CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209884Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 76122

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Peter D. McArdle, DVM
Executive Director, SR. GPRD
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. McArdle:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BAF312 (siponimod).

We also refer to the meeting between representatives of your firm and the FDA on October 10, 2017. The purpose of the meeting was to discuss your plans to submit a New Drug Application for siponimod proposed for the treatment of relapsing forms of multiple sclerosis.

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, Regulatory Project Manager 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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 10, 2017, 1:00 pm – 2:00 pm EST
Meeting Location: FDA White Oak Building 22, Rm 1421

Application Number: IND 76122
Product Name: BAF312 (siponimod) capsules
Indication: Multiple sclerosis
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Billy Dunn, MD
Meeting Recorder: LCDR Nahleen Lopez, PharmD

FDA ATTENDEES

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
John Marler, MD, Clinical Team Leader
Sally Jo Yasuda, PharmD, Safety Team Leader
Jody Green, MD, Clinical Reviewer
Nahleen Lopez, PharmD, Project Manager

Office of Clinical Pharmacology
Jagan Parepally, PhD, Reviewer

Office of Biostatistics
Kun Jin, PhD, Statistical Team Leader
Xiang Ling, PhD, Statistical Reviewer

Controlled Substance Staff
Jovita Randall-Thompson, PhD, Reviewer

Division of Cardiovascular and Renal Products
Shari Targum, MD, Reviewer

SPONSOR ATTENDEES

Danny Bar Zohar, MD - Global Head Neuroscience
Frank Dahlke, MD - Global Program Head
Goeril Karlsson, PhD - Global Program Clinical Head
Nicolas Rouyrre - Director Statistical Scientist
Norman Putzki, MD – VP and Medical Unit Head, Neuroscience (US)
Eric Couture, PhD - Global Regulatory Affairs Neuroscience Head
Peter McArdle, DVM – Sr. Global Program Regulatory Director
Aswinikumar Chelikani – Sr. Global Program Regulatory Manager
Chin Koerner, Regulatory Policy

(b) (4) External Consultant, Patient Safety
– External Consultant, (b) (4)

1. BACKGROUND

The purpose of this meeting is to discuss your plans to submit a New Drug Application for siponimod to treat relapsing forms of multiple sclerosis.

FDA sent Preliminary Comments to Novartis on October 5, 2017.

2. QUESTIONS

Question 1: Effect on disease progression. In March 2017, FDA raised concerns over the evidence available in slowing of disease progression independent of relapses. In acknowledgement of this feedback Novartis have performed additional statistical analyses to provide further evidence of such effects. Does the Agency concur that the entirety of evidence, including results of new analyses, supports an effect on disease progression, independent of relapses [and i]n this context, does the Agency (1) concur that additional analyses of "Effect of siponimod on confirmed disability progression (CDP) in the study patient population of SPMS patients independent of treatment effect on relapses" further substantiate efficacy of siponimod in the overall SPMS population? (2) Does the Agency concur that the definition of the estimand for "Effect of siponimod on CDP in patients that would not relapse regardless of treatment assigned" and its estimate address a scientific question of particular interest in the context of SPMS?

FDA Preliminary Response to Question 1:
This question cannot be answered outside of the context of a detailed NDA review.

Meeting Discussion: No discussion at the meeting.

Questions 2a and 2b: Dose titration related to cardiac effects

a. **Does the Agency agree that dose titration over 6 days to the 2 mg maintenance dose is effective in mitigating bradyarrhythmic effects of siponimod during treatment initiation?**
b. **Does the Agency agree with Novartis' proposals on clinical monitoring of the first dose administration?**

FDA Preliminary Response to Questions 2a and 2b:
Recommendations for dose titration and clinical monitoring of the first dose administration will be a matter of review. Although titration to 2 mg/day over 6 days may mitigate the bradyarrhythmic effects of siponimod on Day 1, bradyarrhythmic effects including asymptomatic and symptomatic ECG changes and cardiac adverse events are observed up to Day 7. The proposal for monitoring during the 6-hour period after the first dose on Day 1 does not address the post-Day 1 findings. In addition, the limited information included in the background material shows that the risk of cardiac events with treatment initiation is present whether patients are categorized as "standard risk" or patients with presumed increased cardiovascular risk. You

should address these findings when justifying dose titration, monitoring based on risk stratification, and duration of monitoring, in the NDA submission.

Your NDA submission should include figures and tables with values for mean hourly heart rate/pulse as well as for minimum hourly heart rate/pulse. The figures and tables should include absolute values, changes from baseline from both pre-dose on Day 1 and from 24 hour screen values, and placebo-subtracted values.

Your NDA submission should include a table of cardiac adverse events (AEs) in the phase 3 study for each day of Week 1. The assessment of AEs should combine the terms "bradyarrhythmia", "bradycardia", "sinus bradycardia", and "heart rate decreased". The table should also include a row with the total number of patients with events. Narratives of cardiac AEs should include the time of day at which the event occurred and the CYP2C9 genotype and phenotype results.

Please submit the results of your thorough QT study with the NDA submission.

The background material for this meeting focuses on cardiovascular safety after initial dosing. We request that, prior to finalizing the NDA, you submit for our review a summary of your general safety findings and the proposed list of adverse events of special interest that you plan to evaluate.

Meeting Discussion: No discussion at the meeting.

Question 3: CYP2C9 genotype-based dosing adjustment and treatment in different CYP2C9 genotypes. The maintenance dose proposed is 2 mg once daily. Siponimod (BAF312) is eliminated from the systemic circulation by metabolism predominantly mediated via the polymorphic enzyme cytochrome P450 CYP2C9 and to a lower extent via CYP3A4. The CYP2C9 genotype has been shown to have a significant impact on siponimod metabolism. For individuals with certain genetic polymorphisms, the activity of this enzyme is reduced resulting in higher chronic systemic exposure. Novartis therefore proposes an adapted maintenance dose of 1 mg once daily for patients with genotypes CYP2C9*1*3 and CYP2C9*2*3 to adjust for the reduced CYP2C9 metabolic activity and avoid potential long-term safety risks of chronic higher exposure. Patients with a CYP2C9*3*3 genotype, i.e. who show the most pronounced reduction of CYP2C9 metabolic activity, have not been studied in Phase III. Novartis therefore proposes to exclude patients with a CYP2C9*3*3 genotype from a marketing authorization. Does the Agency concur that the proposed maintenance dose is appropriate in patients with genotypes CYP2C9*1*3 and CYP2C9*2*3 and to exclude patients with a CYP2C9*3*3 genotype for a marketing authorization?

FDA Preliminary Response to Question 3:
Your approach to adjust the dose in order to compensate for the reduced exposures due to various CYP2C9 genotypes is reasonable. Whether such dose adjustments will ultimately be considered acceptable will be a review issue. You will need to submit subject level genotype

data for all subjects genotyped for CYP2C9 as well as any analyses associated with CYP2C9 genotype and exposure, efficacy, and/or safety.

Meeting Discussion: No discussion at the meeting.

3. Meeting Discussion of Novartis Response to FDA Request of October 5, 2017

Novartis provided a response to the October 5, 2017, FDA request regarding provision of a plan for the Data Analysis Plan for clinical safety for FDA review and Novartis' consideration of comments prior to submitting the NDA. FDA noted that it was acceptable to provide the Data Analysis Plan by the end of October. FDA confirmed that this request applies to the Data Analysis Plan for clinical safety and not for efficacy.

Novartis listed safety areas to be address in the summary of clinical safety. FDA noted that these appear to be appropriate, but that appropriateness would be a matter of NDA review.

FDA confirmed that narratives for discontinuations need to be provided for discontinuations due to adverse events. Novartis confirmed that they plan to provide narratives for deaths, discontinuations due to adverse events, SAEs, and pregnancies, and for AEs of special interest. Novartis also noted that they plan to provide a comprehensive presentation of all SAEs, including following discontinuation. *As a post-meeting note, the sponsor should also provide narratives for discontinuations for reasons other than adverse events, but for which the patients had adverse events within 15 days of discontinuation.*

FDA recommended that presentation of clinical safety data, including laboratory, vital signs, and narratives be consistent with Attachment 2 (General Clinical Safety Requests) in the Written Responses Only minutes from September 8, 2017. FDA also recommended that Novartis submit an eCTD sample and sample standardized datasets for validation tests as noted in Attachment 2 from the September 8, 2017, document.

Novartis provided the following additional comments in a handout in response to recent FDA requests dated October 5, 2017.

4. Additional Meeting Discussion

The sponsor wanted to confirm that if they submitted an NDA for siponimod with a labeled indication for SPMS that it would not lead to a refuse to file (RTF). FDA stated that the requested indication would not be a RTF issue; the indication would be determined after the review is complete. The content of the entire label will reflect the appropriate use of this product, including a description of the studies, with study results and characteristics of the population.

Novartis provided more details about their experience in studying SPMS without relapse and the unmet medical need for this population. Novartis voiced concerns that Study CBAF312A2304, with its statistical analysis plan and primary analysis, were no longer under an SPA agreement. FDA stated that Novartis should provide the pre-specified efficacy statistical analysis plan

(prepared before the dataset was locked) no later than when the clinical module of the NDA is submitted. Novartis should include a clear regulatory history of the product's development.

Novartis and FDA discussed the timing of the NDA submission. Clinical and nonclinical modules are tentatively planned for submission in February, 2018. The CMC module is planned for submission in April, 2018.

Post-meeting comment:

During the meeting, Novartis inquired about the acceptability of a two part rolling submission proposal for the NDA. Novartis should submit a formal request to their IND about the acceptability of submitting their application in two parts. The request should identify the two planned submission dates, and describe the specific application modules that will be submitted on each date. Upon receipt, FDA will make a formal determination regarding the acceptability of the proposal and will communicate the determination in an official communication. Please note, however, that if FDA determines that it is acceptable to submit the NDA in two parts, it does not have any bearing on the type of review designation (i.e., Priority or Standard). The type of review (i.e., Priority or Standard) is determined within the first 60 days of the review period once the application is complete and if the application is fileable.

5. Controlled Substance Staff Post-Meeting Comments:

A. Based on the information summarized in the meeting package, it appears that you have already conducted behavioral studies and accepted CSS's prior recommendations regarding protocols. CSS will review and will consider all abuse-related data submitted under the NDA for siponimod in assessing the abuse potential of siponimod. For the type of data to provide that will allow evaluation of the abuse potential of the drug, we refer you to the guidance for industry, Assessment of Abuse Potential of Drugs (2017).[1]

B. Based on the abuse findings summarized in your meeting package, we did not find a signal of abuse that would appear to warrant a human abuse potential study (HAP). Therefore, we are not recommending a HAP study at this time. This recommendation is reliant on whether study method and parameter recommendations previously conveyed by CSS were addressed and the final study data to be submitted is shown to support the findings presented in the June 29, 2017 meeting packet.

5. DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our August 7, 2017 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore,

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product

development, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

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

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

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

SUBMISSION FORMAT REQUIREMENTS

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

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

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

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

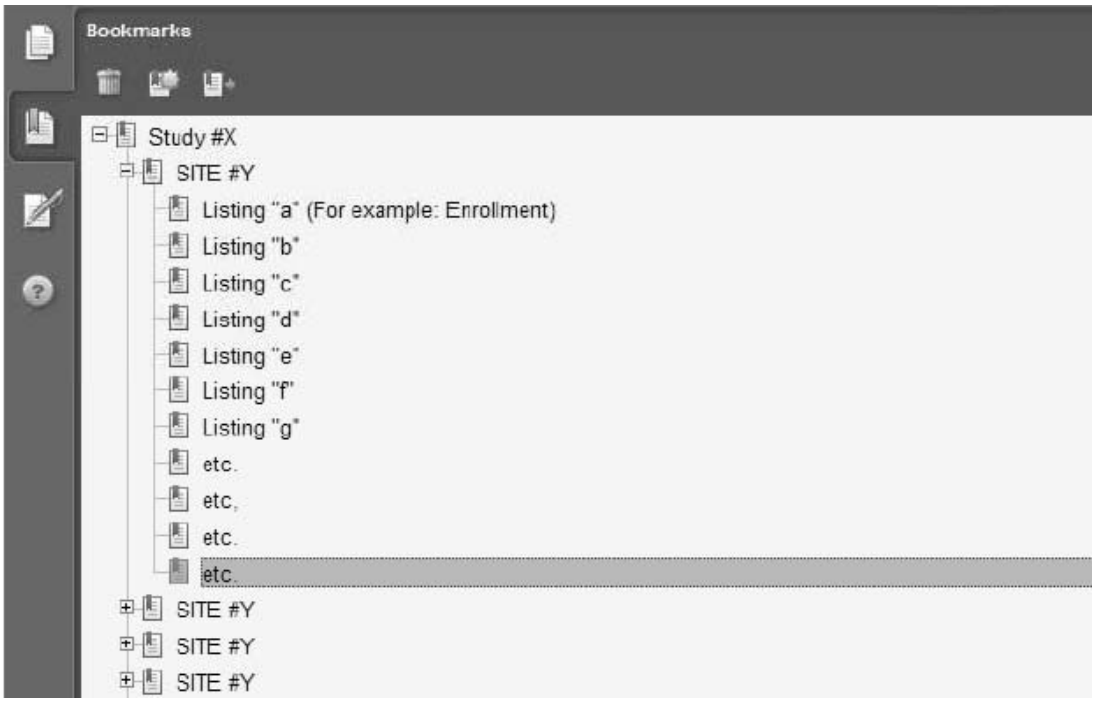
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

DSI Pre-NDA Request Item[2]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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

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

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

References:

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

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

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

6. ISSUES REQUIRING FURTHER DISCUSSION

None.

7. ACTION ITEMS

None.

8. ATTACHMENTS AND HANDOUTS

See Sponsor's attachment.

4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ERIC P BASTINGS
11/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076122

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Thomas J. Watson
Executive Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Watson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BAF312.

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on September 28, 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, Regulatory Project Manager at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes and slides

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: EOP2

Meeting Date and Time: September 28, 2011; 1300 to 1400
Meeting Location: White Oak; building 22 room 1313

Application Number: IND 076122
Product Name: BAF312
Indication: Multiple Sclerosis
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Russell Katz
Meeting Recorder: LCDR Hamet Touré

FDA ATTENDEES

Russell Katz, MD, Division Director
Eric Bastings, MD, Deputy
Billy Dunn, MD, Team Leader
Heather Fitter, MD, Clinical Reviewer
Angela Men, MD PhD, Clinical Pharmacology Team Leader
Xinning Yang, Clinical Pharmacology Reviewer
Kun Jin, PhD, Statistics Team Leader
Xiang Ling, PhD, Statistics Reviewer
Hamet Touré, PharmD MPH, Regulatory Project Manager

SPONSOR ATTENDEES

Gordon Francis, MD	Neuroscience Development Head
Atul Dandekar, MD	Global Program Head
Erik Wallström, MD, PhD	Global Program Medical Director
Harald Pohlmann, MSc	Expert Statistician
Eric Legangneux, MD	Clinical Pharmacology Director
Francois Mercier, PhD	Senior Expert Modeler
Joana Goncalves, MD	Brand Safety Leader
Peter Heining, DVM	Preclinical Safety Director (TC Participant)
Lixin Zhang Auberson, MD, PhD	Medical Scientific Expert
Richard Meibach, PhD	Neuroscience Regulatory Head (TC Participant)
Tom Watson	Global Therapeutic Area Lead, Regulatory
Elspeth Jack, PhD	Global Program Regulatory Director
Manisha Patel, PharmD	Post-Doctoral Fellow, Regulatory
Chin Koerner, PhD	Regulatory

BACKGROUND:

The September 28, 2011, face to face meeting is a type B End of Phase II meeting to discuss your development plan for BAF312 for the treatment of patients with relapsing forms of multiple sclerosis (b) (4) .

QUESTIONS:

Population

Question 1
(1a) ***Relapsing forms of Multiple Sclerosis:*** Does the Agency agree that the McDonald 2010 diagnostic criteria are appropriate for the selection of the proposed study population?

FDA preliminary response: Yes. Using the McDonald 2010 diagnostic criteria for the study population selection is appropriate.

Meeting Discussion: None.

(1b) Does the Agency agree that the proposed recruitment of patients for the Phase III studies is adequate to support an indication (relapses, (b) (4)) for patients with relapsing forms of MS?

FDA preliminary response: If you plan to market this product for the treatment of "Relapsing forms of Multiple Sclerosis (RMS)", then providing safety and efficacy data both for patients with RRMS and for patients with relapsing SPMS would be required. In addition, efficacy findings in the relapsing SPMS population should be consistent with those in the RRMS population. In order to collect sufficient data in the relapsing SPMS population, you should enroll a minimum of 15% of patients with that form of MS.

Your comment in the briefing document on page 10 section 2.1.2 (1b) that refers to FDA's view "that relapsing forms of MS are those in which patients do not recover completely between relapses…." does not adequately represent our view. We conform to the published views on diagnosis and differentiation of subtypes of MS that are described in publications (Lublin, FD et al, 1996, Polman, CH et al 2005, Polman, CH et al 2010). In general the progression from RRMS to SPMS requires identification of various disease characteristics in a patient rather than simply the lack of recovery between relapses.

Meeting Discussion: None.

Clinical

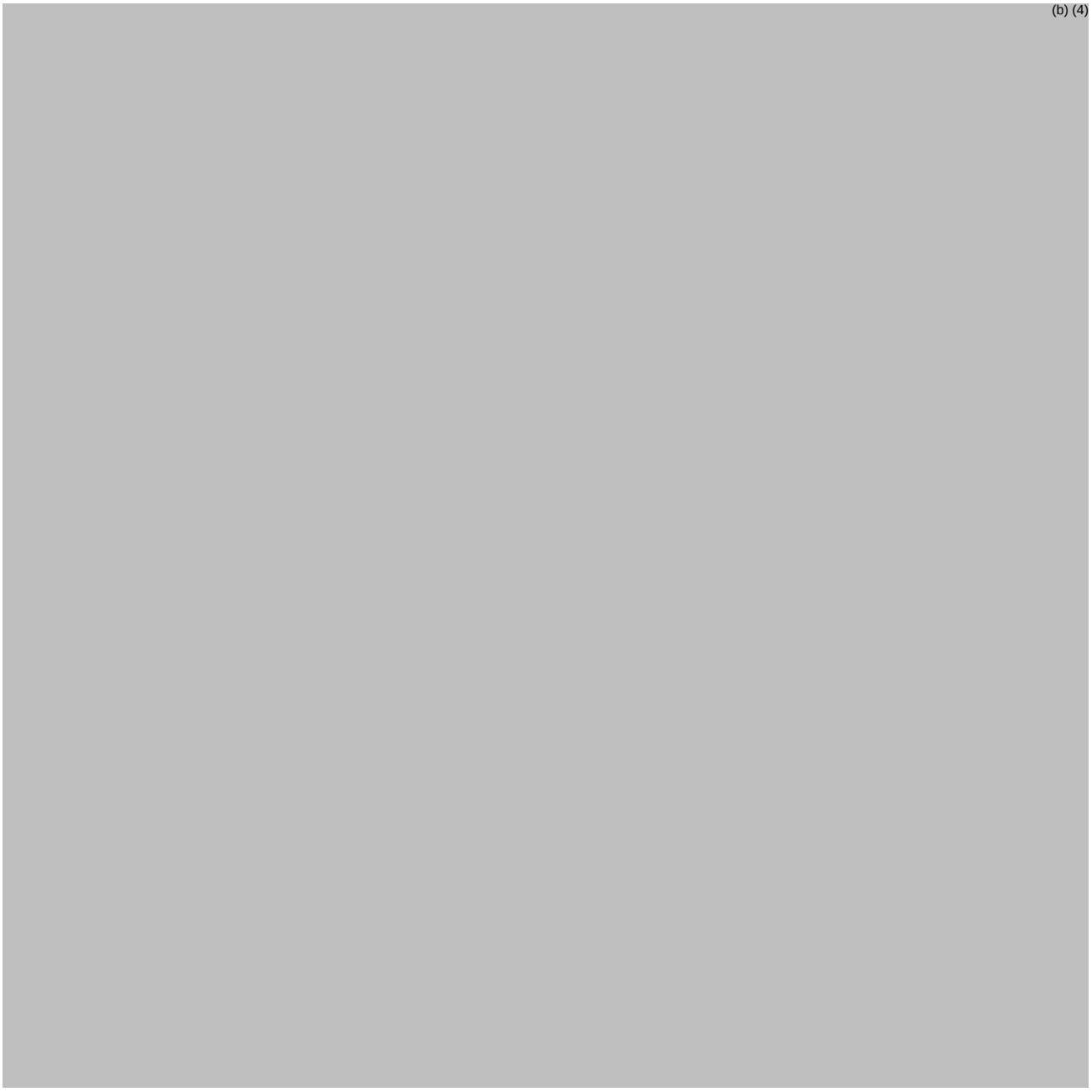
Question 2
(b) (4)

(b) (4)

Question 3

Dosing strategy: Does the Agency agree that the proposed individualized dosing scheme for BAF312, i.e. treatment with the lowest effective dose level (b) (4) once daily) in each individual to (b) (4) is adequate and appropriate to generate the efficacy and safety information needed to support registration?

FDA preliminary response: We believe that your plan would not adequately assess the dose-response relationship for your product. (b) (4)



Question 4

Active comparators: Does the Agency agree that the chosen active comparators interferon beta-1a (Avonex®) and glatiramer acetate (Copaxone®) are appropriate comparators for the proposed Phase III program?

FDA preliminary response: The active comparators chosen are appropriate.

Meeting Discussion: None.

Question 5

Rater-blinding: Does the Agency agree that rater-blinding of key efficacy endpoints is appropriate for the Phase III program?

FDA preliminary response: A double dummy design should be used. Published reports have emphasized the importance of double blinding in MS trials. Rater blinding deals only with a portion of the systematic bias. Blinding is particularly important when the primary outcome variable is not entirely objective, such as the ascertainment of a potential relapse, or of disability progression. Recent trials have demonstrated the feasibility of blinding both patients and raters in trials with similar active comparator design.

Meeting Discussion: The sponsor stated that their plan was to do a long trial to capture the disability endpoint, and that doing a double dummy design which included two products with side effect profiles that would unblind subjects in a majority of patients is not feasible. The sponsor noted that other products studied in MS are currently using a blinded rater only design. FDA stated that a double blind design would minimize bias, and that a trial done with only a blinded rater would have to show a very robust effect in order to counteract the strong effect of bias. FDA stated that other studies using similar products have shown that it is possible to maintain the blind for a substantial fraction of the study population. FDA questioned the sponsor on the procedure for directing a patient to a blinded rater. The sponsor said that a nurse or investigator would evaluate the patient once the patient said they had a relapse, and if there were no other causes for the deterioration, e.g., an infection, they would be immediately directed to the blinded rater and an unblinded investigator. FDA thought this may be problematic because bias may be introduced in this step. It may be best to have the blinded rater systematically assess the patient after the patient reports a relapse, and then follow this up by determining whether this deterioration was in fact a relapse or the result of another condition.

Question 6

Multiplicity control for efficacy claims and type 1 error level: A hierarchical testing procedure will be used: In a first step, the individual study relapse analyses are performed at the 5% level (two-sided). Only when superiority of BAF312 is shown for the relapse endpoint in both studies, the individual patient pooled analysis is performed for the disability progression endpoint (5% level, two sided). Does the Agency agree that an overall type 1 error level of 5% (two-sided) for both efficacy claims (reduction of relapses (b) (4)) is adequately controlled by the planned hierarchical testing procedure?

FDA preliminary response: We agree that the overall type 1 error rate is controlled contingent on the acceptability of the pooling approach. Please see our response to Question 2.

Meeting Discussion: None.

Question 7

***Acceptability of futility assessment*:** It is planned to perform an interim analysis for futility of the relapse endpoint and an independent DMC will be provided with unblinded study results.

Does the Agency agree that it is acceptable to perform such a futility analysis with no statistical penalty?

FDA preliminary response: We agree. However, you also plan to conduct a blinded sample size re-estimation at the same time of the unblinded futility analysis. Please provide the details of the interim statistical analysis plan and DMC charter, including the procedures to ensure that the sample size re-estimation is performed in a blinded fashion. Please be reminded that the interim analysis procedure needs to be fully documented and submitted for review after completion of the study.

Meeting Discussion: None.

Safety

Question 8

Treatment initiation: Does the Agency agree that the proposed initial dose titration and cardiac monitoring scheme is adequate for treatment initiation in the upcoming Phase III program?

FDA preliminary response: We agree that using a dose titration schedule is preferable. The data provided for patients titrated in the phase 1 dose titration study, period 2 of the phase 2 trial (up to 1.25 mg) and the phase 2 extension study IA, suggest that AV block, QT prolongation and bradycardia are reduced by this methodology. The concerns for AV block and QT prolongation are not entirely alleviated, because these events, although reduced by dose titration, were not eliminated. A thorough QT study is needed prior to phase 3 to help deciding what level of monitoring is necessary for your phase 3 program. Information from this study will determine the level of monitoring needed in vulnerable populations as well.

We are supportive of your plan to include patients with cardiac disease in your phase 3 development program, with additional ambulatory cardiac monitoring during the titration phase. We believe that including patients at cardiac risk during the phase 3 program will provide needed data about safety in this subpopulation and may eventually broaden the population that may be indicated for your product.

Meeting Discussion: Based on the data in the briefing packing, FDA is not confident that the proposed cardiac monitoring is sufficient for Group I and Group II. FDA believes that the dose titration schedule mitigates the concern for bradycardia, but believes that a thorough QT study should inform decisions about monitoring for arrhythmia and QT prolongation, with further up titrations after the initial dose titration. Group I does not include ECGs around steady state, since there is a scheduled ECG at 7 days, and then no ECG is scheduled until the 3-month visit. In addition, there is no plan for additional monitoring with up titration. Group II has adequate ECG coverage for the initial dose titration, but doesn't have adequate monitoring planned for steady state and up titrations.

Question 9

Safety Monitoring: Does the Agency agree that the proposed monitoring measures for the entire Phase III program are adequate and appropriate to generate the safety information needed to support registration?

FDA preliminary response: No, we do not agree that the proposed safety monitoring plan is sufficient to support registration of your product. Please refer to the specific safety signal categories below:

Bradycardia: Please see response to question 8.

Macular edema: The risk of macular edema has been demonstrated in the currently approved product of the same class, Gilenya. Although the proposed OCT frequency in this study mimics the labeled recommendations for Gilenya, we believe that the monitoring for your product should also include a 12 month assessment, and follow up assessments in patients report visual symptoms. We agree with your more intensive monitoring schedule in patients with uveitis.

Infections: We agree with your plan to capture information on infection risk with your product due to the clear relationship this product has with the immune system. Please ensure a comprehensive collection of data for adverse events, specifically SAEs related to this systems organ class. Adequate laboratory testing, including WBC counts, and ancillary tests should be collected to allow for accurate diagnosis on a case by case basis.

Neoplasms: We agree with your monitoring plan.

Broncho-constriction: Data from animals and humans exposed to Gilenya support the finding that Gilenya has pulmonary toxicity. This signal isn't fully characterized and will be further explored in the post marketing setting. Since this product is in the same class as Gilenya, and your development program suggests that there may be pulmonary toxicity, this signal must be adequately explored. This is not necessarily a problem that will only surface in patients with previously reported pulmonary disease. Therefore, the development program should include a plan for all patients to have periodic testing of pulmonary function including standard spirometry measurements, DLCO and HRCT. Please include a plan to follow all patients who have abnormalities listed above to recovery.

We do agree with the inclusion of patients with pulmonary disease and would agree that additional monitoring beyond what is being done in the normal pulmonary status patients may be warranted.

Meeting Discussion: Due to limited time, there was no discussion about monitoring for macular edema or pulmonary function testing. The sponsor had provided input by email prior to this meeting that they plan to have periodic pulmonary function testing of spirometry for all patients, but did not plan to require DLCO in all patients. They do plan to include DLCO in the subgroup of patients who do not meet the normal pulmonary status, and would suggest doing DLCO on patients that develop pulmonary symptoms. FDA made a brief comment at the end of the

meeting stating that pulmonary toxicity monitoring will be fully reviewed when the protocol is submitted, and that feedback from internal FDA consultants would be obtained at that time.

Clinical Pharmacology

Question 10
Pharmacology and pharmacokinetics program: Does the Agency agree that the clinical pharmacology and pharmacokinetics program is adequate and sufficient to support registration for BAF312 in the treatment of relapsing forms of multiple sclerosis?

FDA preliminary response:

- The DDI study with β-blocker should be conducted before the start of Phase 3 studies, as there may be safety concern about pharmacological interactions.
- You need to conduct a study to evaluate the impact of CYP2C9 and/or CYP3A4 inducers (e.g., rifampicin) on the PK of BAF312. If this is conducted in parallel with the Phase 3 program, strong inducers of CYP3A4 and/or 2C9 should be prohibited in the Phase 3 studies.
- Plasma protein binding of BAF231 is very extensive (>99.9%). We recommend you conduct in vitro study before the start of Phase 3 trials to evaluate the potential of drug interactions mediated by drug displacement.
- You only mentioned to evaluate the effect of gender on BAF312 PK using population PK approach. We recommend you also explore the impact of other potential covariates on PK of BAF231.
- You mentioned that the impact of the different (CYP2C9) polymorphisms of relevance on BAF312 PK will be investigated in healthy subjects, and will possibly enable the inclusion of homozygous CYP2C9*3 patients in the Phase 3 program. However, in the Table of the PK and clinical pharmacology studies under plan, the healthy subject study you proposed is not included. Please clarify whether you will conduct a dedicated Phase 1 study or just evaluate the polymorphism impact as part of Phase 3 studies.
- Please clarify for hepatic and renal impairment studies whether you plan to include severe impaired patients.
- Please clarify the to-be-marketed product is immediate-release or modified release formulation, and whether it will be used in the proposed two Phase 3 trials.

Additional Comments:

- You need to evaluate the inhibition potential of BAF312 on P-gp in vitro.
- You need to evaluate the induction potential of BAF312 on CYP1A2 and 2B6 in vitro.

Meeting discussion: The sponsor asked if they could conduct the beta blocker study in parallel to the Phase 3 trial since patients on beta blockers would be excluded from the trial. Based on

results from the DDI trial, the sponsor may modify the exclusion criteria in the phase 3 trial. FDA thought the plan was acceptable.

In addition, the sponsor sent responses to other comments via email on Sep 27, 2011, but these were not discussed them during the meeting. Below are the FDA preliminary comments, sponsor responses, and FDA comments to the sponsor's responses:

Plasma protein binding of BAF231 is very extensive (>99.9%). We recommend you conduct in vitro study before the start of Phase 3 trials to evaluate the potential of drug interactions mediated by drug displacement.

Sponsor response: Publications have shown that plasma protein displacement does not lead to clinically significant interactions and therefore we do not believe that an in vitro study should be required.

FDA comment: It is acceptable not conducting plasma protein displacement study, considering that BAF312 is orally administered and mainly eliminated by hepatic clearance.

You only mentioned to evaluate the effect of gender on BAF312 PK using population PK approach. We recommend you also explore the impact of other potential covariates on PK of BAF231.

Sponsor response: Are there specific covariates the FDA recommends to explore?

FDA comment: We do not have recommendation for specific covariates. The covariates usually evaluated include weight, age, race, co-medications and CYP2C9 status in this case besides gender.

You mentioned that the impact of the different (CYP2C9) polymorphisms of relevance on BAF312 PK will be investigated in healthy subjects, and will possibly enable the inclusion of homozygous CYP2C9*3 patients in the Phase 3 program. However, in the Table of the PK and clinical pharmacology studies under plan, the healthy subject study you proposed is not included. Please clarify whether you will conduct a dedicated Phase 1 study or just evaluate the polymorphism impact as part of Phase 3 studies.

Sponsor response: We confirm that a dedicated study will be conducted in CYP2C9*3 healthy volunteers.

FDA comment: We agree.

Please clarify for hepatic and renal impairment studies whether you plan to include severe impaired patients.

Sponsor response: We confirm that severely impaired patients will be investigated in the hepatic and renal impairment studies.

FDA comment: We agree.

Please clarify the to-be-marketed product is immediate-release or modified release formulation, and whether it will be used in the proposed two Phase 3 trials.

Sponsor response: The to-be-marketed product is an immediate-release formulation and will be used in the two Phase III trials.

FDA comment: Noted. In addition, we have one comment about your Population PD analysis of dose-lymphocyte relationship. With a parallel design, it will be impossible to estimate between subject variability on Emax and ED50, and their covariance when each subject is assigned to only one steady state dose. You should evaluate the impact of this problem on the simulation results and relevant dosing selection decisions.

2.4.3 Question 11

QT effect: Does the Agency agree that the TQTc study can be performed in parallel to the upcoming Phase III studies and that specific QT monitoring in patients is not necessary based on the current QTc data which demonstrates that BAF312 does not delay cardiac repolarization?

FDA preliminary response: No, we believe evidence exists to suggest that there may be QT prolongation in humans on this product. A thorough QTc study should be done prior to the phase III trial to ensure safety to the subjects in the trial and to identify the level of monitoring necessary to prevent serious arrhythmias.

Meeting Discussion: The sponsor stated that they felt there was not a signal suggesting QT prolongation in the human exposure data or non-clinical program. FDA stated that while there is no strong evidence of QT prolongation in the data provided in the briefing package, there was insufficient evidence to establish that there is no reason for concern. The Guidance for Industry concerning the clinical evaluation of QT prolongation and Proarrhythmic potential for Non-Antiarrhythmic drugs states that a thorough QT study typically should be conducted early in clinical development to provide maximum guidance for later trials. In this case, such a study would help guide the monitoring plan for phase 3. FDA did not have time to conduct a complete review of the data submitted by the sponsor, some of which came shortly before the meeting. FDA continues to believe that a thorough QT study should be typically conducted before phase 3, but is open to consider an argument that the tQT study may be conducted in parallel with the phase 3 study, based on data from prior studies, and other relevant databases. At that time, the division will obtain advice from the FDA QT review group, and will provide more specific comments about the necessary cardiac monitoring in phase 3.

Suicidality Assessments

Question 12

Does the Agency agree with the proposed suicidality assessments, including the frequency of assessments?

FDA preliminary response: The proposed plan to collect suicidality assessments is acceptable. We have a comment about your plan to exclude patients "with a history of suicide attempt or patients who, in the opinion of the investigator, are at risk of suicide attempt." Although we understand the plan to not include patients who are currently psychologically unstable and may be at risk of a suicide attempt, you may consider not excluding patients that have at some point had a history of a suicide attempt.

Meeting Discussion: None.

Pediatric

Question 13
Pediatric Waiver and Deferral Does the Agency agree with the Novartis proposal seeking a product specific waiver for developing BAF312 in pediatric patients < 10 years and a deferral for studies in pediatric patients between 10 and 17 years old pending data becoming available from the Phase III adult population and from the fingolimod pediatric study?

FDA preliminary response: Pediatric studies for patients 10 years through age 17 should be deferred until the adult phase 3 BAF312 trials can be reviewed and a determination is made on the risk benefit profile. At this time, the division supports a waiver for studies with this product in children under age 10, but a formal determination will be made during the review cycle, in consultation with the Pediatric Review Committee (PeRC).

Meeting discussion: None.

Nonclinical

Question 14
Does the Agency agree that the non-clinical safety assessment studies sufficiently support registration for BAF312 in the proposed indications?

FDA preliminary response: On face, the battery of completed and planned nonclinical studies appears sufficient to support an NDA filing for BAF312. We have the following additional comments:

- The adverse findings from the embryo-fetal development studies in rat and rabbit should be described in your Informed Consent Form.
- In different locations in your briefing package, you note that a "pre- and postnatal study in rats" (page 26) (b) (4) (page 27) will be conducted. The study should be a pre and postnatal development study (*cf. Guideline for Industry: Detection of Toxicity to Reproduction for Medicinal Products, ICH-S5A, 1994*).

- [redacted] (b) (4) you would need to conduct an appropriately designed juvenile animal toxicology study in one species. If and when such a study is needed, we would recommend that you submit a final study protocol for review prior to study initiation.

Meeting discussion: none.

Regulatory

Question 15

Secondary progressive MS program: A single large, randomized, double-blind, placebo-controlled study with flexible follow-up time, powered to show an effect on disability progression in patients with secondary progressive MS (SPMS) (with and without relapses) is being considered. In the view of the Agency, could this single study be considered as sufficient for approval in the SPMS indication based on the proposed study design and if performed; (A) in parallel to the proposed program in patients with relapsing forms of multiple sclerosis (B) as a stand-alone study without a parallel program in patients with relapsing forms of multiple sclerosis?

FDA preliminary response: We refer you to the guidance for Industry on providing clinical evidence of effectiveness for human drug and biological products (May, 1998), which discusses the usual requirement for more than one adequate and well controlled investigation to provide substantial evidence of efficacy, and the circumstances under which a single trial may be acceptable. If your proposed trial meets these conditions, then a stand-alone study could be entertained. Otherwise, the development program in RRMS could be used to support a single additional study in SPMS patients. Regarding the specific study design, we can only offer the following preliminary comment: patients with progressive relapsing MS should be excluded from this study, as this subgroup is already evaluated in the "relapsing forms of MS" studies. A claim for the treatment of progressive MS must establish a drug effect independent of a reduction of the frequency of relapses. Please submit this protocol as an SPA, and we will provide more detailed comments.

Meeting Discussion: None.

Other Clinical comments

1. Provide a justification of why patients with Diabetes Mellitus (DM) are being excluded from this phase 3 development program. If this product goes to market, it would be important to know what to tell Physicians about the risks of this product in patients with DM.

Meeting Discussion: The sponsor proposed studying this patient population at a later stage because specific risk exist in this complex patient population, such as vascular pathology, autonomic dysfunction and /or metabolic disturbances. FDA suggested that these issues should be addressed in the SPA when it is submitted.

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

/s/

ERIC P BASTINGS
10/28/2011