# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022561Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022561

**MEETING MINUTES**

EMD Serono, Inc.
Attention: Dr. DiRoma
Vice President
One Technology Place
Rockland, MA 02370

Dear Dr. DiRoma:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cladribine (oral tablets).

We also refer to the meeting between representatives of your firm and the FDA on January 26, 2010. The purpose of the meeting was to discuss your plans to address all FDA's issues detailed in the RTF correspondence from November 25, 2009.

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

If you have any questions, call Hamet Touré, Regulatory Project Manager at (301) 796-7534.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M. D.
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 A |
| **Meeting Category:** | Refuse to file meeting |
| **Meeting Date and Time:** | January 26, 2010 |
| **Meeting Location:** | White Oak, Bldg. 22, Rm. 1313 |
| **Application Number:** | NDA 022561 |
| **Product Name:** | Cladribine oral tablets |
| **Indication:** | Treatment of patients with multiple sclerosis to reduce the frequency of clinical exacerbations. |
| **Sponsor/Applicant Name:** | EMD Serono, Inc. |
| **Meeting Chair:** | Russell Katz, MD |
| **Meeting Recorder:** | Hamet Touré, PharmD MPH |

**FDA ATTENDEES**
Robert Temple, MD, Center Director
Russell Katz, MD, Neurology Division Director
Eric Bastings, MD, Neurology Division Deputy Director
Billy Dunn, MD, Team Leader
Jody Green, MD, Medical Officer
Robbin Nighswander, Supervisory Regulatory Project Manager
Richard Houghtling, PhD, Reviewer Pharmacologist
Angela Men, PhD, Acting Supervisory Pharmacologist
Antoine El-Hage, Division of Scientific Investigations Inspector
Donghao Lu,
Evelyn Mentari, MD, Neurology Division Safety Team
Felicia Collins, MD, Medical Officer
Hristina Dimova,
Lily Mulugeta, PharmD, Office of Clinical Pharmacology Senior Staff Fellow
Martha Heimann,
Mildred Wright,
Sally Yasuda, PharmD, Neurology Division Safety Deputy Director
Sharon Yan,
Tejashri Purohit-Sheth, MD, Division of Scientific Investigations, Branch Chief, GCP-2
Hamet Touré, PharmD MPH, Regulatory Project Manager

**SPONSOR ATTENDEES**

Tilo Netzer, PhD, Senior Vice President, Global Regulator Affairs
Peter DiRoma, Vice President, Global Regulatory Affairs – US
Bruno Musch, MD, PhD, Senior Vice President, Head of Neurodegenerative Diseases, Global Clinical Development
Steve Greenberg, MD, Global Clinical Development
Susan Kenley, PhD, Vice President, Head of Global Biostatistics
Enrica Alteri, MD, Head of Risk Management & Epidemiology
Howard Mayer, MD, Chief Medical Officer - US
(b) (4)
(consultant)
Holly Leonard, Manager Global Regulatory Affairs
Dorothee Krumwieh, Senior Director, Head of Global Product Unit

## 1.0 BACKGROUND

EMD Serono, Inc. requested this meeting on December 23, 2009 following the FDA's refuse to file letter dated November 25, 2009. The purpose of the meeting was to address all the issues detailed in the refuse to file correspondence.

The FDA provided preliminary comments in regards to the briefing document on January 25, 2010. EMD Serono, Inc., in turn, replied to these comments in the format of a Powerpoint presentation the same day. The presentation is enclosed at the bottom of this document.

## 2. DISCUSSION

| **Sponsor's Question - #1** |
|---|
| a. Can FDA confirm that EMD Serono has all of the relevant documents related to the FDA inspections of the Scripps-C study?<br>b. EMD Serono has performed source data verification to address the issues that are mentioned in the RTF letter. We also plan to provide all of the CRFs from the Scripps-C study in the NDA resubmission. This should ensure that the datasets from the Scripps-C study are reliable and can be fully analyzed by FDA to support this study as a pivotal study. Based on this additional information, does FDA agree that the Scripps-C study can be considered as a second pivotal study? |

**FDA Preliminary Response**

***1a. It appears that EMD Serono is in possession of the pertinent documents related to the FDA Inspection conducted from December 1, 1998 to January 22, 1999 at Dr. Beutler's site at Scripps Clinic.***

***1b.*** ***No. Given that significant data integrity issues were identified at Dr. Beutler's site, which was the only site that enrolled subjects for the Scripps-C study, providing the CRFs will not be sufficient to support the datasets reliability without verification of the information on the CRFs with source documentation. Furthermore, as the FDA inspection of Dr. Beutler's site identified significant data integrity issues based on a limited number of subject records reviewed, FDA is unable to comment upon the reliability of the data for the other subjects whose records were not reviewed during the FDA inspection. An independent third party audit will need to be conducted of all subject records for the Scripps-C study with 100% source document verification of all data documented on the CRFs for all enrolled subjects. The full audit reports will need to be provided to FDA for review in addition to a summary of the audit findings.***

**Meeting discussion**

The sponsor agreed to conduct an independent, third-party, 100% source documentation verification audit of all data documented on the case report forms for Scripps-C and submit a summary report to the NDA, as well as the third party audits themselves. The FDA stated that it will evaluate the findings of the full audit reports once submitted to the NDA and that it will become a review issue.

| **Sponsor's Question - #2** |
|---|
| a. Are the proposed revised relapse and MRI analysis dataset specifications for the CLARITY study, as provided in Section 7.2, acceptable for FDA review? If acceptable, all datasets will be revised accordingly.<br>b. Does the FDA agree that the proposed content of the source and derived analysis datasets (as shown in **Error! Reference source not found.**) are acceptable to support NDA review? APPEARS THIS WAY ON ORIGINAL |

**FDA Preliminary Response**

***No. The revised datasets are an improvement, but still lack important information. For example, we need you to provide the date and other information of each individual relapse, not just the qualified relapses. We suggest you provide the data in a vertical structure instead of a horizontal structure, so that each***

***individual relapse and MRI value at each visit can be described completely. The following table provides details of the relapse dataset that we would like to have.***

| subj id | ITT | PP | Trt | trtcd | Date SD1 | Date relapse | Qualify relapse | Time to this relapse | Date 1st rescue | Total num relapse | Total num relapse after imput | [1]Relapse free status | BL num relapse | Date compl or withdrw | Days to compl or withdraw | Censor for 1st qualify relapse | [2]Other DEMO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | 1 | 1 | Plcb | 3 | (b) (6) | | Yes | 100 | (b) (6) | 2 | 3 | 0 | 2 | (b) (6) | 315 | 1 | To be filled |
| | 1 | 1 | Plcb | 3 | | | Yes | 245 | | 2 | 3 | 0 | 2 | | 315 | 1 | To be filled |
| | 1 | 1 | Plcb | 3 | | | No | 302 | | 2 | 3 | 0 | 2 | | 315 | 1 | To be filled |
| | 1 | 1 | 3mg | 2 | | | . | . | | 0 | 0 | 1 | 1 | | 729 | 0 | To be filled |

***1. Relapse free-status indicates whether a subject had any qualified relapse during the study.***
***2. Other DEMO includes region/country/site, age, sex, and race.***

***Label each variable clearly and provide codes for the variable. For example, for the variable censor, it should be labeled as event for 1st qualifying relapse, and you should provide a code column such as 1=with qualifying relapse; 0=without qualifying relapse.***

***The MRI and other datasets can be constructed in a similar way, as in the following example.***

| Subjid | ITT | PP | Trt | Trtcd | Visit | Visitn | BL T1-Gd num | T1-Gd num | T1-Gd chg | Other MRI variables | Other DEMO |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | 1 | 1 | Cladribine 3.5 mg | 1 | Screening | 1 | 5 | . | . | | |
| | 1 | 1 | Cladribine 3.5 mg | 1 | Baseline | 2 | 5 | 5 | 0 | | |
| | 1 | 1 | Cladribine 3.5 mg | 1 | Week 12 | 3 | 5 | 4 | -1 | | |
| | | | | | | | | | | | |
| | 1 | 1 | Cladribine 3.5 mg | 1 | Follow-up | 10 | 5 | . | . | | |

***In addition, all relevant information, not just minimally necessary information, must be provided. If you cannot decide whether or not information should be included, you can include such information in a separate dataset, named clearly, such as RLPADDIT, MRIADDIT, and match the subject ID and visit number to the main dataset.***

***You need to provide information for any data that deviate from the actual data, except those prospectively planned in the protocol or SAP such as imputed relapse number. For example, you need to explain the "derived date of qualifying relapse" and the difference among "actual qualifying relapse free status" and "qualifying relapse free status" and "impres qualify relapse free status" in you previous data submission.***

**Meeting discussion**

The FDA confirmed that both study completion or withdrawal and treatment completion or withdrawal data are needed. The data should include an indicator to specify if the treatment was completed or withdrawn.

Footnotes are not needed; instead, variables can be explained in a separate document with a link in the define.pdf. Normally, variable labels and codes should be sufficient in describing variables. A comment column could be added for further clarification in the define.pdf, not in the dataset. FDA needs all variables that are relevant, not just the necessary ones. If the sponsor is not sure whether or not a variable should be included, the sponsor may include it in a separate dataset, which should be in a vertical structure as well.

Missing data should be identified, for example with a dot in the dataset.

FDA reiterated the need to clearly differentiate real from imputed data. Data should not be imputed if imputation is not specified in the SAP. FDA asked for an explanation of the imputed date of relapse, and the sponsor explained that patients with missing relapse information had their relapse and date of relapse imputed. FDA stated that such relapses cannot be considered as a qualified relapse, and asked the sponsor to detail such patients in the study report.

FDA stated that each dataset should be referenced completely.

The sponsor asked that a teleconference be scheduled to wrap-up statistical comments.

The sponsor agreed to send variables for the ISS dataset within the following weeks; discussion between FDA and sponsor will follow.

The sponsor agreed to put secondary data in another dataset.

The sponsor agreed to meet the FDA submission requirements for statistical analysis.

| **Sponsor's Question - #3** |
|---|
| a. The key variables in all CLARITY analysis datasets will be updated to include the missing variables that have been requested by the FDA, as well as the original 9 key variables (study identification [ID], site ID, subject ID, treatment code, intent-to-treat [ITT] population indicator, safety population indicator, age, race, and sex). The variable "Subject completion or withdrawal status" will be split into the following 2 variables: 1) subject completion or withdrawal status from treatment, and 2) subject completion or withdrawal status from study. Is this acceptable to FDA?<br><br>b. It is proposed that the key variables for the Integrated Summary of Safety (ISS) datasets be the original 9 key variables (as described above for CLARITY), as well as the following key variables that were suggested by FDA for CLARITY: 1) the date of study Day 1 for each study, 2) the time in days in study for each study, 3) the subject completion or withdrawal status from treatment, and 4) the subject completion or withdrawal status from study. Are the proposed key variables in the ISS analysis datasets acceptable to FDA?<br><br>c. It is proposed that the key variables for the Scripps-C datasets be the original 9 key variables (as described above for CLARITY), as well as the following key variables that were suggested by FDA for CLARITY: 1) the date of study Day 1, 2) the time in days in the study, 3) subject completion or withdrawal status from treatment, and 4) study completion or withdrawal status from study. Are the proposed key variables in the Scripps-C analysis datasets acceptable to FDA? |

**FDA Preliminary Response**

***3a. and 3c. Please refer to question 2.***
***3b. Our response to question 3b will be sent at a later date.***

| **Sponsor's Question - #4 (Variables not labeled properly)** |
|---|
| Is the proposed approach acceptable to FDA? |

***FDA Preliminary Response***

***Please refer to question 2.***

| **Sponsor's Question - #5 (Excessive information without distinction of differences)** |
|---|
| Does the FDA agree with this approach? |

***FDA Preliminary Response***

***Please refer to question 2.***

| **Sponsor's Question - #6** |
|---|
| Does the FDA agree with the approach, as shown in Section 7.2, for explaining the variables in the analysis dataset specifications? |

***FDA Preliminary Response***

***Please refer to question 2.***

| **Sponsor's Question - #7** |
|---|
| All CRFs from the Scripps-C study will be provided in the NDA resubmission in portable document format (PDF). This will allow FDA to review all of the CRFs, including those for any subjects who had serious adverse events or died (none of the subjects discontinued treatment because of adverse events). Is this acceptable to FDA? |

***FDA Preliminary Response***

***Yes, receiving all CRFs for the Scripps C Study is acceptable.***

***In addition, please note that we request narratives and CRFs for all discontinuations in the Safety Data, as per the minutes from the July 24, 2009 Pre-NDA meeting; see the following meeting minutes excerpt (from the FDA response to Sponsor Question 4):***

4. Discontinuations-

Please provide both narratives and CRFs for all discontinuations including

- SAE
- lost to follow-up
- other
- physician decision
- patient decision

Please define "premature termination," "dropouts," and "discontinuation" if all used in the context of your NDA.

**Meeting discussion**

No further meeting discussion

| **Sponsor's Question - #8 (missing information in subject narrative summaries)** |
|---|
| Is this proposal acceptable to FDA? |

***FDA Preliminary Response***

***We request narrative summaries as per the minutes from the July 24, 2009 Pre-NDA meeting; see the following meeting minutes excerpt (from the FDA response to Sponsor Question 4). We request narratives, with all information that is applicable from the list below, for all discontinuations. The narratives should include pertinent medical history (MS-related and non-MS related) and discussion of adverse events experienced by the subject.***

3. Please provide narrative summaries for deaths, discontinuations, and SAEs using a common template that is easy to review. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following items should be included:
   - Patient age and gender
   - Signs and symptoms related to the adverse event being discussed
   - An assessment of the relationship of exposure duration to the development of the adverse event
   - Pertinent medical history
   - Concomitant medications with start dates relative to the adverse event
   - Pertinent physical exam findings
   - Pertinent test results (e.g., lab data, ECG data, biopsy data)
   - Discussion of the diagnosis as supported by available clinical data
   - For events without a definitive diagnosis, a list of the differential diagnoses
   - Treatment provided
   - Re-challenge results (if performed)
   - Outcomes and follow-up information

   If more than one event is contained in a single narrative then there should be a line listing at a minimum for each event. It is preferable, however, especially if events in an individual are separated by 6 months or more, to have separate narratives.

**Meeting discussion**

No further meeting discussion

| **Sponsor's Question - #9** |
| --- |
| To alleviate the concern with respect to the acceptability and interpretation of the data from the foreign sites, we propose to submit an analysis of the baseline demographic and disease-related characteristics and primary and main secondary efficacy endpoints by region, with the United States being a separate region in the analysis, to show that the |

| Sponsor's Question - #9 |
| --- |
| results are consistent across regions. Is this proposal acceptable to FDA? |

***FDA Preliminary Response***

***Given that it appears your original intent for the CLARITY study was to include a larger number of subjects from the United States, but the delay in initiating the study led to their underrepresentation, this remains a potential issue for review. Although your explanation is informative, it does not alleviate the original concern. Your approach regarding analysis of the data with regard to the underrepresented US subjects appears reasonable, but a determination of the applicability of the study results to the US population will be a matter of review.***

***Please provide an additional summary table for the CLARITY study such as is found in section 2.7.3.3.1 in Tables 5 and 6 that compares the US region to other regions.***

***Please ensure that the demographic dataset has a column for region in addition to site, as well as baseline EDSS, disease duration, weight, number relapses prior year, # T1 Gd+ lesions, # T2 lesions, and prior treatment with disease modifying drugs.***

**Meeting discussion**

No further meeting discussion

| Sponsor's Question - #10 |
| --- |
| Is this proposal acceptable to FDA? |

***FDA Preliminary Response***

***No, this proposal is not acceptable. Because EKG measurements occurred at one time between 0.5 to 3 hours post-dose, QT interval measurement may not have occurred at the time of Tmax and steady state in each subject. A thorough QT study will be necessary to evaluate the QT interval effects of cladribine. While a thorough QT study may not be advisable in healthy volunteers, an adequate assessment of QT effects in MS patients is necessary. We request that you submit a protocol for review by the QT review team.***

**Meeting discussion**

The sponsor presented four points related to question 10, and asked if FDA required a thorough QT clinical trial:

1. The rationale for capturing EKGs on day 1 was based on the fact that patients received higher doses on this day and that there was no accumulation of drug exposure with time.
2. Doses (number of tablets) were adjusted based on body weight.
3. Primary samples of EKGs were collected around Tmax.
4. In the linear regression analysis of cladribine concentration and QTcF, only three observations exceeded 450 ms.

The FDA stated that a QT clinical trial may not be necessary. The FDA will evaluate the data and is not in a position to discuss them further as it is a matter of review.

| **Sponsor's Question - #11 (Inclusion of safety data from clinical pharmacology studies in the ISS)** |
|---|
| Is this approach acceptable to FDA? |

***FDA Preliminary Response***

***The approach outlined in Section 6.2.2.1 of the briefing document is acceptable.***

**Meeting discussion**

No further meeting discussion

| **Sponsor's Question - #12 (Inclusion of both primary and secondary system organ class terms in adverse event datasets)** |
|---|
| Is this approach acceptable to FDA? |

***FDA Preliminary Response***

***No. Safety Data needs to be coded according to a single system of adverse event terminology in order to allow an integrated evaluation of all Safety Data. We request that Primary, Secondary, and all other alternative System Organ Class (SOC) terms be provided for all adverse events.***

**Meeting discussion**

FDA stated that the coding system for adverse events must be the same. While it is not necessary to submit datasets for the Phase I studies (25803, 26127, and 26486), FDA requests that adverse events from these studies also be coded with MedDRA version 11.0 and that Primary and all alternative SOCs be used in classifying Phase I adverse events.

| **Sponsor's Question - #13** |
|---|
| As requested by FDA, we will provide the rationale for a full pediatric waiver in the NDA resubmission based on low MS prevalence rates and difficulties encountered in the diagnosis and treatment of MS in the pediatric age group. Can FDA confirm that both the Pediatric Review Committee (PeRC) and the Division agree that this is an acceptable approach? |

***FDA Preliminary Response***

***Upon further internal discussion, we recommend that you submit a partial waiver request for pediatric MS studies in children 0 to < 10 years old and a deferral request for studies in children 10 to < 17 years old to allow for the collection of additional adult safety data.***

***A pediatric plan also must be submitted with the deferral request. A pediatric plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/ pharmacodynamics, safety, efficacy) that will be conducted. The pediatric plan should address the development of an age-appropriate formulation and any intention to extrapolate pediatric effectiveness from adult studies, as appropriate. In addition, the pediatric plan must contain a timeline for the completion of pediatric studies. We recommend that the timeline include the following dates: (1) protocol submission; (2) study completion; and (3) submission of study reports. The Pediatric Review Committee (PeRC) is an FDA internal committee that provides recommendations on all pediatric assessments, plans, waiver requests and/or deferral requests prior to Divisions taking an approval action. Ultimately, we determine if NDA submissions adequately satisfy the requirements of the Pediatric Research Equity Act (PREA) based on our review of all available data and recommendations.***

**Meeting discussion**

The sponsor asked if the pediatric plan could be submitted during the NDA review period. FDA clarified that the pediatric plan should include an outline of the studies; the full protocols can be submitted subsequently. FDA also reminded the sponsor that the Pediatric Research Equity Act (PREA) requires the submission of a pediatric assessment or the submission of waiver request, deferral request and/or a corresponding pediatric plan at the time of NDA submission. FDA also stated that the timeline for conducting pediatric studies will depend on the adult safety profile of the drug as determined during the review cycle. Thus, additional adult safety data may or may not be needed prior to initiating pediatric studies. With the additional clarification, the sponsor will plan to submit the pediatric plan with the NDA.

The sponsor proposed to conduct studies in adolescents, 12 to 17 years old, and to ask for a partial waiver in children < 12 years old. FDA said it would consider this request during the review cycle. FDA clarified that the distribution of pediatric patients by age should be consistent with the epidemiology of disease in pediatric patients. Thus, a non-homogeneous age distribution of pediatric patients, 10 to < 17 years old, may be acceptable.

| Sponsor's Question - #14 (Clinical pharmacology) |
|---|
| Is this explanation adequate? |

***FDA Preliminary Response***

***Yes. Please include this (volume) information in Section 3.2.P.2, paragraph 2.1.6.2 in the NDA resubmission.***

***Please also provide the dissolution data of cladribine 10 mg tablet in a tabular format in the NDA resubmission using U.S. Pharmacopeia (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.***

No further meeting discussion

| Sponsor's Question - #15 (Clinical pharmacology) |
|---|
| Is the provided explanation acceptable to FDA? |

***FDA Preliminary Response***

***Yes.***

**Meeting discussion**

No further meeting discussion

| Sponsor's Plan to Address CMC Issue |
|---|

***FDA Preliminary Response***

***The information specified under 21 CFR §314.50(e) should be included in Module 3.2.R of the application. Analytical methods and validation reports may be linked to the same PDF files as for the information provided in Module 3.2.P.5.3.***

**Meeting discussion**

No further meeting discussion

| **Sponsor's Question - #16 (Adverse event data for ongoing studies of cladribine)** |
|---|
| Is this proposal acceptable? |

***FDA Preliminary Response***

***The cutoff date for submission of adverse event data for ongoing blinded studies of cladribine depends on the details of the NDA resubmission plan, including the anticipated date of resubmission. We will establish the cutoff date once the NDA resubmission plan is discussed in greater detail.***

**Meeting discussion**

No further meeting discussion

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22561 | GI-1 | EMD SERONO INC | CLADRIBINE |

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

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/s/

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RUSSELL G KATZ
03/19/2010

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-561

EMD Serono, Inc.
Attention: Peter DiRoma
Vice President
One Technology Place
Rockland, MA 02370

Dear Mr. DiRoma:

Please refer to your September 29, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cladribine (oral tablets).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

## Clinical

1. We have determined that the Scripps C study, one of your two pivotal trials presented as a demonstration of effectiveness, is compromised with respect to its reliability and integrity and cannot be used to support the filing of this NDA. This determination was arrived at as a result of our review of the regulatory history of cladribine, in particular NDA (b) (4) which preceded NDA 22561. This revealed that NDA (b) (4) was withdrawn in 1999 after the prior sponsor received a warning letter from the Agency which stated that data from the Scripps C study should not be used. This was based on an audit that revealed numerous violations, some of which were severe, examples of which include the improper count of relapses, subjects entering the trial before signing the informed consent, and the inclusion of subjects that did not meet the entry criteria.

2. The provided datasets for the CLARITY study are deficient. There are multiple instances of missing variables and mislabeled variables. In addition, the datasets are presented in a way that remains confusing despite diligent and repeated efforts to understand the presentation. The problems these issues cause prevent even an initial cursory verification of the primary and secondary endpoints of the CLARITY trial let alone any more sophisticated analysis. See the statistical comments below for a more detailed discussion of these deficiencies.

## Statistical

### Dataset Deficiencies

The provided datasets for the CLARITY study are deficient. The deficiencies listed below can be found throughout the datasets, including datasets for primary and secondary endpoints. The listed problems are only selected examples from dataset ADQLAPSE.XPT.

#### 1. Missing Information

The following key information is missing:

1. The date of Study Day One
2. The date the rescue medication was taken
3. Time in days in study
4. Time in days from SD1 to rescue
5. Number of relapses before rescue
6. Number of relapses after rescue while on study
7. Subject completion or withdrawal status
8. Original document of SAP
9. Original document of site pooling and definition of region

#### 2. Variables Not Labeled Properly

Many variables, including ones that related to key information, are not labeled properly or are not labeled in terms or language that is understandable.

1. Variable QLAPDDT, labeled as "derived date of first qualifying relapse". It is unclear how the relapse date could be derived rather than an actual primary measurement.
2. Variables RELAPQDT and RREONSDT are labeled exactly the same as "date of first res qualifying relapse".
3. Variable REFLAGYN is labeled "Is RELAPQDT equal to RREONSDT" (see item 2). It is unclear how a patient could have two different dates for "first res qualifying relapse".
4. Variable EVENTCD is labeled as "time to event", with values 0=no and 1=yes. This is unclear as the variable labeled as such would appear to represent time in days to a specific event (e.g., first qualifying relapse).
5. Variable QRELAPCD is labeled as "qualifying relapse", with values of 0=no and 1=yes. It is not clear whether it refers to the first relapse or to all relapses.

#### 3. Excessive Information without Distinction of Differences

There is excessive information that makes it difficult or impossible to understand the difference among the variables.

Example 1

There are four variables for relapse free status at Week 96: QRAD96CD (labeled as Actual Qual Rlapse Free Status SD1-QK96), QRID96CD (labeled as Imp Res Qualifying Relapse Free Status Wk96), QRRD96CD (labeled as Res Qualifying Relapse Free Status Wk96), and QRSD96CD (labeled as Qualifying Relapse Free Status SD1 – Wk96).

If a subject had no relapse during the study, the subject should not have taken the rescue medication; the subject is relapse free, no matter how the data were imputed. If a subject had a relapse, regardless of whether rescue medication was taken or not or whether data were imputed or not, the subject is not relapse free. It is unclear why there is a need to have four variables for the relapse-free status.

Example 2

The six variables in the following table provided time on study for different periods in study.

| Variable Name | Variable label | Type | Decodes\ Format | Origin | Comments |
|---|---|---|---|---|---|
| TOSSD24 | Time on Study (days) SD1-Week 24 | Num | | Derived | See Derived Data Specs: Page 146 |
| TOSSD48 | Time on Study (days) SD1-Week 48 | Num | | Derived | See Derived Data Specs: Page 147 |
| TOSSD72 | Time on Study (days) SD1-Week 72 | Num | | Derived | See Derived Data Specs: Page 147 |
| TOS2448 | Time on Study (days) Week 24-Week 48 | Num | | Derived | See Derived Data Specs: Page 146 |
| TOS4872 | Time on Study (days) Week 48-Week 72 | Num | | Derived | See Derived Data Specs: Page 146 |
| TOS7296 | Time on Study (days) Week 72-Week 96 | Num | | Derived | See Derived Data Specs: Page 146 |

We only need two variables: Time on Study (days) SD1-Week 96 and time on study (days) SD1-rescue. Both of these are missing. If time on study SD1-Week 96 is 200, for example, it is clear that the subject stopped between Week 24 and Week 48. The key variables are missing and the 6 presented seem extraneous.

## 4. Variables not Explained Properly

For all variables, instead of providing a label that is intelligible and using the comment column for further clarification, lengthy programming language for deriving the variables is given in the comment column. The comment for one variable includes many other variables, and each of them has their own comment which further links to many more variables. Many variables used in the comment section are from other datasets. The location of those variables among the approximately 3000 variables is unknown, and no hyperlinks were provided to locate these variables.

Example 1

| Variable Name | Variable label | Type | Decodes\ Format | Origin | Comments |
|---|---|---|---|---|---|
| AREONSDT | Date of First Qualifying Relapse | Num | DATE9. | Derived | See Derived Dataset Specs Page 137 |

On page 137, the comment given for the variable is as follows.

| Variable Name | Variable label | Type | Decodes\ Format | Origin | Comments |
|---|---|---|---|---|---|
| AREONSDT | Date of First Qualifying Relapse | Num | DATE9. | Derived | Actual date associated with QRELAPCD = 1. FREONSDT = minimum REONSDT, where REONSDT ≥ RNDT. |

Variables REONSDT and RNDT in the second comment are not found in the same dataset.

Example 2

| Variable Name | Variable label | Type | Decodes\ Format | Origin | Comments |
|---|---|---|---|---|---|
| QRID96CD | Imp Res Qualigy Relapse Free Status WK96 | Num | 0=No 1=yes | Derived | See Derived Dataset Specs Page 152 |

On page 152 of Analysis Dataset Specifications, the variable is given a lengthy comment as follows:

| Variable Name | Variable label | Type | Decodes\ Format | Origin | Comments |
|---|---|---|---|---|---|
| QRID96CD | Imp Res Qualigy Relapse Free Status WK96 | Num | 0=No 1=yes | Derived | QRID96CD = QRRD96CD if QRRD96CD is not missing.<br>If QRRD96CD is missing then do the following:<br>Find the proportion of subjects with known free status, i.e., number of<br>subject with QRRD96CD = 1/ (number of subjects with (QRRD96CD = 1 + QRRD96CD = 0) across all treatment groups, call this proportion ‘p’.<br>2) Find the number of subjects in each treatment group with QRRD96CD =<br>missing (.), say ‘n1’, n2’ and ‘n3’ respectively.<br>3) Multiple ‘n1’, n2’ and ‘n3’ by ‘p’ call the results ‘r1’, ‘r2’ and ‘r3’. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Round ‘r1’, ‘r2’ and ‘r3’ to the nearest integer, call the results ‘s1’, ‘s2’ and ‘s3’.<br>4) Randomly assign ‘s1’ of the ‘n1’ subjects to QRID96CD = 1 and the remainder to QRID96CD = 0. Repeat this procedure for the other two treatment groups.<br>How to randomly assign: Generate ‘n1’ numbers between 0 and 1 using RANUNI and a seed of 2600. Rank the generated numbers from 1 to ‘n1’. Assign the lowest ‘s1’ numbers a value of 1 and the remainder a value of 0. See section 9.5.1 of the SAP for the SAS code.<br>QRRD96CD from ADQLAPSE. |

## Safety

1. No case report forms were submitted for subjects who discontinued due to adverse events in the Scripps C study. This is still required despite our Clinical comment #1.

2. FDA specified items for inclusion in narrative summaries for death, discontinuations, and SAEs. (This list may be found in FDA’s response to Question 4 in the Clinical section of the minutes from the pre-NDA meeting on May 9, 2009.) Specified items, including concomitant medications with start dates relative to the adverse event and physical exam findings, were frequently omitted in the narrative summaries for the both the CLARITY study and the Scripps C study.

## Additional Issues Not Related to the Refuse to File Decision

Although the following deficiencies cannot serve as the basis for refusing to file the application, we cannot perform an adequate independent review of your application until they are addressed.

Clinical

1. The application did not present analyses of the number of subjects screened, number of subjects who failed screening, and reasons for screening failures in the CLARITY trial and the Scripps C trial. We request that you present analyses of the number of subjects screened, number of subjects who failed screening, and reasons for screening failures for the pivotal trials.

2. The application did not present adequate justification for the small number of US sites and subjects, and the inclusion of large numbers of foreign sites and subjects. This is of particular concern with respect to the acceptability and interpretation of the data from these foreign sites.

3. The CLARITY study (Study 25643) evaluated QT before and between 0.5 and 3 hours post-dose on several occasions following administration of cladribine in a Phase 3 study. There is no documentation that EKGs were obtained at Tmax and steady state in each individual study subject. This issue was brought up at the May 9, 2009 pre-NDA meeting (see the FDA's response to Clinical Pharmacology Question 3 in the pre-NDA meeting minutes), but it appears that the FDA's request for more detailed information was not addressed in the NDA submission.

Statistical

1. It would be helpful if the datasets that are provided for the calculation of the primary and secondary endpoints in the CLARITY trial contain only the essential raw data and limit derived data to what is essential for the calculation of these endpoints. The variable labels should be in plain English without substantial use of abbreviations and jargon.

CMC

1. You have not submitted the Methods Validation Package as required under 21 CFR §314.50(e). Although we are not considering this a reason to refuse to file the NDA, the required information should be included to allow for initiation of any methods validation studies that are deemed necessary.

Safety

Note: Despite the limitations discussed above regarding data from the Scripps Clinic and Research Foundation site, safety information from trials conducted at this site remains essential to the full evaluation of the available safety data on cladribine. We request that safety data from the Scripps Clinic and Research Foundation site be presented in a manner consistent with FDA guidelines and/or in a manner previously requested by the Division.

1. The submitted Integrated Summary of Safety (ISS) for oral cladribine did not discuss safety data, including all adverse events and discontinuations, for subjects in PK and bioavailability studies (a total of 175 subjects). We request that you present information on all adverse events and discontinuations for all Phase 1 subjects.

2. The Scripps C study protocol does not prescribe which standard medical terminology is used to classify adverse events. We request that the standard medical terminology used to classify adverse events be clearly described for each study.

3. The submitted adverse event datasets included only Primary System Organ Class (SOC) terms. Both Primary and Secondary SOC terms are necessary to evaluate adverse events. We request that the adverse event datasets include both Primary and Secondary SOC Terms.

Pediatric Issues

1. We acknowledge receipt of your request for a full waiver of pediatric studies due to evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups. We recommend that you consider requesting a full waiver of pediatric studies due to necessary studies being impossible or highly impracticable and provide data on the number of pediatric multiple sclerosis patients potentially available for studies in the U.S. For more information, please refer to the PREA Guidance for Industry at *http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf*.

Clinical Pharmacology

1. BCS classification

   According to the FDA Guidance: Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, an IR drug product is rapidly dissolving if more than 85% of the labeled amount of the drug substance dissolves within 30 minutes using U.S. Pharmacopeia (USP) Apparatus I/II in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

   There is no indication of volume/type of media in the dissolution profiles you have provided in Section 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods. If this information has been provided in the application, please indicate its location.

2. Please clarify the discrepancies regarding the metabolite exposures in plasma and urine between recent studies in MS patients (25803) and earlier studies in patients with malignancies (reported in the literature by Albertioni et al. 1995 and Lindemalm et al. 2004).

3. Please provide all datasets (NONMEM format) for population PK analyses along with programs and outputs.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference.

If you have any questions, call James H. Reese, Ph.D., RAC, Senior Regulatory Health Project Manager, at 301-796-1136.

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

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22561 | ORIG-1 | EMD SERONO INC | CLADRIBINE |

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

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/s/

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RUSSELL G KATZ
11/25/2009