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APPLICATION NUMBER:

022561Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM

DATE: February 27, 2011

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: File, NDA 22561

SUBJECT: Action Memo for NDA 22561, for the use of (b) (4) (cladribine) Tablets for the treatment of patients with Relapsing Remitting Multiple Sclerosis (RRMS)

NDA 22561, for the use of (b) (4) (cladribine) Tablets for the treatment of patients with Relapsing Remitting Multiple Sclerosis (RRMS), was submitted by EMD Serono, Inc., on 5/27/2010. Cladribine injection is currently approved for the treatment of hairy cell leukemia. The pre-submission history of this product is somewhat complicated, and will be described briefly below.

Cladribine is a chlorinated purine nucleoside analogue of deoxyadenosine. In cells, it is phosphorylated by deoxycytidine kinase (DCK) to CdAMP, CdADP, and CdATP, the active moiety. Mechanisms of the drug's effect include inhibition of DNA repair of dividing cells, defective repair of DNA strand breaks, and cell death. CdATP is degraded by 5'-nucleotidase (5'NTase). DCK is high, and 5'NTase is low, in lymphocytes. For this reason, CdATP accumulates in lymphocytes preferentially. The resulting decrease in circulating lymphocytes is presumably the basis for the drug's effect in patients with MS.

The application has been reviewed by Dr. Jody Green, medical officer, Dr. Evelyn Mentari, safety medical officer, Dr. Sally Yasuda, safety team leader, Dr. Sharon Yan, statistician, Dr. Melissa Banks, pharmacology reviewer, Dr. Lois Freed, pharmacology team leader, the Interdisciplinary Review Team for QT Studies, Drs. Qin Ryan and Ann Farrell, Division of Hematology Products, Dr. Antoine El-Hage, Division of Scientific Investigations, Dr. Houda Mahayni, Office of New Drugs Quality Assessment (ONDQA; Biopharmaceutics), Dr. Donghao (Robert) Lu, ONDQA (Chemistry and Manufacturing Controls), Drs. Hristina Dimova and Xinning Yang, Office of Clinical Pharmacology, the Executive CAC, and Dr. Billy Dunn, neurology team leader.

The review team recommends that the application not be approved, primarily because of a signal for an increased risk of malignancies in clinical trials. Below, I will briefly review the relevant effectiveness and safety data.

History

As noted above, the pre-submission history of this application is somewhat complex, and is well recounted in Dr. Green's review.

Briefly, the development of cladribine for RRMS was initially undertaken by RW Johnson, who submitted an IND in April, 1994. RWJ licensed the rights to 5 trials in patients with MS performed at the Scripps Institute; ultimately, 4 controlled trials were performed at the Institute, 3 of which were in patients with Progressive MS; only Scripps C was conducted in patients with RRMS. These studies were all done with parenteral cladribine.

The sponsor submitted an NDA for RRMS on 8/14/98, but withdrew the application in April, 1999, one week before a scheduled Advisory Committee (AC) meeting. The reason the company withdrew the application was that they had received a Warning Letter from the Agency relating to the integrity of the data (multiple deficiencies in the recording of study data) collected in these studies.

Ultimately, the rights to cladribine were licensed to IVAX Corporation, then to an affiliate of Serono. The division met with the sponsor in November, 2004 to discuss the development of oral cladribine for MS. We told the sponsor that a single, robustly positive study with the oral product, in conjunction with Scripps C could support an approval (at this time, the division did not recollect that a Warning Letter had been issued 5 years earlier about the integrity of the data in Scripps C, and the [new] sponsor did not inform us of this history in 2004).

The sponsor submitted the NDA on 9/29/09. The division refused to file the application (letter dated 11/25/09), due to deficiencies in the data for Scripps C, and multiple deficiencies in the presentation of the data for the new trial with the oral tablets, the CLARITY trial.

The NDA was re-submitted on 5/27/10. The division's review of a new audit of Scripps C revealed that the data were, still, unacceptable. Nonetheless, given what appeared on a brief review, to be very robust results of the CLARITY trial, the application was filed for review.

Effectiveness

As discussed above, the application contains the report of a single trial (CLARITY) of cladribine tablets in patients with RRMS. This was a multi-national, randomized, double-blind study in which patients were randomized to receive one of two dose regimens of cladribine, or placebo. The design was somewhat complicated, and is described below:

Low dose: Patients received a total of dose of 3.5 mg/kg as follows:

0.875 mg/kg/course: each course is given as once a day dosing for 4-5 days. The first course is given on Day 1; the second course is given a month later. A third course is given a month after that, and a fourth course is given a month after that. In the low dose group, the third and fourth courses are placebo.

Starting at Week 48 of the study, patients received another course of 0.875 mg/kg/course over 4-5 days, and then another course of 0.875 mg/kg/course over 4-5 days a month later (that is, only 2 courses).

High dose: Exactly as for the low dose, but for the third and fourth courses, these patients receive 0.875 mg/kg/course.

Placebo: As above, only all courses are given as placebo.

The primary outcome measure was the qualifying relapse rate over 96 weeks.

Qualifying relapses were defined by certain prescribed increases in the Kurtzke Functional Systems. Multiple secondary outcomes were assessed (proportion of patients relapse free; disability progression; multiple MRI measures).

Results

A total of 1326 patients were randomized as follows:

High dose: 456

Low dose: 433

Placebo: 437

About 90% of patients in each group completed the study. Patients were enrolled from 155 sites in 32 countries. About 39% of the patients randomized were from Eastern Europe, about 23% were from Russia, about 20% from Western Europe, about 10% from the rest of the world, and about 10% were from the Americas (Brazil-1; Canada-36; US-94). The results for the major outcomes are given below:

Primary outcome-Annualized Qualifying Relapse Rate

	Rate	P-value compared to placebo
High dose	0.15	<0.001
Low dose	0.14	<0.001
Placebo	0.33	

Multiple sensitivity analyses yielded similar robust results (see Dr. Green's Table 17, page 51 of her review). In addition, analyses of all, not just qualifying, relapses yielded similar relative reductions in both dose groups relative to placebo.

Proportion of Relapse Free Patients

	Proportion	P-value compared to placebo
High Dose	78.9%	<0.001
Low Dose	79.7%	<0.001
Placebo	60.9%	<0.001

Analyses of Time to First Qualifying Relapse gave similar results.

Time to Sustained Disability Progression

	Hazard Ratio	P-value compared to placebo
High dose	0.69 (62 events)	0.026
Low dose	0.67 (58 events)	0.018
Placebo	82 events	

Mean Number of Combined Unique (CU) Lesions (new T1 Gd enhancing lesions, new T2 non-enhancing lesions or enlarging lesions):

	Mean # CU	P-value compared to placebo
High dose	0.33	<0.001
Low dose	0.39	<0.001
Placebo	1.65	

Analyses of other MRI measures gave similar results.

Analyses of results by region in general gave similar results. In particular, in the Americas (N=131), the annualized relapse rate for the low dose was 0.16, and for the placebo was 0.44 (p-value=0.004). The rate for the high dose was 0.27 (p=0.07).

The results did not differ between the groups that had not been previously treated with disease modifying drugs (N=402) and those who had been previously treated (N=924) (see Dr. Green's review, Table 28, page 62).

Safety

A total of 1587 patients with MS have received cladribine (oral or parenteral) in completed placebo-controlled trials. A total of 889 patients have received oral cladribine in CLARITY (median duration of follow-up was 1.8 years). The application also notes that there are 3 on-going studies with oral cladribine in patients with MS: ONWARD, a placebo controlled trial in which cladribine is added onto interferon-beta (with a similar treatment regimen to that used in CLARITY, with 2 courses, followed by two courses a year later; as of 12/09, there were 214 patients enrolled); ORACLE MS, a high dose, low dose, placebo controlled trial in patients assessing conversion to MS (apparently essentially identical dosing regimen as in CLARITY; as of 12/09, there were 194 patients enrolled); and the CLARITY extension study.

In the CLARITY extension study, patients previously randomized to placebo received cladribine. Patients randomized to any dose of cladribine in CLARITY were randomized in a 2:1 ratio to receive either cladribine or placebo. Apparently, all patients receiving cladribine in the extension received 1.75 mg/kg/year, with a duration of treatment/follow-up of 2 years.

Deaths

There were 6 deaths in the CLARITY study, 2 each in each treatment group. In placebo, there was one case each of suicide and hemorrhagic stroke; in the high dose group, one case each of tuberculosis and drowning; in the low dose, one case each of pancreatic cancer and myocardial infarction. In all completed controlled MS trials, there was an additional death in MS-Scripps, a parenteral cladribine study, in which a patient died of fulminant Hepatitis B.

In completed uncontrolled trials, there were 7 deaths (2.7%) in cladribine treated patients, and 1 placebo death (2.6%). Among the cladribine deaths, there was one MI and one cardiac arrest.

It has not been possible to completely rule out a contribution of cladribine to the deaths described, although they are all, to some extent, confounded.

There are an additional 3 deaths reported from on-going trials with cladribine. There is no evidence that any were related to cladribine.

Serious Adverse Events (SAEs)

In placebo controlled trials, 112/1073 (10.4%) cladribine-treated patients experienced at least one SAE compared to 42/514 (8.2%) of placebo patients; the same percentage of cladribine patients who received a cumulative dose of between 2.63 and 4.38 mg/kg had an SAE, but the incidence of SAEs increased with increasing cumulative dose (43% in patients with a cumulative dose >6.13 mg/kg. The greatest incidence of a given SAE was in infections (3.6% cladribine

vs. 2.3% placebo). Pneumonia (n=8), urinary tract infection (N=n=7), pyelonephritis (n=3), and adnexitis (n=2), pyrexia (n=3), asthenia (n=3), ankle fracture (n=2), fall (n=2), nausea (n=2), suicide attempt (n=3), dyspnea (n=2), lymphopenia (n=4), neutropenia (n=2), menorrhagia (n=2), spontaneous abortion (n=2), hypertension (n=2), hypersensitivity (n=2), were the only SAEs (besides malignancies and MS related terms) that occurred in more than one patient (see Dr. Mentari's Table 75, pages 56-64).

In CLARITY, 8.4% of low dose (9% of high dose) and 6.4% of placebo patients reported at least one SAE. The incidence of infection was 2.9%, 2.3%, and 1.6% for high dose, low dose, and placebo, respectively. The most frequent infection in all three groups was pneumonia, occurring in 3 patients in each group.

In CLARITY, rare SAEs occurred in more than one patient in any treatment group (see Dr. Mentari's Table 72, pages 50-55). The only SAEs that occurred in 3 patients in any treatment group were uterine leiomyoma (2 in high dose, 3 in low dose) and lymphopenia (3 in low dose).

A total of 22.1% (49/222) of patients in the uncontrolled phases of completed studies experienced at least one SAE. In these phases, SAEs of interest were pyrexia (n=6), pancytopenia (n=2), and deep vein thrombosis (n=3); few other specific SAEs were seen in more than one patient.

In on-going studies 38/1205 (3%) of patients experienced at least one SAE (though not all of these patients were receiving cladribine). Only two SAEs (herpes zoster and back pain) occurred in more than one patient (2 each); they both occurred in the 797 patients in the CLARITY extension.

Discontinuations

In CLARITY, 9.5%, 3.5%, and 2.3% of high dose, low dose, and placebo patients, respectively, discontinued treatment due to an adverse event.

Of these patients, events of interest included the following:

Event	High dose (n)	Low dose (n)	Placebo (n)
Lymphopenia	2% (9)	0.5% (2)	0
Leukopenia	0.7% (3)	0	0
Lymphocyte count Decreased	1.3% (6)	0.2% (1)	0
Hepatitis	0.4% (2)	0	0

This does not include several additional cases of lymphopenia in patients who were withdrawn for reasons characterized by the sponsor as not being related to

AEs, but who Dr. Mentari concluded had AEs on-going at the time of discontinuation.

In other controlled trials, similar events that led to discontinuations in CLARITY were also seen, including 3 cases (0.3%) of thrombocytopenia (see Dr. Mentari's Table 81, pages 110-11).

Adverse events of interest

As described by Dr. Mentari, several AEs of interest were noted.

A total of 5.3% of cladribine and 2.9% of placebo-treated patients reported herpes virus infections, and the incidence correlated with increasing lymphopenia. Four of these cases were considered serious; all 4 were herpes zoster infections, 2 involving the eye, and 2 involving peripheral nerves.

Cardiac events

In placebo controlled trials, 4.9% and 2.7% of cladribine and placebo-treated patients, respectively, experienced an arrhythmia and/or a conduction abnormality. The most common of these were syncope (1.5%; n=16 compared to 0.8%; n=4, for placebo); palpitations and tachycardia (each 1.1%, compared to 0.6% and 0.4%, respectively, for placebo patients). The one syncopal episode that was considered an SAE occurred a year after the last dose, and occurred after the patient ingested 3 times her usual dose of ropinerole.

A 20 year old man with no cardiac history developed acute cardiac failure, pulmonary edema, and atrial fibrillation 11 days after his first dose of cladribine. Myocarditis was diagnosed by MRI. The patient was discharged from the hospital about 3 weeks after the onset of symptoms.

Hypersensitivity

In CLARITY, a total of 6.4% of cladribine and 3.9% of placebo-treated patients experienced an event classified as Hypersensitivity. A total of 1.6% of cladribine and 0.7% of placebo-treated patients had an event classified as Rash, but several more patients had events that were clearly also rash, but that were classified differently (e.g., Rash generalized).

There was no increased incidence of angioedema on cladribine compared to placebo.

Common Adverse Events

Of course, numerous common adverse events were noted (see Table 43, Dr. Mentari's review, pages 135-137). Of interest is the high rate of lymphopenia,

occurring in 31.5%, 21.6%, and 1.8% of high dose, low dose, and placebo patients, respectively.

Hematologic toxicity

As noted above, cladribine is preferentially taken up into, and the active moiety accumulates in, lymphocytes. Its primary mode of action is based on a reduction in circulating lymphocytes. It is entirely expected, therefore, that significant decreases in circulating lymphocytes is a common phenomenon in cladribine-treated patients.

In CLARITY, the mean baseline lymphocyte count in both cladribine treated groups was about 1.9 X 10^9 /L. Significant decreases in both dose groups were seen at Week 5. At Week 16 (2 months after 2 active courses in the low dose group and just after the 4th active course in the high dose group), there was a 62% mean decrease from baseline in lymphocyte counts in the high dose and a 40% mean decrease in the lymphocyte count in the low dose group. There were essentially no changes in the placebo group.

By Week 48, the lymphocyte counts were about 46% and 33% of baseline in the high dose and low dose groups, respectively. By Week 55 (after the second course of the re-treatment dosing), similar decreases in lymphocyte counts were seen as were seen at Week 16. By Week 96, levels were recovering, but we still about 50% of baseline in both groups.

The greatest decreases were seen in CD4 and CD8 cells.

The nadirs in both groups were seen at Weeks 16 and 55 (mean 0.7 X 10^9 /L for the high dose group and 0.8 X 10^9 /L for the low dose group).

In placebo controlled studies, 93% of cladribine patients had an incidence of decreased lymphocytes (<1.0 X 10^9 /L) compared to an incidence of 19% in the placebo-treated patients. A total of 41% of cladribine-treated patients had lymphocyte counts <0.5 X 10^9 /L compared to 1.2% of placebo-treated patients.

Cladribine also caused mild decreases in neutrophil, total white blood cell, and platelet counts.

Carcinogencity

As of November 10, 2010, a total of 35 malignancies were reported from completed and on-going controlled trials in patients with MS. Thirty three (33) of these occurred in patients who had been treated with cladribine, and 2 were in patients treated only with placebo at the time of diagnosis of the malignancy. Three (3) of the 33 malignancies reported as having occurred in patients treated with cladribine actually occurred while the patients were on other treatments than

cladribine (they occurred in the extension phase of CLARITY; 2 of the patients were receiving placebo, one was receiving Rebif).

There were 4 cladribine-treated patients in CLARITY who developed malignancies, compared to 0 placebo patients. Overall, 19 patients in studies of oral cladribine developed malignancies (18 on drug, 1 on placebo), and 16 patients in studies of parenteral cladribine developed malignancies (15 on drug, 1 on placebo). Eleven (11) of the malignancies were reported from the CLARITY extension study.

The following table, taken from Dr. Mentari's Table 37, page 226, show the various malignancies reported:

Malignancy	Number
Basal cell	6
Breast cancer	4
Malignant melanoma	3
Colon and rectal cancer	3
Myelodysplasia	2
Bladder carcinoma	2
Ovarian cancer	2
Skin cancer (unspecified)	2

There was one each of pancreatic, cervical, cervical in situ, renal cell, chorio, esophageal, and thyroid carcinoma.

The 3 tumors that occurred in patients who received cladribine in CLARITY and who were not receiving cladribine in the extension were malignant melanoma and thyroid cancer (placebo) and basal cell (Rebif).

The 2 placebo carcinomas were one each of ovarian and basal cell.

Of the 35 malignancies reported, 11 occurred in patients after their participation in studies was completed (so-called "post-study" patients). In the analyses that follow, these patients are not included, nor were the cases of myelodysplasia. In addition, two other malignancies were not included, because they occurred after the sponsor's cut-off date of June 21, 2010.

In these analyses, time on placebo was counted for subjects who never received cladribine, and the time on placebo for patients who received placebo in CLARITY [these patients also had time on cladribine calculated for the time they received cladribine in the extension]. For those patients who received placebo in the extension, this time was not included as placebo time.

In oral cladribine trials, there were 8.2 malignancies/1000 patients treated with cladribine (13/1579), compared to 0 in placebo (N=672). The incidence was 3.8 cases/1000 patient years (3387 patient years) on cladribine, compared to 0 (1088 patient years) on placebo.

Although based only on 3 malignancies, the incidence in the US (18.3 cases/1000 patients; 10.2 cases/1000 patient years) in patients treated with oral cladribine (compared to 0 in placebo patients) was greater than the rate elsewhere.

As can be seen fro Dr. Mentari's Table 5, page 228 of her review, there is no obvious increase in malignancy incidence with increasing cumulative dose. For both oral and parenteral cladribine, the greatest incidence occurred at a cumulative dose of 2.63-4.38 mg/kg (29 cases/1000 patient-years and 8.4 cases/1000 patient-years, for parenteral and oral cladribine, respectively). The greatest rates in the US also occurred at a cumulative dose of 2.63-4.38 mg/kg (29/1000 patient-years and 21/1000 patient years for parenteral and oral, respectively).

There was little evidence that the incidence of the diagnoses of the malignancies was related to the time of observation of patients, as can be seen from Dr. Mentari's Table 7, page 230. The incidence of malignancies was about 3.8 cases/1000 patients treated with oral cladribine, for patients followed for > 48 weeks, >96 weeks, and >144 weeks, though the incidence goes up slightly with increasing time of observation, and the incidence and rate both go up with increasing time of observation in the US (see Dr. Mentari's Table 7, page 231 for the US data).

The median latency to diagnosis (from first dose of cladribine) was 3.2 years; 4 cases occurred at approximately one year, 3 occurred between 1.5 and 2.5 years, and the rest occurred at greater than 3 years after the first dose of cladribine.

SUMMARY

Cladribine has been studied in one adequate and well-controlled trial in patients with RRMS. Although the division had originally agreed with the sponsor that a single robustly positive study with oral cladribine, in conjunction with Scripps-C, a study done with parenteral cladribine, might support approval of the application, we have concluded that Scripps-C is unreliable, based on inspectional findings. We did, however, agree to consider the possibility that the drug could be found to be effective on the basis of the CLARITY study alone.

The review team has concluded that the CLARITY study, by itself, establishes the effectiveness of cladribine in the treatment of patients with RRMS.

I agree.

The results of the CLARITY study are extremely robust. Both doses have been shown to be effective, based on comparisons to placebo on multiple relevant clinical (including measures of relapse and function), as well as imaging, outcomes. Because the law requires, for an approval based on a single study, that the Agency determine that there exists confirmatory evidence, I would consider the imaging outcomes, given the clearly different domains that they assess compared to the clinical outcomes, to constitute the required confirmatory evidence.

Clearly, however, cladribine is not a benign drug. Dr. Mentari has noted numerous significant toxicities, some of which might be related to treatment with cladribine, others almost definitely related. Clearly, cladribine induces a profound and long-lasting decrease in various lymphocyte populations, and, although this is presumably the basis for its effectiveness, this effect is not without adverse consequences.

Of greatest concern, as expressed by the entire clinical team, is the apparent increase in the occurrence of malignancies in cladribine-treated patients, as well as the absolute rate seen in these studies. CLARITY provides the best data on which to base this conclusion.

The sponsor offers several arguments that they believe mitigate the risk of cancer with cladribine.

They have, for instance, compared the rates of malignancy in this development program to epidemiologically derived rates in a general population. Given the vagaries inherent in this sort of approach (especially concerns about the comparability of this background population to the patients in the CLARITY study), this approach cannot trump conclusions based on data from a well designed and conducted, randomized, placebo controlled trial like CLARITY.

Further, they suggest that many of the malignancies seen in this database are cancers that rarely metastasize, and that can typically be cured by surgery. This argument fails on many levels, including the fact that drug-induced malignancies may act differently than malignancies that arise “naturally”. Further, given the myriad tumor types seen in the database, the assertion that most of these do not metastasize and can reliably be cured by surgery appears to be patently false.

The sponsor also suggests that pre-existing risk factors may have pre-disposed cladribine-treated patients to the occurrence of cancer. The argument is weak, especially given that patients were randomized to receive drug or placebo, and that the sponsor has not made a clear case that these risk factors (whatever they are) were mal-distributed between drug and placebo treated patients.

The sponsor also notes that there was significantly longer follow-up in cladribine treated than placebo treated patients. This is true. As Dr. Mentari notes, the paucity of placebo controlled data beyond 2 years makes it difficult to interpret the longer term data. Nonetheless, not only is the signal arising from this longer term data troubling (what rate in this experience should we consider to be of no concern?), there is clearly a signal arising from the controlled portion of CLARITY (albeit from only 4 cases). The signal from CLARITY deserves a comment.

There is a view that drug-induced malignancies would most likely require a substantial latency before they can be considered biologically plausible. Although this may be true for certain drug-induced cancers, shorter latencies, for example, the latencies of the cancers seen in the controlled portion of CLARITY, may indeed by biologically plausible, given the (relatively novel) mechanism of action(s) associated with cladribine. For this reason, we have determined that the effect seen in the controlled portion of CLARITY, by itself, raises significant concerns.

Finally, the sponsor proposes a post-marketing registry to assess the risk of malignancy. It is entirely unclear how such a registry would mitigate the risk of malignancies in patients treated with cladribine.

For these reasons, we do not believe that the sponsor has provided adequate evidence undermining the conclusion that cladribine causes (multiple types of) malignancies, and the have proposed no mechanism to prevent malignancies in patients treated with cladribine. Although the effectiveness has been demonstrated, and the effectiveness seems to be on a par with the most effective treatments (although, of course, cross-study comparisons are not in any way definitive), the risk of cancer appears too great, absent any compelling counter argument about the true risk, to approve the treatment at the moment.

It may be worth noting in this regard that this application was granted Fast Track status because no oral MS treatment was approved at the time this application was submitted. That is no longer true. Gilenya (fingolimod) was recently approved. That drug has a treatment effective comparable to what was seen here with cladribine. Although that treatment is not without adverse effects (some of which may become more apparent with widespread, longer term exposure), we are not aware of any signal for malignancy with that drug.

Finally, unrelated to malignancies, other points are worth noting.

As described by Dr. Dunn, Dr. Banks has recommended additional data to address some concerns about the adequacy of the non-clinical assessment of the carcinogenicity of HPbetaCD, an excipient. Dr. Freed, the pharmacology team leader, however, believes that existing data support the acceptability of the amounts of this excipient in the drug product, in part based on the fact that the

amount of HPbetaCD to which patients would be exposed when given cladribine is less than that to which some patients are currently exposed via Sporanox, an approved product. Therefore, I agree with Dr. Freed that no additional studies would be required.

In addition, Dr. Mahayni recommends that the sponsor adopt dissolution specifications more consistent with the actual performance of the product.

Finally, Dr. Mentari has numerous questions related to additional analyses that the sponsor must conduct on a variety of safety issues.

In summary, then, I have concluded that the signal for cladribine-induced malignancies precludes the approval of this application at this time, despite the conclusion that there is robust evidence that cladribine is effective in the treatment of patients with RRMS. We will ask the sponsor for further clarification and discussion of the cancer signal, including a request for a more detailed discussion of their calculation of (and justification for the use of) background cancer rates for comparative purposes and further discussion about potential imbalances in risk factors between cladribine and placebo-treated patients. However, it is likely, I suspect, that responses to these requests will not adequately address the question of cladribine's potential to cause cancer. Although I agree that the data submitted to date do not establish with any certainty that cladribine causes cancer, the data are strongly suggestive, and further clarification on this point will be necessary before approval can be considered.

It may be possible that a long-term prospective study may be necessary to more adequately address this question. A long-term, adequately powered, active control trial may be useful in this regard.

Further, and in any case, at some point I believe the sponsor should conduct a trial using a cumulative dose lower than 3.5 mg/kg, given that they have not adequately identified the minimum, maximally effective dose.

One other additional clinical issue needs to be discussed.

The sponsor has not proposed dosing beyond the regimen studied in CLARITY. That is, they have not discussed whether or not dosing can continue beyond Weeks 48-52, nor have they justified any proposal beyond this regimen. It may be that they believe that cladribine should not be given beyond this limited number of doses, but they have provided no real discussion of this matter. We will ask them to do so.

For these reasons, then, I will issue the attached Complete Response letter.

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/s/

RUSSELL G KATZ
02/28/2011