advisory committee input, the need for an advisory committee meeting will be determined after submission of the application. Issues that emerge during review may suggest the need for advisory committee input.

**Question 7: Does the Agency agree with Celgene’s revised plan (ie, timing of cut-off date and content) for the 4-Month Safety Update?**

*FDA Response to Question 7:*

Your proposal for the updated ISS, including tables, figures, listings, and datasets for Pools B, C, and D, and the data cutoff date for ongoing studies, is acceptable. Please include relevant narratives, as discussed for the original submission. We also expect narratives, as discussed for the original submission. See response to Question 1b, above.

For comments regarding updated data from clinical pharmacology studies, see response to Question 4.

**Question 8: Can the Agency confirm that the planned contents for the assessment of abuse potential is adequate to support the ozanimod NDA submission? If the Agency subsequently determines that additional investigations of abuse potential may be warranted, can this data be provided following registration, as a post-marketing requirement(s)?**

*FDA Response to Question 8:*

We will provide a response to this question in the final meeting minutes.

**3. ADDITIONAL FDA COMMENTS**

Note: We are willing to review and provide comment on a sample dataset for any of the datasets recommended in the following comments.

1. Include a table that identifies the time of key milestones for the key trials and their corresponding extensions. Milestones should include:
  - a. Protocol approvals
  - b. Protocol amendments
  - c. Statistical Analysis Plan (SAP) approvals
  - d. SAP amendments
  - e. First subject randomized
  - f. Last subject randomized
  - g. Last subject randomized
  - h. First subject completes follow-up
  - i. Last subject completes follow-up
  - j. Database lock
  - k. Interim analyses (labeled as blinded or not, and for efficacy and/or safety).
  - l. DMC meetings and teleconferences
2. Include in the dataset that documents the inclusion and exclusion criteria columns that indicate which of the criteria for disease activity were met (i.e., criteria 5a and 5b for studies RPC01-201 and RPC01-301). Provide an analysis of the impact of meeting or not meeting these criteria on the key outcome analyses.

3. For each study include a CONSORT diagram of patient disposition with an indication of populations used in analyses of efficacy and safety. Indicate the number of subjects who did not receive the treatment to which they were randomized and how these subjects were handled. Provide complete accounting of all discontinuations and withdrawals from study treatment and withdrawals from the trial including any reasons for discontinuation or withdrawal. Identify those discontinuations due to a relapse or worsening MS. Provide an accounting of subjects whose relapse and EDSS outcomes you exclude from the analysis following the use of alternative MS treatment.
4. Document in detail the sequence of times and criteria used for identification of relapses from the initial subject report of a potential relapse, the results from the telephone questionnaire conducted by the treating investigator, the determination by the treating investigator that a relapse assessment should or should not be scheduled, and the determination by the treating investigator that the event represented a protocol-defined relapse, including meeting the required change in EDSS/FSS scores. The datasets should include the times that the potential relapse events were first reported by the subject, the time that the event was first evaluated by the treating and blinded investigator. Include an analysis for any potential bias in the determination that a relapse assessment should be scheduled and the determination that the event represented a protocol-defined relapse. Provide sensitivity analyses based on relapses as reported by subjects, all relapses that were assessed by the treating investigator, all relapses referred for a blinded EDSS assessment as well as all protocol-defined relapses and as determined by the treating investigator. Provide an analysis of the time from relapse symptom onset to the time of the unscheduled relapse assessment visit, time to the blinded EDSS assessment, and time to final determination of a protocol-defined relapse. Discuss the impact of any differences in the results of these analyses. Provide a clear indication of any values that were imputed for these analyses.
5. Provide a complete accounting of all EDSS determinations. Include documentation of the process used to arrive at the final EDSS score. Provide a dataset that has one row per subject and which includes a column for each EDSS determination by visit (including screening, baseline, and unscheduled visits) and the time interval (in study days) between the time of randomization and each EDSS determination. Please place all scheduled EDSS assessments, for example, screening, baseline, and all subsequent visits, in the same column for all subjects. Identify and assign sequential identification numbers for those EDSS assessments that were performed at unscheduled relapse assessments and place each of them in the same column for all subjects, e.g., “unscheduled relapse assessment #1”, etc. The identification term used should map to the same events if they appear in other datasets. Flag the EDSS assessment used as the baseline. Flag those EDSS scores that met the protocol-defined criteria for progression of disability and those which contributed to the determination of confirmed/sustained progression of disability. Provide an analysis of the impact of any missing baseline EDSS or missing confirmatory EDSS values. Describe the process for the EDSS certification. Flag EDSS scores that were from an assessment by a noncertified examiner. Describe the process for assessment of the internal consistency of the determination of EDSS scores and any process for assessment of the consistency of the EDSS score with other clinical assessments.

6. Provide an explanation for any duplicate EDSS scores for the same assessment.
7. To assist review of outcome events, relapses and sustained disability, a log of events relevant to these clinical events for each patient is required for a full understanding. Include a dataset of important trial events for each patient with one row per patient per event. The dataset should have few columns and many rows. Columns should include the patient identifier, trial name, name of event, treatment arm, event-specific comment (such as reason for discontinuation, reason for unscheduled visit, EDSS score, name of new medication, preferred term for adverse event). There should be a column for the date and time of the event, and a column for the time since randomization. The events must include:
  - a) Sign consent form (date and time)
  - b) Randomization (date and time)
  - c) Start study medication (medication, date and time)
  - d) Discontinue study medication (reason, date and time)
  - e) Start treatment for acute relapse (medication, date and time)
  - f) Scheduled visits (visit number, date and time)
  - g) Every EDSS determinations (EDSS Visit Number Indicator, total score, type of EDSS, scheduled or not, etc., and date and time, rater)
  - h) EDSS score entered into data system, (EDSS Visit Indicator)
  - i) EDSS score changed in audit trail (date and time, previous score, new score)
  - j) Start alternative MS medication (medication name and date and time).
  - k) Patient reports of relapses to clinic (type of contact: patient calls site, during clinic visit, clinic calls patient, date and time)
  - l) Relapse evaluation visits (date and time, evaluator, confirmed relapse or not)
  - m) Unscheduled visits (reason, date and time)
  - n) MRI scan performed (lesion count)
  - o) Last subject contact (date and time)
  - p) Adverse event (preferred term, date and time)
  - q) Use of corticosteroids (date and time)
  - r) Relapse event confirmed (date and time of relapse)
8. For survival curves, the Y-axis should start with zero and end with 1 or 100%. The X-axis labels should include the time from 0 and the number of subjects in each treatment arm for each tick mark. The final proportion surviving and study arm should be indicated clearly.
9. Include tables and figures for the efficacy analysis of the primary endpoint and important secondary endpoints in key subpopulations (by demographic and baseline characteristics, regions, and other important factors) with point estimates, confidence intervals, and nominal p-values of the treatment difference.
10. Provide a detailed accounting of all missing primary and key secondary endpoint values. Provide a detailed accounting of all missing MRI scan values. Flag all imputed endpoint values. Identify the extent of missing data in all tables, figures, and graphs.

11. Provide an accounting of subjects whose relapse and EDSS outcomes you exclude from the analysis following the use of alternative MS treatment. Provide a sensitivity analysis in which these subjects are included as “treatment failures”.
12. Provide an analysis of injection-related adverse events as a potential factor in unblinding subjects or investigators to treatment assignment.
13. Describe the MRI scan protocols for sites and reviewing center and the extent of deviation from the protocol-defined MRI methods. Describe the process for assessment of the reliability and reproducibility of the central reader(s). Describe the methods for determination of MRI lesion volumes. Provide a detailed accounting of all missing primary and key secondary endpoint values. Provide a detailed accounting of all missing MRI scan values. Flag all imputed endpoint values. Identify the extent of missing data in all tables, figures, and graphs.
14. Include in the MRI datasets and tables the following
  - a) Date and time the MRI was performed
  - b) Date the MRI was received and when it was reviewed at the MRI centralized reading center
  - c) Detail the imputation method(s) employed.
15. List any fields that were collected in the CRF but which were not included in the datasets.
16. Provide a dataset with a row for each site with fields in each row that are needed to evaluate the extent of participation at the different sites. The fields to include in the table are the following: (Unique)SiteID, contact individual, address, city, (state/territory/province), country, mail code, region, telephone number, fax number, email address for contact individual, fields for the number of subjects randomized to each arm of the key trials, the number enrolled in the corresponding extension trials, fields showing the number of randomized patients in each arm of the trials who experienced relapses and progression of disability events, fields to list the total number of progression of disability events and total number of relapses for all patients, fields with the number of patients who did not complete the trial in each of the treatment arms, fields to provide the number of patients who completed each required MRI study with acceptable quality for each arm.
17. Provide an analysis and a summary addressing the extent to which the sites with clinical investigators who disclosed financial interests contributed to the outcome of the trial. The analysis and summary should include a comparison of the primary outcome for the key trials at sites that had investigators who disclosed financial interests with those sites that did not. Also, please discuss the significance of the percentage of U.S. sites with investigators who made disclosures compared to non-U.S. sites. Provide comparable analyses of the high-level safety results (for example, overall incidence of serious adverse events, discontinuations due to adverse events, and the incidence of any adverse events of special interest such as liver toxicity).

18. Provide an assessment of possible uncertainties in the data including bias. Estimate the potential for patients, investigators, and raters to introduce bias at each step in the process of determination of key endpoints. This should include any bias in the selection of potential relapses for further evaluation following the telephone subject report of new symptoms. We also recommend an analysis of the use of NSAIDs as an indicator that subjects or investigators had become aware of comparator treatment assignment. Provide an analysis of injection-related adverse events in each of the study arms as a potential factor unblinding subjects or investigators to treatment assignment. Assess whether knowledge of the previous EDSS scores may have influenced the determination of current EDSS scores.
19. Include a sample of active treatment and placebo packaged and labeled as received at study sites.
20. Describe the site monitoring process and document when monitoring visits occurred and the personnel who conducted the visit. Document the extent of source data verification.
21. Relapse data should be organized by the occurrence of relapses rather than by visits. Any patient who did not have a relapse should have one record representing the censored information. Patients who had N relapses should have N+1 records with N records of relapses in the order of the date of occurrence and one record of censoring due to discontinuation or due to study completion.
22. Disability/EDSS data should be organized by visit, including unscheduled and relapse visits. Unscheduled and relapse visits should be clearly indicated by a variable.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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REBECCA N LOPEZ  
11/24/2017