CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213498Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 101722

MEETING MINUTES

Actelion Pharmaceuticals Ltd.
c/o Janssen Research & Development, LLC
Attention: Monique Franc, PhD
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Dr. Franc:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ponesimod.

We also refer to the meeting between representatives of your firm and the FDA on September 4, 2019. The purpose of the meeting was to discuss submission of a new drug application.

A copy of the official minutes of the meeting/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 Susan Daugherty, Regulatory Project Manager at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Acting Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 4, 2019
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1417 Silver Spring, Maryland 20903
Application Number:	IND 101722
Product Name:	ponesimod
Indication:	Multiple sclerosis
Sponsor Name:	Actelion Pharmaceuticals Ltd.
Meeting Chair:	Eric Bastings, MD
Meeting Recorder:	Sandy Folkendt

FDA ATTENDEES

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Acting Director
Nick Kozauer, MD, Acting Deputy Director
Paul Lee, MD, PhD, Team Leader
David Jones, MD, Clinical Reviewer
Michelle Campbell, Stakeholder Engagement and Clinical Outcomes
Sandra Folkendt, Regulatory Health Project Manager
(b) (6) Pharmacy Student

Office of Biostatistics
Xiang Ling, PhD, Biometrics Reviewer, Biometrics I

Division of Clinical Outcomes Assessment
Onyeka Illoh, Reviewer
Sarrit Kovacs, Team Leader

Office of Clinical Pharmacology
Angela Men, DO, PhD, Team Leader, Division of Clinical Pharmacology I

Office of Surveillance and Epidemiology
Ingrid N Chapman, Risk Management Analyst, Division of Risk Management
Chad Morris, Safety Evaluator, Division of Medication Error and Prevention Analysis

Controlled Substance Staff
Jovita Randall-Thompson, PhD, Pharmacologist

SPONSOR ATTENDEES

Luc Truyen, MD, PhD, Global Head, Development and External Affairs
Juergen Haeussler, MD, Head of Full Development
Volker Breu, PhD, Compound Development Team Leader
Tarek El-Akkad, MD, Clinical Leader/Clinical Science Head
Tatiana Scherz, MD, PhD, Clinical Project Physician (Neurology)
Michel Burcklen, PhD, Clinical Project Scientist
Andrea Vaclavkova, MD, Medical Safety Officer
Partha Nandy, PhD, Clinical Pharmacology Leader
Brian Hennessy, MSc, Clinical Project Statistician
Suzanne Foy, MRPharmS, Global Regulatory Affairs Leader
Monique Franc, PhD, US Regulatory Affairs Leader
Chuck Thompson, PhD, Drug Metabolism and Pharmacokinetics Leader
Alexander Keenan, MSc, Global Market Access Leader
(b) (6) Director, (b) (6)
(b) (6) CEO and Strategic Lead; (b) (6) (via telephone)

1.0 BACKGROUND

Actelion Pharmaceuticals requested a Type B, Pre-NDA meeting on July 1, 2019, to discuss the format and content of a new NDA submission.

FDA sent Preliminary Comments to the sponsor on August 30, 2019.

2. DISCUSSION

2.1. CLINICAL

Question 1: Does the Agency agree that the totality of safety and efficacy data from the Phase 3 OPTIMUM superiority study (and safety data from its long-term extension study [AC-058B303]), supported by the Phase 2 AC-058B201 study (and its long-term extension study [AC-058B202]), is adequate for an NDA filing to support the indication of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults?

FDA Response to Question 1: On face, it appears that Studies AC-058B301, AC-058B201, and their extensions, have the potential to support an NDA submission. The adequacy of the findings from these studies to support filing will be a matter of review.

Meeting Discussion:
The sponsor stated that it was its intention to include all findings, including the 12- and 24-week confirmed disability accumulation findings that did not achieve statistical significance, in Section 14 of the proposed labeling to be included in the NDA submission. The Division stated that while the sponsor may propose and provide a rationale for the inclusion of any trial findings in labeling, it is unlikely that a failure to show any treatment effect on disability accumulation in a single clinical trial would be included in final negotiated labeling.

Question 2: The sponsor has conducted all requested psychometric analyses for deriving and interpreting meaningful change on the Fatigue Symptoms Impact Questionnaire (FSIQ) Symptoms domain.

Does the Agency agree that a (b) (4)-point change on the FSIQ Symptoms domain is an acceptable threshold for interpreting within-subject change from baseline at Week 108?

FDA Response to Question 2: Based on your current submission we do not agree there is sufficient evidence or justification to support that your proposed (b) (4)-point change threshold in the FSIQ Symptoms domain score is clinically meaningful to patients. We are more interested in what constitutes a clinically meaningful within-patient change in scores (i.e., improvement threshold), from the patient perspective, rather than a "minimal" improvement threshold.

You will need to provide justification to the Agency regarding the clinical meaningfulness of a (b) (4)-point change threshold. It is important to understand what constitutes a meaningful improvement in the 11-point PGIS scale ratings based on the patient perspective; this would aid in determining an appropriate point change in the PGIS scale to be used as the anchor to define improvement in the FSIQ Symptoms domain score. It would also be useful to understand whether the meaningfulness of the designated point change on the PGIS anchor scale varies depending on patients' baseline PGIS ratings (e.g., going from a rating of "10" to a rating of "7" versus going from a rating of "5" to a rating of "2"). As was previously stated in the Written Responses letter dated February 1, 2019, justification for your FSIQ Symptoms domain change threshold could be supported by data from exit interviews with patients. Thus, your current proposal of a (b) (4)-point change threshold will be a review issue.

Additionally, please make sure the scoring for the FSIQ is consistent across your documents in an NDA submission, including the final protocol and the SAP.

Meeting Discussion:
The sponsor stated that it is in the process of developing a psychometric analysis report including results from post hoc analyses supporting its proposed (b) (4)-point change threshold, four additional tables, and a PRO evidence dossier. The

sponsor stated that it will submit this additional information for Agency review and comment as part of an NDA submission.

2.2. CLINICAL PHARMACOLOGY

Question 3: Does the Division agree that the proposed clinical pharmacology and biopharmaceutics package is adequate to support filing of an NDA for ponesimod?

FDA Response to Question 3: We do not agree [redacted] study AC-058-117 [redacted] The CSR for this study is needed at the time of the NDA submission as this is a critical study to guide treatment recommendations for patients who are on beta blockers. In addition, the report of the discontinued study AC-058-111 (interaction between a single dose of ponesimod 10 mg with diltiazem and atenolol) needs to be submitted in the NDA as well.

You claim that:

1. When ponesimod was administered as the [redacted] in capsule, food showed no clinically relevant effects on the PK of ponesimod (Study AC-058-101).
2. The PK of ponesimod administered in a fasted state were comparable following oral administration of Form A and Form C (Study AC-058-103).
3. The PK of ponesimod administered as polymorphic [redacted] was similar between the tablet and capsule formulations when administered under fasting conditions (Study AC-058-108).

It appears that you assume that, similar to polymorphic [redacted] capsule, there would be no effect of food for polymorphic [redacted] to-be-marketed tablet. You need to provide justification for this assumption.

We note that to-be-marketed formulation was provided [redacted]

Meeting Discussion:
The sponsor agreed to submit the DDI study report with beta-blocker in the NDA submission.

The Agency stated that the justification for a food effect study on the [redacted] tablet is acceptable on face. In the meeting presentation, the sponsor provided the Population PK analysis based on Phase 1 study data which showed no effect of food or formulation on drug exposures. The sponsor agreed to update this POP PK analysis with P2 and P3 studies data having food as a covariate in the NDA submission.

The provided dissolution profiles for ponesimod 20 mg film-coated tablet versus [redacted] (b) (4) ponesimod 20 mg film-coated tablet was tested at PH 4.5 only. To make sure [redacted] (b) (4) will not have impact on ponesimod bioavailability, the Agency advised the sponsor that it needs to provide justification on why the results obtained at PH 4.5 can be applied to other PHs. Otherwise, dissolution tests at various PH are needed.

Question 4: Does the Division agree that the proposed pharmacometrics package is adequate to support the filing of an NDA for ponesimod?

FDA Response to Question 4: The proposed pharmacometrics package appears acceptable but adequacy for filing is a matter of review.

The following are the general expectations for submitting pharmacometric data and models:

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

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

A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

The response to Question 4 wasn't discussed at the meeting.

2.3. NONCLINICAL

Question 5: Does the Division agree that the proposed nonclinical package is adequate to support the filing of an NDA for ponesimod?

FDA Response to Question 5: Based on the information provided in the briefing document, we have the following comments:

1) In Table 20, the pre- and postnatal development study is listed as a draft report. Only final study reports are to be submitted in an NDA.
2) As we previously stated (see EOP2 correspondence, dated January 27, 2012), a signed and dated pathology report needs to be submitted for each pivotal toxicology study. A signed and dated Statement of Compliance is not an adequate substitute for a signed pathology report.

The adequacy of all data is a matter of review.

Meeting Discussion
The sponsor agreed to include the final study report for the pre- and postnatal development study and a signed and dated pathology report for each pivotal toxicology study in the NDA submission.

2.4. BIOSTATISTICS

Question 6: Does the Division agree with the proposed structure of Integrated Summary of Safety (ISS) datasets?

FDA Response to Question 6: The ISS datasets appear acceptable. Refer also to Attachment 1 in our Written Response dated February 1, 2019, for the Division's general requests for safety data submissions.

The response to Question 6 wasn't discussed at the meeting.

Question 7: Does the Division agree to the proposed plan for the submission of SAS programs?

FDA Response to Question 7: The SAS programs for the phase 2 study AC-058B201 should also be submitted.

Meeting Discussion
The sponsor agreed to include the requested SAS programs in the NDA submission.

Question 8: Does the Division agree with the data standardization approach for the ponesimod NDA as outlined in the SDSP?

FDA Response to Question 8: From a technical standpoint, the data standardization approach as outlined in the SDSP appears acceptable.

The response to Question 8 wasn't discussed at the meeting.

2.5. ABUSE POTENTIAL

Question 9: Does the Division agree that the abuse potential information to be included in the application is adequate to support the review of abuse potential?

FDA Response to Question 9: We agree. The data and information as summarized in your briefing package appears adequate to support filing of an NDA for ponesimod. However, our final determinations about the abuse potential of a proposed drug product are made following a comprehensive review of all abuse potential-related data submitted under an NDA. If significant signals of abuse potential are identified beyond the data you summarized (e.g., further cases of abuse-related AEs that code to euphoric mood) further abuse-related studies may be needed.

We also recommend the following:

1. Continue monitoring for abuse-related adverse events in your clinical studies. We direct you to the guidance for industry, *Assessment of Abuse Potential of Drugs (2017)*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

   You should report all potential abuse-related adverse events (AEs) from your clinical studies with ponesimod and provide detailed narratives for these AEs as recommended in section V.B. of the 2017 Guidance mentioned above. Provide the list of terms that prompt these reports (including abuse-related AE terms such as euphoric mood, disturbance in attention, psychomotor effects, inappropriate affect, patient dropouts, overdoses, misuse, lost or unaccounted for medication, and unjustified dose increases). Where narratives are provided, they should include time of onset and duration for the event, dose of drug taken, severity, and outcome. If available, pharmacokinetic values for each individual subject who experienced these AEs should be provided to understand if there is a temporal correlation between drug plasma levels and AEs.

2. You should report all possible cases of abuse (subjects taking the drug for nontherapeutic purposes, e.g., for psychoactive effects such as high or euphoria) occurring in your clinical trials. In such cases, information collected by the

investigator should include explanations from the subjects when there are drug accountability discrepancies. Towards this end:

i. Provide data in tabular form for all reports of abuse, overuse, lost/stolen/missing or unaccounted product that occurred in clinical trials. These data should include study number, and type of study, subject ID number, narratives, case description, and details.

ii. Provide narratives for cases where patients drop out from studies for reasons that might be coded as “protocol violation,” “lack of efficacy” (to capture aberrant behavior in patients who drop out of the study supposedly due to lack of efficacy), “lost to follow up,” “non-compliance to study medication or procedures,” “over compliance,” or for “other.” Case reports should be provided separately.

iii. Report any use of the investigational formulation by individuals other than the patients (family member, health care practitioner, etc.).

3. Submit final study reports on all studies you reference to support your assertions with respect to the abuse potential of ponesimod.

Meeting Discussion

The sponsor indicated that it can provide the requested information on abuse potential in the initial NDA and sought confirmation on the following points:

1. The sponsor proposed to include, in the abuse potential assessment in the NDA, narratives for adverse events coding to the following MedDRA (v21.0) preferred terms based on the Guidance:

   Aggression, Confusional state, Decreased activity, Dependence, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug abuse, Drug abuser, Drug dependence, Drug detoxification, Drug diversion, Drug rehabilitation, Drug tolerance, Drug tolerance increased, Drug use disorder, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Euphoric mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Hallucination, Hallucination, auditory, Hallucination, gustatory, Hallucination, olfactory, Hallucination, synaesthetic, Hallucination, tactile, Hallucination, visual, Hallucinations, mixed, Inappropriate affect, Mental impairment, Product tampering, Psychomotor hyperactivity, Psychotic disorder, Rebound effect, Somatic hallucination, Somnolence, Substance abuser, Substance dependence, Substance use, Substance use disorder, Substance-induced mood disorder, Substance-induced psychotic disorder, Thinking abnormal, Withdrawal arrhythmia, Withdrawal syndrome.

The Agency agreed that the list of MedDRA terms the sponsor provided for identifying abuse-related adverse events in Phase 1, 2 and 3 is acceptable. If there are any changes to the list of terms, the Agency advised the sponsor that those changes should be delineated in the abuse potential assessment in the NDA for ponesimod.

2. Regarding "patient dropouts, overdoses, misuse, lost or unaccounted for medication, and unjustified dose increases", the sponsor stated they can provide the requested information, where applicable, for Phase 1 and Phase 3 studies. However, owing to a different process employed at the time of conduct of the Phase 2 studies, which focused on general drug accountability (under-compliance), the sponsor explained that information on these cases is only available in source documents, and can be provided in an updated abuse potential assessment with the Day 120 Safety Update.

   The Agency agreed with the Phase 2 assessments for "patient dropouts, overdoses, misuse, lost or unaccounted for medication, and unjustified dose increases" being submitted in an updated abuse potential assessment with the 120-Day Safety Update.

2.6. REGULATORY

Question 10: Subject Narratives and Case Report Forms

a. Does the Division agree with the proposed plan for providing narratives and case report forms (CRFs)?

b. Does the Division agree with the sample narrative that has been provided from a subject who had more than 1 SAE and participated in the controlled and extension studies?

FDA Response to Question 10: Your proposed plan for providing narratives and case report forms, and the sample narrative you provided, appear acceptable. Refer also to Attachment 1 in our Written Response dated February 1, 2019, for the Division's general requests for safety data submissions.

The response to Question 10 wasn't discussed at the meeting.

Question 11: As advised by the Agency, the sponsor plans to submit to the NDA the agreed iPSP accompanied by a letter summarizing the planned changes to the iPSP.

Does the Division agree with the proposed format of the letter of planned changes?

FDA Response to Question 11: You may submit the agreed-upon iPSP and a letter summarizing the planned changes to the iPSP as we advised previously; however, agreement with the revisions to the iPSP will be a matter of review.

The response to Question 11 wasn't discussed at the meeting.

Question 12: Does the Division agree with the proposed list of covered studies for which financial certification and/or disclosure for clinical investigators will be provided in the NDA?

FDA Response to Question 12: The proposed list of covered studies for which financial certification / disclosure for clinical investigators will be provided (AC-058-110, AC-058-115, AC-058-201, AC-058-202, AC-058-301, and AC-058-303) appears reasonable. If, during review, we identify any additional studies with reporting obligations under 21 CFR 54, we will clarify any relevant financial certifications and disclosures via Information Requests.

The response to Question 12 wasn't discussed at the meeting.

Question 13: Does the Division agree that the proposed content and eCTD format of the NDA, as outlined in the attached eCTD Content Outline, are acceptable to form the basis of a complete NDA?

FDA Response to Question 13: The proposed approach for your eCTD format of the submission is acceptable except for submitting documents at the proposed levels under 2.3.S and 2.3.P, 2.3.A, and 3.2.P.2. Please refer to FDA guidance https://www.fda.gov/media/71551/download

Refer also to Attachment 2 in our Written Response dated February 1, 2019, for the Division's additional requests for the submission of findings related to effectiveness.

The adequacy of the content of your data submission to support the filing of a complete NDA will be determined after review of the entire submitted application (see response to Question 1).

Meeting Discussion
The sponsor agreed to make the necessary changes to render the eCTD submission compliant with the referenced FDA guidance. The sponsor also acknowledged the submission requests in Attachment 2 of the Written Response dated February 1, 2019.

Question 14: Does the Division agree with the proposed content and data cutoff date for the Day-120 Safety Update?

FDA Response to Question 14: The proposed data cutoff date for the 120-Day Safety Update appears acceptable. In addition to cumulative exposure and safety information, this Safety Update should also include relevant narratives in the same format as the initial submission (see response to Question 10.) Refer also to Attachment 1 in our Written Response dated February 1, 2019, for the Division's general requests for safety data submissions.

The response to Question 14 wasn't discussed at the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

Handouts used at the meeting are appended to these minutes.

6.0 ADDITIONAL IMPORTANT INFORMATION

Discussion of the Content of a Complete Application

- The content of a complete application was discussed. No agreements were made for late submissions.

- 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.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan, and it was concluded that a REMS does not appear to be needed at this time.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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 an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP 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 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*.[1] 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 FDA.gov.[2]
&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 gran

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[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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*.

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

Discussion of Safety Analysis Strategy for the ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The

meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

Abuse Potential Assessment

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[5]

Manufacturing Facilities

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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 items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

[6] https://www.fda.gov/media/85061/download

Question 2: Patient Reported Outcomes

FDA Response to Question 2: Based on your current submission we do not agree there is sufficient evidence or justification to support that your proposed (b) (4)-point change threshold in the FSIQ Symptoms domain score is clinically meaningful to patients. We are more interested in what constitutes a clinically meaningful within patient change in scores (i.e., improvement threshold), from the patient perspective, rather than a "minimal" improvement threshold. You will need to provide justification to the Agency regarding the clinical meaningfulness of a (b) (4)-point change threshold. It is important to understand what constitutes a meaningful improvement in the 11-point PGIS scale ratings based on the patient perspective; this would aid in determining an appropriate point change in the PGIS scale to be used as the anchor to define improvement in the FSIQ Symptoms domain score. It would also be useful to understand whether the meaningfulness of the designated point change on the PGIS anchor scale varies depending on patients' baseline PGIS ratings (e.g., going from a rating of "10" to a rating of "7" versus going from a rating of "5" to a rating of "2").

Janssen discussion points. *Janssen prespecified a series of psychometric analyses in the psychometric analysis plan, including anchor- and distribution-based analyses to contribute to the interpretation of change using a patient global assessment of change as the anchor. Global anchors have been identified in the 2009 PRO Guidance, as well as the updated draft guidance, as key measures to aid in the interpretation of the derived endpoint of interest (eg., FSIQ Symptoms domain). At the time of protocol development and review, the Agency suggested 11-point NRS scales as anchor response scales; however, it is acknowledged that the field has shifted to verbal response scales. In this prespecified analysis, a full evaluation of the distribution of change on the FSIQ Symptoms domain considering the anchor-based uncollapsed and collapsed psychometric evaluation as well as the change from baseline on the PGIS as requested in the Written Responses letter dated February 1, 2019 was conducted. These analyses address both minimum and meaningful change from the patient's perspective. However, the request for additional justification will be addressed in supportive, post-hoc psychometric analyses to understand how the magnitude of change on FSIQ Symptoms domain score varies according to the patient's baseline PGIS rating.*

Janssen is prepared to share 4 tables for the related outputs with the Agency following this meeting to further support the meaningful change threshold derivation. Will the Agency be willing to review and provide written feedback on these post-hoc analyses to support the responder analysis for the NDA submission?

FDA Response to Question 2, continued: As was previously stated in the Written Responses letter dated February 1, 2019, justification for your FSIQ Symptoms domain change threshold could be supported by data from exit interviews with patients.

Janssen discussion points. *Janssen acknowledges the suggestion and potential benefit of conducting exit interviews with patients from the Written Responses letter dated February 1, 2019, however, at the time of the suggestion, the study was fully enrolled with 85% of patients having either completed treatment or withdrawn from the study. The ability to develop and conduct an*

exit interview study to be included as part of the phase 3 trial design was not feasible at the time that this was suggested for consideration. As noted above, Janssen has included patient-reported anchors which, as hypothesized, have shown to discriminate, monotonically, along the severity continuum of the FSIQ Symptoms domain. The additional post-hoc analyses proposed above could further support this.

FDA Response to Question 2, continued: Additionally, please make sure the scoring for the FSIQ is consistent across your documents in an NDA submission, including the final protocol and the SAP.

Janssen discussion points. *Janssen will present the full psychometric report and relevant sections of the PRO Evidence Dossier as part of the NDA submission. All information related to final scoring will be included.*

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Question 9: Abuse Potential

FDA Response to Question 9: You should report all potential abuse-related adverse events (AEs) from your clinical studies with ponesimod and provide detailed narratives for these AEs as recommended in section V.B. of the 2017 Guidance mentioned above. Provide the list of terms that prompt these reports (including abuse-related AE terms such as euphoric mood, disturbance in attention, psychomotor effects, inappropriate affect, patient dropouts, overdoses, misuse, lost or unaccounted for medication, and unjustified dose increases). Where narratives are provided, they should include time of onset and duration for the event, dose of drug taken, severity, and outcome. If available, pharmacokinetic values for each individual subject who experienced these AEs should be provided to understand if there is a temporal correlation between drug plasma levels and AEs.

Sponsor Discussion Points:

The sponsor can provide the requested information on abuse potential in the initial NDA and seeks confirmation on the following points:

1. The sponsor proposes to include, in the abuse potential assessment in the NDA, narratives for adverse events coding to the following MedDRA (v21.0) preferred terms based on the Guidance…:

   Aggression, Confusional state, Decreased activity, Dependence, Disorientation, Dissociation, Dissociative disorder, Dizziness, Drug abuse, Drug abuser, Drug dependence, Drug detoxification, Drug diversion, Drug rehabilitation, Drug tolerance, Drug tolerance increased, Drug use disorder, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Euphoric mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Hallucination, Hallucination, auditory, Hallucination, gustatory, Hallucination, olfactory, Hallucination, synaesthetic, Hallucination, tactile, Hallucination, visual, Hallucinations, mixed, Inappropriate affect, Mental impairment, Product tampering, Psychomotor hyperactivity, Psychotic disorder, Rebound effect, Somatic hallucination, Somnolence, Substance abuser, Substance dependence, Substance use, Substance use disorder, Substance-induced mood disorder, Substance-induced psychotic disorder, Thinking abnormal, Withdrawal arrhythmia, Withdrawal syndrome.

2. Regarding "*patient dropouts, overdoses, misuse, lost or unaccounted for medication, and unjustified dose increases*", the sponsor can provide the requested information, where applicable, for Phase 1 and Phase 3 studies. However, owing to different process employed at the time of conduct of the Phase 2 studies, which focused on general drug accountability (under-compliance), information on these cases is only available in source documents, and can be provided in an updated abuse potential assessment with the Day 120 Safety Update.

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

/s/

NICHOLAS A KOZAUER
09/26/2019 09:51:52 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101722

MEETING MINUTES

Actelion Clinical Research, Inc.
Attention: Patricia Palumbo, BSN, JD
Director, Global Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Ms. Palumbo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ponesimod (ACT-128800) Tablets.

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on December 6, 2011.

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 Hamet Touré, PharmD MPH, Regulatory Project Manager at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: EOP2

Meeting Date and Time: December 6, 2011; 1300-1400
Meeting Location: White Oak; Building 22, room 1315

Application Number: IND 101722
Product Name: Ponesimod
Indication: RRMS
Sponsor/Applicant Name: Actelion Clinical Research, Inc.

Meeting Chair: Russell Katz, MD
Meeting Recorder: LCDR Hamet Touré

FDA ATTENDEES

Russell Katz, MD, Division Director
Eric Bastings, MD, Deputy Director
Billy Dunn, MD, Team Leader
Heather Fitter, MD, Clinical Reviewer
Angela Men, MD PhD, Clinical Pharmacology Team Leader
Hristina Dimova, PhD, Clinical Pharmacology Reviewer
Joo-Yeon Lee, PhD, Pharmacometrics Reviewer
Martina Sahre, PhD, Clinical Pharmacology Fellow
Lois Freed, PhD, Nonclinical Team Leader
Richard Houghtling, PhD, Nonclinical Reviewer
Kun Jin, PhD, Statistics Team Leader
Xiang Ling, PhD, Statistics Reviewer
Martha Heimann, PhD, CMC Team Leader
Akm Khairuzzaman, PhD, CMC reviewer
Monica Fiszman, MD PhD, Cardiology Reviewer
Banu Karimi-Shah, MD, Pulmonary Team Leader
Nicole Bradley, PharmD, Regulatory Project Manager
LCDR Hamet Touré, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES

Marisa Bacchi, PhD, VP, Head of Biostatistics
Ouali Berkani, MSc, Associate Director, Senior Clinical Project Scientist
Beate Bittner, PhD, Director, Senior Clinical Pharmacologist

Guy Braunstein, MD, EVP, Head of Global Clinical Development
Stephan Brodbeck, MSc, Associate Director, Senior Technical Project Leader
Volker Breu, PhD, Senior Director, Life Cycle Leader
Mireille Collombat, PharmD, Director, Global Regulatory Affairs
Daniele D'Ambrosio, MD, PhD, Clinical Area Head
Alberto Gimona, MD, VP, Head of Clinical Science
Ulrich Mentzel, PhD, VP, Head of Toxicology
Per Nilsson, MD, PhD, VP, Head of Strategic Development
Patricia Palumbo, BSN, JD, Director, US Regulatory Affairs

BACKGROUND:

The December 6, 2011, face to face meeting is a type B End of Phase 2 meeting to discuss the Phase 3 development plan of ponesimod for the treatment of relapsing-remitting multiple sclerosis (RRMS).

QUESTIONS:

QUALITY

Question 1:Drug Substance Starting Materials

The proposed starting materials for the synthesis of the ponesimod (ACT-128800) drug substance are [redacted] (b) (4) [redacted] (b) (4) Does the Agency agree with the proposed starting materials for manufacture of the drug substance?

Rationale

The proposed starting materials [redacted] (b) (4) [redacted] are defined in line with the International Conference on Harmonisation (ICH) Guideline Q7 entitled *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*.

Each of the starting materials [redacted] (b) (4) [redacted]

Impurity profile specifications for the starting materials that are based on the evaluation of the preliminary fate of impurities along the synthesis are provided in Section 10.1.1. They will be continually refined based on further process improvements and based on refined investigations of the fate of impurities. See Section 10.1.1 for more details.

FDA Preliminary Response: Your proposed designation for the starting materials appears to be reasonable. However, [redacted] (b) (4) [redacted] in order to make the final conclusion. Additionally, we recommend that you continue to evaluate the impact of future starting material manufacturing/source changes on the quality of the final drug substance.

Meeting Discussion: None.

Question 2:Manufacturing Overage

The current drug product manufacturing process of ponesimod film-coated tablets allows for a [redacted] (b) (4) drug substance manufacturing overage to compensate for drug substance losses during manufacture. Actelion initiated an investigation with the aim of identifying and eliminating the

root cause of the drug substance losses. However, if the investigation indicates that the root cause cannot be eliminated, and the need for including a drug substance overage persists, Actelion proposes that a drug substance overage will be included as an integral part of the batch formula. Does the Agency agree?

Rationale:

A (b) (4) overage was defined based on batch release results from clinical batches over a range of dose strengths (see Section 10.1.2). To date, with the inclusion of the overage to compensate for apparent losses, all release data have been found to be within specifications.

A pharmaceutical development program has been initiated to identify the root cause or process step of the drug substance losses. Ongoing investigations encompass drug substance properties and the drug product manufacturing process of a (b) (4) .

Current data suggest that losses may be due to (b) (4) Therefore, a development program with an experimental design approach was initiated to investigate the influence of the (b) (4)

Actelion is of the opinion that the actions that it has taken and is taking are adequate and appropriate to identify the root cause of the drug substance losses.

If overages continue to be required by the time of commercialization then Actelion would plan (b) (4)

See Section 10.1.2 for further details.

FDA Preliminary Response:

We allow overage to compensate based on demonstrated manufacturing loss. At this moment we do not have any data that reveals the actual reason for the drug loss during the manufacturing process. Additionally, we observed a trend of higher assay (4 out of 9 batches showed (b) (4) %, average (b) (4) %) in batches manufactured with overage compared to those without overage.

Meeting Discussion: None.

NONCLINICAL

Question 3:Nonclinical Development Plan

The standard battery of nonclinical pharmacology, drug metabolism and pharmacokinetics (DMPK), safety pharmacology, and toxicology studies have been conducted to support the

initiation of Phase 3. Does the Agency agree that, together with the additional studies to be conducted during Phase 3, the overall nonclinical package is sufficient to support a New Drug Application (NDA)?

Rationale

Nonclinical DMPK, safety pharmacology, and toxicology studies were performed according to the ICH Guideline M3(R2) entitled *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.

Actelion has completed single- and multiple-dose DMPK studies in rats and dogs, and *in vitro* and *in vivo* safety pharmacology studies in rats, guinea pigs, and dogs. It has also completed multiple-dose toxicology studies in mice, rats, and dogs. These include rodent studies (up to 13 weeks in mice and 26 weeks in rat) and dog studies (up to 52 weeks). In addition, male and female fertility studies in rats, and embryo-fetal development studies in rats and rabbits have been conducted.

The results of the tests conducted to date have provided safety margins and allowed identification of target organs; this information has been taken into account in the design of the Phase 3 clinical studies.

Prior to filing the NDA for ponesimod, Actelion plans to conduct pre- and post-natal development studies in rats and 2-year carcinogenicity studies in rats and mice.

See Section 10.2.1 for more details.

FDA Preliminary Response:

On face, your nonclinical program appears to be sufficient to support NDA filing; however, there is concern regarding the arterial lesions identified in the 26- and 52-week oral toxicity studies in dog. The NOAEL (3 mg/kg/day) for these lesions is associated with plasma exposures only ≈4 times that anticipated in humans at the maximum dose proposed for the Phase 3 clinical trial. We recommend that you conduct studies to further investigate these findings in order to identify, if possible, the mechanism(s) underlying the findings and a strategy for monitoring humans to prevent similar toxicity.

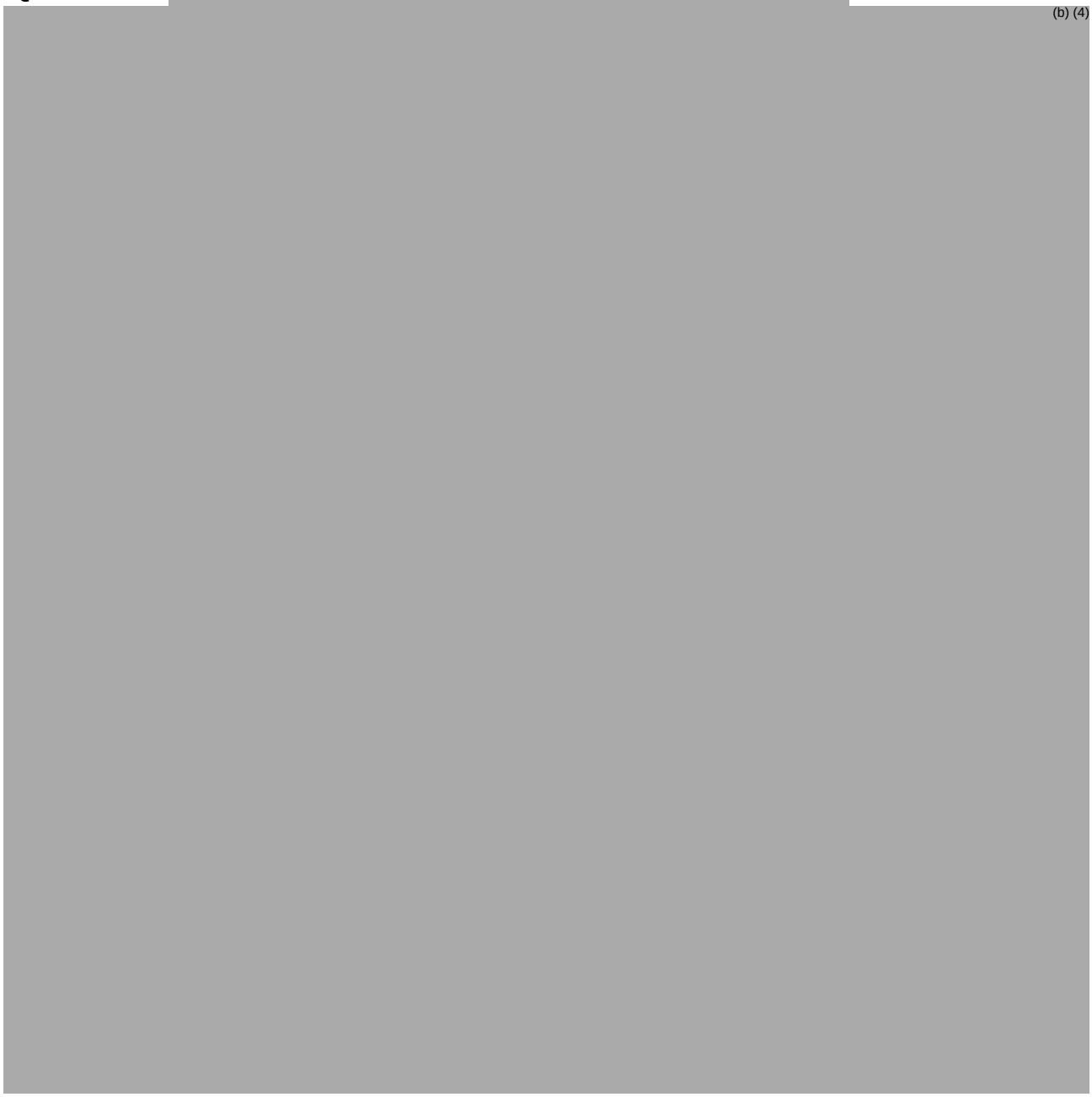
A signed and dated Pathology Report needs to be submitted for each pivotal toxicology study, including the 26-week rat (No. T-05.134) and the 52-week dog (Study No. T-06.186) studies.

Meeting Discussion: The sponsor summarized the results of *in vitro* mechanistic studies, which, according to the sponsor, demonstrate that the arterial lesions are species-specific. The division recommended that the sponsor provide a document summarizing all available data considered to support that position. The division noted the apparent lack of data confirming the relevance of the *in vitro* findings to the arterial lesions detected *in vivo*, and suggested that the sponsor consider conducting a study to assess the potential for arterial lesions in another nonrodent species, such as the monkey or minipig. The sponsor stated that studies in a second non-rodent

species had been considered but were not conducted, since it was uncertain that these data would be sufficient to dismiss the concerns regarding the arterial lesions.

The division corrected the reference to "intracardiac hemangiomas" included in the Preliminary Response to Question 7: hemangiomas were not among the arterial lesions detected in dog.

Question 4: (b) (4)



Meeting Discussion: None.

CLINICAL PHARMACOLOGY

Question 5:Clinical Pharmacology Program

Actelion is of the opinion that the clinical pharmacology program for ponesimod is adequate to support the initiation of Phase 3 and to support an NDA for the indication of the treatment of RRMS. Does the Agency agree?

Rationale

The clinical pharmacology studies that have been conducted in healthy subjects (10 completed studies with over 200 subjects), produced data on pharmacokinetics (PK), pharmacodynamics (PD), drug-drug interactions (DDI), and safety and tolerability. The results obtained in these studies supported the initiation of Phase 2 studies (including a long-term extension study) and would also support initiation of Phase 3 in patients with RRMS. DDI studies conducted with ponesimod include a study with oral contraceptives (AC-058-104) and a study with calcium channel blockers or beta blockers (AC-058-111). The results from these studies have also been considered in the design of the planned Phase 3 studies.

During Phase 3, the following additional studies are planned for inclusion in the NDA:

- A thorough QT (TQT) study (Study AC-058-110)
- A study in hepatically impaired subjects (Study AC-058-112)
- A study in renally impaired subjects (Study AC-058-113)
- An absolute bioavailability study (Study AC-058-114)

See Section 10.3.1 and 10.3.2 for more details.

FDA Preliminary Response:

In addition to the above studies, FDA requests that you :

- Identify the enzymes involved in the metabolism of ponesimod. Based on the results, in-vivo drug-drug interaction studies may need to be conducted.
- Provide mechanistic static/PBPK models to justify the claim that ponesimod is unlikely to inhibit CYP2C9 and CYP2C19 isoenzymes, or conduct in-vivo drug-drug interaction studies.
- Evaluate the in-vitro inhibition/induction potential of all major circulating metabolites of ponesimod. Based on the results from the in-vitro inhibition/induction assessments, in-vivo drug-drug interaction studies may need to be conducted.
- Assess the effect of ponesimod on antibody response for new vaccines and boosters. We will provide feedback at a later date regarding how to obtain this information.

Meeting Discussion: None of the Clinical Pharmacology related questions was discussed at the meeting due to lack of time. The sponsor will send additional information together with some Clinical Pharmacology related questions as a separate submission.

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(b) (4)

(b) (4)

(b) (4)

Question 6: Dose Selection for Phase 3

The choice of the 20 mg maintenance dose of ponesimod for the Phase 3 studies is based on the results of the recently completed Phase 2 dose-finding study AC-058B201 and preliminary data from its ongoing extension, AC-058B202. (b) (4)

(b) (4)

(b) (4)

Does the Agency agree with the dose regimen that Actelion has selected for Phase 3 studies with ponesimod?

Rationale

The Phase 2 dose-finding study AC-058B201 evaluated the effects of ponesimod at maintenance doses of 10, 20, and 40 mg versus placebo over 24 weeks. The study enrolled a representative RRMS population of 464 patients, and demonstrated clear effects of ponesimod on relevant magnetic resonance imaging (MRI) variables, and on the PD variable of lymphocyte count reduction. The observed effect was statistically significant at all three doses versus placebo on the primary endpoint, cumulative number of new T1 gadolinium-enhancing (Gd+) lesions from Week 12 to Week 24, and was greater with ponesimod 40 mg and 20 mg than with 10 mg. A highly significant ($p < 0.0001$) dose response was estimated, using the MCP-Mod approach. The estimated dose-response curve, as well as the estimated minimally effective dose (MED), showed robustness to the inclusion of lymphocyte count in the model.

Ponesimod at doses of 10 and 20 mg was well tolerated, while the 40 mg dose was associated with an increased incidence of adverse events (AEs) of dyspnea, edema, and cough and, possibly, infection-related AEs.

For details of the results, refer to the summaries of efficacy and safety data for Study AC-058B201 in Section 11.2, and to the preliminary data from the extension study AC-058B202 in Section 11.3. For additional details regarding dose selection for Phase 3 studies, refer also to Section 10.4.1. For ease of reference, a brief, tabulated summary of findings in study AC-058B201 important for understanding the Phase 3 dose selection is presented in Table 1. In addition, brief safety information from the study is presented in Table 2, Table 3, Table 4 and Table 5.

Table 1 AC-058B201 – Summary of main efficacy results – MRI, Clinical and pharmacodynamic endpoints

MRI Endpoints (Per-protocol set)		**Ponesimod 40 mg (N=93)**	**Ponesimod 20 mg (N=98)**	**Ponesimod 10 mg (N=88)**	**Placebo (N=110)**
Cumulative no. of new T1 Gd+ lesions from Week 12 to Week 24. (primary endpoint)	Mean (SD)	1.4 (3.24)	1.1 (1.96)	3.5 (7.27)	6.2 (13.42)
	Treatment effect ratio (95% CI)	0.226** (0.133 , 0.384)	0.170** (0.100 , 0.289)	0.566* (0.337 , 0.952)	
Cumulative no. of new T1 Gd+ lesions after baseline to Week 24.	Mean (SD)	5.2 (11.74)	4.2 (7.49)	7.5 (13.81)	9.3 (17.72)
	Treatment effect ratio (95% CI)	0.560* (0.349 , 0.898)	0.454* (0.284 , 0.724)	0.802 (0.497 , 1.293)	
Clinical Endpoint (All-treated set)		**Ponesimod 40 mg (N=119)**	**Ponesimod 20 mg (N=114)**	**Ponesimod 10 mg (N=108)**	**Placebo (N=121)**
Aggregate ARR up to Week 24 (confirmed relapses)	No of relapses	12	20	15	28
	ARR estimate from NB model	0.251	0.417	0.332	0.525
	Treatment effect ratio (95% CI)	0.478* (0.240 , 0.954)	0.793 (0.440 , 1.432)	0.632 (0.332 , 1.202)	
Pharmacodynamic Endpoint (All-treated set)		**Ponesimod 40 mg (N=119)**	**Ponesimod 20 mg (N=114)**	**Ponesimod 10 mg (N=108)**	**Placebo (N=121)**
Percent lymphocyte count reduction from baseline to end of treatment	Percent change from baseline:				
	Mean	-68.62	-64.89	-50.53	1.34
	Median	-70.87	-66.48	-50.00	-0.53

**p < 0.0001; *p < 0.05; ARR: annualized relapse rate; CI = confidence interval; Gd+ = gadolinium-enhancing; MRI = magnetic resonance imaging; NB: negative binomial; SD = standard deviation.

- Even though all doses of ponesimod showed significant efficacy versus placebo on the primary MRI endpoint, the effect size of 10 mg was clearly below that of the higher doses.

The 40 mg dose conferred little additional efficacy in comparison with the mid-dose of 20 mg.

- The same pattern was replicated in other MRI endpoints, on which ponesimod 10 mg did not show significant efficacy, was also seen in the more long-term data available from the extension study AC-058B202 [Section 11.3], and is supported by the outcomes of dose-/exposure-response modeling [Section 10.4.1].
- For the clinical endpoint of annualized relapse rate, no clear differentiation between doses was detected, either in AC-058B201, or its extension AC-058B202. Importantly, this was not the goal of the study and, given the low number of relapses and limited period of follow-up available, this observation does not detract from the important finding of consistent dose response for MRI variables. It should also be noted that the smaller observed effect on relapses of ponesimod 20 mg when compared to 10 mg was influenced by relapses actually observed during the first week of treatment, when patients in all dose groups received 10 mg.
- Ponesimod was associated with a dose-related reduction of total lymphocyte count, with the effect of 10 mg clearly below that of 20 mg and only a small incremental effect of 40 mg over that of 20 mg. Modeling indicated a clear relationship between lymphocyte count reduction and reduction of T1 Gd+ lesion counts [Section 10.4.1]. These analyses also support that a lymphocyte count reduction greater than that achieved with ponesimod 10 mg may be necessary for relevant efficacy on inflammatory MRI lesion activity, findings borne out also by the more long-term data from the extension study AC-058B202 (Section 11.3).

Table 2 AC-058B201 – Adverse events leading to discontinuation, overall, and by selected SOC

AE leading to premature discontinuation by SOC (All-treated set) N° of pts with at least one AE (%)	Ponesimod 40 mg (N=119)	Ponesimod 20 mg (N=114)	Ponesimod 10 mg (N=108)	Placebo (N=121)
All System Organ Classes	16 (13.4%)	6 (5.3%)	12 (11.1%)	4 (3.3%)
Infections and infestations	1 (0.8%)	-	1 (0.9%)	1 (0.8%)
Respiratory system disorders	7 (5.9%)	-	2 (1.9%)	-
Hepatobiliary disorders and liver function	3 (2.5%)	1 (0.9%)	1 (0.9%)	-
Cardiac disorders	2 (1.7%)	2 (1.8%)	5 (4.6%)	-
Eye disorders	-	2 (1.8%)	-	-
Neoplasms	-	-	1 (0.9%)	1 (0.8%)

AE = adverse event; pts = patients; SOC = system organ class.

Table 3 AC-058B201 – Adverse events, overall, and of special interest

SAEs, AEs overall and AEs of Special interest by System Organ Class N° of pts with at least one AE (%)	Ponesimod 40 mg (N=119)	Ponesimod 20 mg (N=114)	Ponesimod 10 mg (N=108)	Placebo (N=121)
SAEs overall	3 (2.5%)	7 (6.1%)	7 (6.5%)	5 (4.1%)
AEs overall	88 (73.9%)	88 (77.2%)	83 (76.9%)	90 (74.4%)
Infection-related AEs	4 (3.4%)	1 (0.9%)	-	2 (1.7%)
Pulmonary-related AEs	38 (31.9%)	19 (16.7%)	10 (9.3%)	8 (6.6%)
Hepatobiliary disorders and liver function AEs	11 (9.2%)	7 (6.1%)	9 (8.3%)	2(1.7%)
Cardiovascular-related AEs	4 (3.4%)	7 (6.1%)	6 (5.6%)	-
Eye disorders-related AEs	1 (0.8%	5 (4.4%)	-	1 (0.8%)
Neoplasms	-	-	1 (0.9%)	1 (0.8%)

AE = adverse event; pts = patient; SAE = serious adverse event; SOC = system organ class.

Table 4 AC 058B201 – Pulmonary function test

Pulmonary Function Test (All-treated set)		Ponesimod 40 mg (N=119)	Ponesimod 20 mg (N=114)	Ponesimod 10 mg (N=108)	Placebo (N=121)
Proportion of patients with a decrease of >	FEV_1	31.6%	13.5%	10.5% (11/105)	3.3%

Pulmonary Function Test (All-treated set)		**Ponesimod 40 mg (N=119)**	**Ponesimod 20 mg (N=114)**	**Ponesimod 10 mg (N=108)**	**Placebo (N=121)**
20% from baseline (observed at least once during treatment)	FVC	(37/117) 9.4% (11/117)	(15/111) 5.4% (6/111)	5.7% (6/105)	(4/120) 0.8% (1/120)
Mean change from baseline to Week 24 in % of predicted value	FEV_1 % of predicted	–10.8	–6.9	–5.5	–08
	FVC % of predicted	–4.7	–2.6	–2.5	–0.3
Mean change from baseline to Week 24 in absolute value	FEV_1 (L)	–0.37	–0.24	–0.18	–0.04
	FVC (L)	–0.19	–0.11	–0.09	–0.02

FEV_1 = Forced expiratory volume in 1 second; FVC = forced vital capacity.

Table 5 AC-058B201 – Liver function tests

Liver Function Tests (All-treated set)	**Ponesimod 40 mg (N=119)**	**Ponesimod 20 mg (N=114)**	**Ponesimod 10 mg (N=108)**	**Placebo (N=121)**
Proportion of patients with an increase of ALT or AST ≥ 3 × ULN (observed at least once during treatment)	4.2% (5/117)	4.5% (5/111)	2.8% (3/105)	0 (0/120)
Proportion of patients with an increase of total bili > 2 × ULN	0/117	0/111	0/105	0/120

ALT = alanine aminotransferase; AST = aspartate aminotransferase; bili = bilirubin; ULN = upper limit of normal.

- Ponesimod 40 mg was associated with signals of reduced tolerability in the form of peripheral edema, dyspnea, cough and, possibly, infection-related AEs, and with higher discontinuation rates, mainly due to respiratory system AEs. There was no consistent difference between the two lower doses of 20 mg and 10 mg for these or other types of AEs [Section 11.2].
- Ponesimod was associated with dose-dependent and reversible effects on pulmonary function tests, mainly FEV_1. The difference in effect between the 10 mg and 20 mg doses was small [Section 11.2].
- Liver aminotransferase elevation was more common on ponesimod than placebo. No clear dose-response was observed [Section 11.2]
- No dose-/concentration response relationship was identified between lymphocyte count reduction with ponesimod in this study and infections/infestations system organ class (SOC) AEs [Section 10.4.1].
- Cardiovascular AEs were related to the first-dose effects of ponesimod, and not relevant for the selection of the maintenance dose [Section 11.2].

Based on the efficacy, safety, and tolerability results from this Phase 2 study, further supported by modeling of dose/concentration-response relationships, Actelion is of the opinion that the dose of 20 mg is the most appropriate maintenance dose to take forward into the Phase 3 program.

FDA Preliminary Response:

The data presented in the meeting package suggest that the 20 mg dose may be effective, and better tolerated than the 40 mg dose. The data also suggest that the 10 mg dose may be effective. Due to concerns about posenimod's toxicity with both short and long term exposure, it is important to identify the lowest dose that provides a desirable clinical benefit. We suggest that you continue to study both the 20 and 10 mg doses in your Phase 3 program.

In addition, we have a comment about your proposed (b) (4) . In your trial that looked specifically at 3 different up-titration schemes with close cardiac monitoring (AC-058-105), the effect on heart rate with a 10-mg daily starting dose regimen (Treatment C) was slightly more pronounced than that reported with the other two regimens (Treatment A or B). If the safety profile with treatment A and B is more benign (e.g., no AV-block reported) than that with treatment C, treatment A or B would be preferable.

The Phase 2 study used 10 mg ponesimod initially and then weekly up titrations. AV-block was reported in nine subjects on ponesimod and one on placebo. All AEs related to heart rate and rhythm effects (i.e., bradycardia, AV-block 1st and 2nd degree, AV dissociation, idioventricular rhythm) occurred on Day 1 after administration of the initial 10 mg dose of ponesimod. Overall, nine patients (2.6%) on ponesimod (compared with none on placebo) discontinued prematurely due to cardiac AEs at initiation of treatment. The most frequent cardiac AE leading to premature discontinuation was AV block 2nd degree (in three patients). You should consider a titration schedule similar to Treatment B, which incorporates a 5 mg dose given bid for several days, prior to initiating the 10 mg dose.

Meeting Discussion:

The sponsor believes that the 20 mg dose is optimal for phase 3 development from a safety and efficacy standpoint. FDA recommended that the sponsor also look at a lower dose option (e.g., 10mg); it could be critical to have a lower dose option if the 20 mg dose turns out to be associated with unacceptable safety findings. FDA also mentioned that there appeared to be efficacy at the 10 mg dose, as clinical endpoints for the 10 mg dose appeared better than for the 20 mg dose (FDA acknowledges there was a small number of events, and the study was not powered for clinical endpoints), although MRI measures looked better for the 20 mg dose. The sponsor expressed concern about showing this level of effect in a study where an active comparator would be used as the control. FDA suggested that it may be worth evaluating whether the effect at 10 mg would persist in a longer term study. FDA suggested that the sponsor could build in a process to identify futility of the 10 mg dose prior to the end of the study.

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(b) (4)

[redacted]

FDA Preliminary Response:

You are proposing to enroll into the trial patients with relapsing remitting multiple sclerosis, which would be the population reflected in the labeled indication. If you intend your labeled indication to include patients with relapsing forms of MS, you would need to modify your study population to include patients with all relapsing forms of MS. For that purpose, the study population should include at least 15% of patients with relapsing (secondary) progressive MS. Efficacy findings in the subgroup of patients with relapsing progressive MS would have to be consistent with the overall results (i.e., trend positively).

We agree with the use of the ARR as the primary endpoint, and with the number of new and enlarging T2 lesions as your key secondary endpoint.

Regarding your proposed group sequential adaptive design, we have major concerns about the unblinding of data, which can result in operational biases. Presumably, if both trials show a statistically significant treatment effect on ARR, you would submit the ARR results to the Agency for review. At that time, the results would be openly known to many parties, questioning how the necessary blinding could be possible.

The fixed sequence testing approach and the proposed analyses methods (negative binomial regression for ARR and MRI and log-rank test for time to disability progression [TDP]) appear acceptable. However, it is unclear how you plan to adjust for multiple testing of the total population and of the subgroup of patients with high disease activity for the TDP endpoint. Please submit a detailed SAP well in advance of data unblinding.

We also have the following comments about your safety monitoring:

Pulmonary Monitoring: We are unable to agree with the proposed pulmonary safety monitoring at this time. Given the spirometry findings in your 24-week phase 2 studies (Table 4, Briefing Package), a pulmonary safety monitoring program will be necessary in your phase 3 program. Prior to initiation of phase 3, you should provide a detailed plan describing how pulmonary safety will be monitored in pivotal studies. This plan should provide information regarding:

1) Pulmonary function testing (PFT)
   - Adherence to accepted criteria (American Thoracic/European Respiratory Society) during conduct and interpretation of PFTs to ensure quality and reliability of the data
   - Specific PFTs to be collected (i.e., spirometry, DLco, measures of respiratory muscle strength) and frequency of assessment
   - The number of patients in whom PFTs will be collected
   - A monitoring/intervention plan for those study participants who experience a significant decline in pulmonary function.

2) Imaging Studies
   - We note your plan to include CXR monitoring. Provide justification for the imaging modality to be used (chest x-ray vs. high resolution CT) for safety monitoring
   - The number of patients in whom imaging data will be collected
   - The manner in which the imaging data will be read (i.e. central, blinded reader, using pre-defined criteria)
   - A monitoring/intervention plan for those study participants who experience a clinically significant change in imaging.

3) Underlying Lung Disease
   - Proposal for handling patients with underlying lung disease (i.e. asthma or COPD) in your program, if these co-morbidities are common in the proposed patient population.

4) Pulmonary Adverse Events
   - Definition of pulmonary adverse events of special interest, including, but not limited to: cough, dyspnea, interstitial lung disease, pleural effusions.

Cardiac Monitoring: Collect 12-lead ECGs at pre-dose and 2, 4, 6, 8 and 10 hours post-dose on Day 1. Blood pressure and heart rate should be monitored as well using the same schedule. Study subjects should not be discharged from the monitored setting before vital signs return to near baseline values.

Once data of the TQT study are analyzed and the final version of the phase 3 study protocol is submitted, we will provide additional comments. In general, we advise sponsors to submit TQT study results before beginning of Phase 3 studies, so that findings can be incorporated into cardiac safety monitoring plans for the pivotal trials.

In nonclinical studies performed in dogs, animals developed intracardiac hemangiomas in a dose-dependent manner. Echocardiography performed on dogs in these studies did not show significant abnormalities. In the human studies, no differences in echocardiography findings between ponesimod treatment groups and the placebo group were observed over a 6 month period. Provide a discussion of your understanding of this safety issue and a plan for monitoring patients within the phase 3 program to ensure that a similar lesion is not present. Options may include periodic Cardiac magnetic resonance (CMR) or multidetector CT for those that cannot undergo CMR, due to implanted ferromagnetic devices or orthopnea[1].

Ophthalmological monitoring: Ophthalmological exams are planned frequently throughout the trial. Please clarify whether an ophthalmologist will be examining patients and if direct ophthalmoscopy will be used. OCT is planned at baseline only. Due to the macular edema signal with your product and other products in this class, please incorporate OCT at 4-6 months and yearly, in addition to what was proposed.

In addition, we believe that dermatological exams should be done at baseline, yearly, and if symptoms arise.

We have the following comments regarding the proposed exclusion criteria:

- You should exclude patients with renal/hepatic impairment until the results of your study in hepatically impaired subjects and in renally impaired subjects are known; we strongly recommend that you conduct these studies before phase 3, so that inclusion/exclusion criteria can be adapted as soon as possible.
- You should exclude concomitant medications with narrow therapeutic index metabolized by CYP2C9 and CYP2C19 isoenzymes.

Meeting Discussion:

Pulmonary Safety Monitoring: In general, the sponsor agreed to provide a detailed pulmonary safety monitoring plan per the outline provided in the preliminary responses. The sponsor requested clarification regarding the following points:

- Measurement of respiratory muscle strength: The Agency clarified that measurement of respiratory muscle strength, using evaluation of negative inspiratory force, for example, would provide a means for assessing the progression of underlying neurological disease as it contributes to decline in lung function, as compared with a primary pulmonary effect.

[1] Hoey E., Mankand K., Puppala S., Gopalan D., Sivananthan M.U. (2009) MRI and CT appearances of cardiac tumours in adults. Clinical Radiology 64, 1214-1230.

- Imaging studies: FDA clarified that FDA preliminary comments did not imply that the sponsor choose one imaging modality over the other, but rather provide a plan and justification for the imaging that would be conducted in Phase 3. The plan should include defined criteria regarding interpretation of the imaging studies.

Discussions about Cardiac monitoring focused on several points:

1) First dose monitoring: The sponsor suggested monitoring for six hours after the first dose, rather than ten hours, as suggested by FDA in the preliminary comments. FDA asked if the protocol stated that ponesimod had to be given in the fasted state. The sponsor said there was no restriction. FDA asked about the PK variability seen with a food effect. If there was a delayed Tmax when ponesimod was administered with food, FDA suggested that monitoring be proposed based on available data, accounting for PK variability and including outliers.

2) Up-titration: The sponsor believes that the data support (b) (4) . They suggested that using the 5 mg bid dosing regimen would introduce additional difficulties in terms of monitoring the dose administered in the evening. FDA stated that the TQT study may provide additional information about the level of monitoring needed, not just in terms of QT prolongation, but in terms of PR interval prolongation and the risk of AV block, and bradycardia. FDA did not feel there was sufficient evidence to warrant not including extended first dose monitoring for 10 mg q day.

3) Arterial lesions seen in nonclinical studies: Please see meeting minutes under question # 3 for this discussion.

4) TQT study and timing: FDA stated that it was preferable to use the results of the TQT study to guide the cardiac monitoring in the phase 3 program. The sponsor stated that they would probably have preliminary results prior to submitting the final protocol for the phase 3 trials, and that they would submit these results so they can be reviewed at the time of the protocol review. FDA suggested that the sponsor submit the protocol as an SPA.

There was a discussion about the value of doing OCT during the trial. The sponsor summarized the experience to date with macular edema and their product. FDA stated that although there were frequent ophthalmologic evaluations planned during the phase 3 trial, OCT contributes more objective information than ophthalmologic exams about all cases of macular edema, whether symptomatic or not. Phase 3 is the time to obtain the majority of the safety data on a product; therefore, it is important to include adequate monitoring to ensure that the macular edema signal is well characterized.

There was discussion about the indication statement, and the sponsor questioned why they would not be able to enroll patients with RRMS and obtain an indication for patients with relapsing forms of MS, since this is what is described in most other products on the market for MS. FDA stated that the indication statement would reflect the patients that were enrolled in the trial, and that in order to describe this broader population, data in patients with secondary progressive MS with relapses would be needed; also, the treatment effect would have to show a trend in this

subgroup similar to that of the larger population. The sponsor expressed concerns about including patients with secondary progressive MS in their trial. FDA stated that it was up to them if they wanted to expand their population, but the indication statement would be representative of the patient population enrolled.

There was a discussion about the planned interim analysis and about the bias that would be introduced by continuing the study for the time to disability progression (TDP) endpoint, once the data were unblinded. Although the sponsor ensured that there would be a firewall, and that the group looking at the unblinded data would be different from the group involved in the "disability progression extended study", the integrity of the study would be compromised after the blind is broken. FDA recommended that the sponsor conduct blinded sample size re-estimation prior to the final analysis for the primary endpoint (ARR) and the unblinded interim analysis of TDP.

Question 8:NDA Safety Database

The Sponsor considers the size of the safety database available with the NDA to be sufficient for filing and subsequent approval. Does the Agency agree?

Rationale

Approximately 1,530 patients are projected to have been exposed to ponesimod by the time of NDA submission, with more than 950 RRMS patients treated with ponesimod for at least 2 years. The maximum duration of RRMS patient exposure to ponesimod by the time of NDA is expected to be more than 5.5 years. As the size and scope of the resulting safety database is anticipated to exceed the ICH requirements, the Sponsor considers it adequate to support approval.

For more details, refer to Section 10.4.2.

FDA Preliminary Response:

At this point, the proposed exposure seems adequate, but a larger database may be required if a safety signal of concern is identified during your product's development. Also, concern for potential safety issues with longer term exposure may justify a requirement for a postmarketing safety.

Meeting Discussion: None.

Question 9: [redacted] (b) (4)

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Meeting Discussion: None.

PEDIATRICS

Question 12: Pediatric Plans: Deferral and Subpopulations Waiver Requested

a) [redacted] pediatric study in patients aged 10–17 years. [redacted] Actelion proposes to defer conducting such study until more information on the use of ponesimod in the adult population with RRMS becomes available. Does the FDA agree that a deferral is acceptable?

b) Actelion requests a waiver of the pediatric study requirement for ages from birth to less than 10 years. Does the Agency agree?

Rationale

Actelion proposes deferring the conduct of the pediatric study until additional safety and efficacy data in adult patients in RRMS treated with ponesimod are available.

Actelion is requesting a waiver for the pediatric study requirement in the age group < 10 years because the necessary studies would be impossible or highly impracticable. The number of pediatric patients less than 10 years of age with multiple sclerosis is too small.

[redacted]

For more details, refer to Section 10.5.2.

FDA Preliminary Response:

The division is open to deferring the conduct of studies in patients aged 10-17 until later in development, and waiving the pediatric study requirement for patients less than 10 years. This plan will be formally reviewed once the NDA is submitted by the FDA Pediatric Review Committee (PeRC).

Meeting Discussion: None.

Post-meeting comment: FDA is reevaluating whether patients younger than age 10 should be included in pediatric studies. This issue should be revisited at the pre-NDA meeting.

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RUSSELL G KATZ
01/27/2012