

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs
Advisory Committee Meeting

Alemtuzumab (BLA 103948\5139)
Background Package

November 13, 2013

DISCLAIMER STATEMENT

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MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Date: October 16, 2013
From: Billy Dunn, MD, Acting Deputy Director, Division of Neurology Products
Through: Eric Bastings, MD, Acting Director, Division of Neurology Products
To: Members of the Peripheral and Central Nervous System Drugs Advisory Committee
Subject: Supplemental BLA 103948/5139 for alemtuzumab

As you know, the Peripheral and Central Nervous System Drugs Advisory Committee will meet on November 13, 2013, to discuss supplemental Biologics License Application (BLA) 103948/5139 for alemtuzumab. In preparation for that meeting, the Division of Neurology Products is providing the following reviews for your consideration:

- Clinical safety, by Evelyn Mentari, MD
- Clinical efficacy, by John Marler, MD
- Statistics, by Sharon Yan, PhD

Please note that alemtuzumab may also be identified as Campath (currently approved tradename) and Lemtrada (proposed tradename) in the advisory committee meeting briefing package. Also, the briefing package is being prepared at a time when final aspects of the review process are ongoing. The division will update the members of the committee about any relevant new findings that arise prior to the meeting.

Genzyme has submitted a supplemental BLA to support the marketing of alemtuzumab, an intravenous infusion to be indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). The applicant originally proposed an indication for the treatment of patients with relapsing forms of multiple sclerosis to slow or reverse the accumulation of physical disability and reduce the frequency of clinical exacerbations. During the review of the application, the applicant changed the proposed indication to the treatment of patients with relapsing forms of multiple sclerosis. This change was made in consultation with the division to align the proposed indication with the indications of recently approved drugs for MS. The committee should note that this change does not represent any underlying change in the content of the application.

Alemtuzumab was originally approved (with the tradename Campath) in 2001 for the treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL). Alemtuzumab

depletes T and B lymphocytes via binding to the cell surface antigen CD52. It is believed that any effects in MS are mediated through this action. In September 2012, the applicant removed alemtuzumab (as Campath) from the commercial market in preparation for a commercial relaunch of the product as Lemtrada, if approved. The applicant currently makes alemtuzumab available through a non-commercial “Campath Distribution Program” that is free of charge.

As used in the MS clinical trials and as proposed for the treatment of MS, alemtuzumab has a unique dosing regimen of two cycles (the first lasting 5 days and second lasting 3 days) of 12 mg/day, the second given one year after the first.

As discussed by Drs. Mentari, Marler, and Yan, significant concerns exist regarding the safety profile of alemtuzumab and the adequacy of the efficacy data. These issues will be the primary focus of the advisory committee meeting.

Dr. Mentari’s review discusses numerous safety concerns associated with the use of alemtuzumab for MS. These include the incidence of an array of autoimmune diseases including immune thrombocytopenia (ITP), autoimmune hemolytic anemia, immune pancytopenia, anti-glomerular basement membrane (Anti-GBM) disease, membranous glomerulonephritis, thyroid disorders, endocrine ophthalmopathy, acquired hemophilia A, type 1 diabetes mellitus, acute epitheliopathy of the retina, autoimmune skin disease, and undifferentiated connective tissue disorders, along with the incidence of malignancies, notably including thyroid cancer and melanoma. As these concerns are serious and potentially fatal, Dr. Mentari does not recommend approval of alemtuzumab unless substantial clinical benefit exists.

Dr. Marler’s review discusses various concerns associated with the data presented by the applicant in support of a demonstration of clinical benefit. These stem from issues involved with the adequacy of the design of the primary trials on which the application relies for support. In particular, Dr. Marler has grave concerns that the failure to blind patients and treating physicians in the open-label design of the trials introduced bias that confounds interpretation of their ostensible results. Because of these issues, Dr. Marler finds that the applicant has not submitted evidence from adequate and well-controlled studies to support the effectiveness of alemtuzumab for treating multiple sclerosis.

Dr. Yan’s review discusses the statistical aspects of the data presented by the applicant in support of a demonstration of clinical benefit, and largely reinforces the concerns of Dr. Marler. Dr. Yan also feels that troublesome design issues and the presence of bias in the trials prevents reliance on their results, and that a valid, accurate, and interpretable effect on the two main clinical outcomes of interest, relapse rate and sustained accumulation of disability, has not been established. Dr. Yan finds, like Dr. Marler, that the applicant has not provided evidence from adequate and well-controlled studies in this application and that such studies still need to be conducted to establish the effectiveness of alemtuzumab for the treatment of patients with multiple sclerosis.

We seek the committee's assistance in considering whether the applicant has provided adequate and well-controlled studies that demonstrate substantial evidence of effectiveness of alemtuzumab for the treatment of MS. If the committee feels that the sponsor has provided such evidence, we ask the committee to consider whether the risks to be expected in a population of MS patients who would be expected to receive the treatment if the application is approved preclude approval. We refer you to the Draft Points to Consider to guide your discussions regarding these issues.

We look forward to seeing you in November, and thank you for the work you have done in preparation for the meeting, and for your efforts at the meeting itself.

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

DRAFT POINTS TO CONSIDER

November 13, 2013

1. An adequate and well-controlled trial distinguishes the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. Has the applicant demonstrated substantial evidence of effectiveness from adequate and well-controlled trials of alemtuzumab for the treatment of patients with relapsing forms of multiple sclerosis?
2. Has the applicant provided substantial evidence that alemtuzumab has a beneficial effect on disability?
3. In the context of the purported benefits of alemtuzumab, do the safety concerns preclude approval?
4. If the available data support approval, should alemtuzumab be indicated as a first-line therapy?
5. If the available data support approval, does the Agency's proposed risk mitigation strategy adequately address the safety risks without being unduly burdensome?
 - a. What additional strategies could be used to improve the proposed REMS?
 - b. How should compliance with the laboratory monitoring requirements be documented and reported through the REMS?
 - c. Discuss the appropriate infusion setting and duration of post-infusion monitoring.

CLINICAL REVIEW

Application Type	Supplemental BLA
Application Number(s)	Efficacy supplement Sequence 0122 to BLA STN 103948/5139
Priority or Standard	Standard
Submit Date(s)	November 27, 2012
Received Date(s)	November 27, 2012
PDUFA Goal Date	December 27, 2013
Division / Office	DNP/OND
Reviewer Name(s)	Evelyn Mentari, M.D., M.S.
Review Completion Date	October 1, 2013
Established Name	Alemtuzumab
(Proposed) Trade Name	Lemtrada
Therapeutic Class	Humanized monoclonal antibody
Applicant	Genzyme Corporation
Formulation(s)	Intravenous
Dosing Regimen	Initial treatment course: 12 mg/day for 5 consecutive days (60 mg total dose). Second treatment course: 12 mg/day for 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course.
Indication(s)	Relapsing forms of multiple sclerosis (MS)
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Multiple serious and potentially fatal safety issues have been reported in patients treated with alemtuzumab for MS. The Sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS), components of which will be discussed with the relevant safety sections of this review. In addition, Genzyme plans to submit, post-approval, a protocol for a long-term safety study to determine the incidence of adverse events of special interest, specifically ITP, autoimmune cytopenias, nephropathy, serious infections, serious thyroid disorders, and malignancies in a “real-world” setting. However, because of the serious and potentially fatal safety issues, unless alemtuzumab shows substantial clinical benefit, this reviewer recommends that FDA not approve Genzyme’s application to market alemtuzumab for relapsing forms of MS.

Safety issues potentially preventing the approvability of alemtuzumab

In the opinion of this reviewer, the main safety concerns potentially preventing the approvability of alemtuzumab for the treatment of MS are autoimmune diseases and malignancies:

- Autoimmune diseases
 - Autoimmune cytopenias
 - Immune thrombocytopenia (ITP)
 - Autoimmune hemolytic anemia
 - Immune pancytopenia
 - Autoimmune kidney diseases
 - Anti-glomerular basement membrane (Anti-GBM) disease
 - Membranous glomerulonephritis
 - Thyroid disorders (including Graves’ disease and thyroiditis)
 - Endocrine ophthalmopathy
 - Acquired hemophilia A (anti-Factor VIII antibodies)
 - Type 1 diabetes mellitus
 - Acute epitheliopathy of the retina
 - Autoimmune skin disease
 - Undifferentiated connective tissue disorders
- Malignancies
 - Thyroid Cancer
 - Melanoma

Autoimmune Cytopenias (Section 7.3.5.1.3)

Immune Thrombocytopenia (ITP)

Twenty six of 1485 (1.8%) of all alemtuzumab-treated subjects (Pool C) have been diagnosed with confirmed ITP.¹ One subject died of a fatal cerebral hemorrhage (index case CAMMS223 Subject 113-1125). Spontaneous, life-threatening, or fatal bleeding can occur with ITP, especially in subjects with a platelet count of less than 10,000 - 20,000 platelets/mm³. Seventeen subjects with ITP (1.1% of all Pool C subjects) had nadir platelet counts less than 20,000 platelets/mm³. Cases of ITP have been reported up to 39 months after the last dose of alemtuzumab.

In CAMMS223, 5 of 6 alemtuzumab-treated patients with ITP were positive for anti-platelet antibodies, confirming the autoimmune nature of the thrombocytopenia.² The presence of anti-platelet antibodies did not precede the onset of ITP, but appeared simultaneously with a drop in platelets.³

Based on European population-based studies,⁴ the estimated incidence of ITP in adults is approximately 2 cases per 100,000 person-years. The incidence of ITP in alemtuzumab-treated subjects in Genzyme trials was 443 cases per 100,000 person-years.⁵ There were no cases of confirmed ITP in IFN β -1a subjects in controlled trials in this supplement.

Autoimmune Hemolytic Anemia (AIHA)

There were 3 cases of autoimmune hemolytic anemia (AIHA) in Genzyme studies of MS, all in alemtuzumab-treated subjects. Nadir hemoglobin levels ranged from 2.9-8.6 g/dL in these subjects. The incidence of AIHA in alemtuzumab-treated subjects in Genzyme studies was 51 cases per 100,000 person-years.⁶ Autoimmune hemolytic anemia (AIHA) is a rare disease with an estimated incidence of 0.8 cases per 100,000 person-years in a U.S. population-based study.⁷

Autoimmune Pancytopenia

In controlled trials, 2 of 1188 (0.2%) alemtuzumab-treated subjects had autoimmune pancytopenia, compared to 0 of 496 IFN β -1a subjects. One subject with autoimmune

¹ 4-Month Safety Update, p. 101. Submitted to sBLA 103948 on March 19, 2013. Data cut-off November 26, 2012.

² ISS p. 447. One alemtuzumab-treated patient with ITP did not test positive for either serum or platelet-associated APA, however, this patient was not tested at the time of ITP onset.

³ ISS p. 447.

⁴ Fogarty PF. The epidemiology of immune thrombocytopenic purpura. *Curr Opin Hematol.* 2007 Sep;14(5):515-9.

⁵ As of April 20, 2013, the total number of person-years of follow-up in alemtuzumab-treated subjects (all doses) was 5874. Information on total number of person-years of follow-up in Genzyme trials was submitted to sBLA 103948 on May 14, 2013.

⁶ As of April 20, 2013, the total number of person-years of follow-up in alemtuzumab-treated subjects was 5874.3. Information submitted to sBLA 103948 on May 14, 2013.

⁷ Lechner K. *Blood* September 16, 2010 vol. 116 no. 11 1831-1838

pancytopenia died from sepsis. There was also a post-study case in which the patient presented to the hospital with hemoglobin 2.7 g/dL, platelets $57 \times 10^9/L$, WBC $1.7 \times 10^9/L$.

Reviewer comment: Because of the risk for life-threatening or fatal bleeding and infection, rapid diagnosis of autoimmune cytopenias is imperative. Genzyme has recommended monitoring complete blood counts at monthly intervals for 48 months following treatment with alemtuzumab. It is unclear to what degree patients will adhere to monthly laboratory monitoring for 4 years. The proposed postmarketing monitoring plan provides less frequent surveillance, compared to what was done in clinical trials. Subjects in Genzyme trials were scheduled to receive either a complete blood count laboratory measurement or a symptom monitoring survey every 2 weeks. If alemtuzumab is granted marketing approval, there is risk of increased rates of morbidity and mortality from ITP as compared to rates observed in clinical trials.

Autoimmune kidney diseases (Section 7.3.5.1.5)

In Genzyme studies, there was 1 adverse event of anti-glomerular basement membrane (anti-GBM) disease (also called Goodpasture's disease) and 2 cases of membranous nephritis. In all alemtuzumab follow-up, the incidence of anti-GBM disease (calculated using 1 case in Subject 122-1319) was 170 per million person-years,⁸ compared to the reported general population incidence of approximately 0.5-1 case per million person-years.⁹⁻¹⁰

Two published cases¹¹⁻¹² describe Anti-Glomerular Basement Membrane (Anti-GBM) Disease leading to End Stage Renal Disease (ESRD) after alemtuzumab treatment. Two postmarketing cases of subjects treated with alemtuzumab for MS, who subsequently developed anti-GBM disease requiring kidney transplantation or chronic hemodialysis, have been submitted to Medwatch. In these cases, patients developed end-stage kidney disease despite treatment. Based on this experience, additional cases of end-stage kidney disease related to anti-glomerular basement membrane disease with alemtuzumab will likely occur, despite recommendations for laboratory monitoring.

Thyroid disorders (Section 7.3.5.1.1)

In the active-controlled studies, the incidence of thyroid AEs was higher in the alemtuzumab 12 mg/day group (18.3%) than in the IFNB-1a group (5.4%). The risk of experiencing a first thyroid

⁸ As of April 20, 2013, the total number of person-years of follow-up in alemtuzumab-treated subjects was 5874.3. Information submitted to sBLA 103948 on May 14, 2013.

⁹ Salama AD, Levy JB, Lightstone L, Pusey CD. Goodpasture's disease. *Lancet* 2001; 358: 917-20.

¹⁰ Turner AN, Rees AJ. Anti-glomerular basement membrane disease. In: Davison AM, Cameron JS, Grunfeld J-P, Kerr DNS, Ritz E, Winears CG, eds. *Oxford Textbook of Nephrology*. Oxford: Oxford University Press, 1998; 645-66.

¹¹ Clatworthy MR, Wallin EF, Jayne DR. Anti-glomerular basement membrane disease after alemtuzumab. *N Engl J Med*. 2008 Aug 14;359(7):768-9. *This paper describes Subjects 1 and 2.*

¹² Coles AJ, et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. *J Neurol*. 2006 Jan;253(1):98-108. *This paper describes Subject 1, also described in the Clatworthy paper.*

AE was greatest between Months 6 and 42. First thyroid AEs continued to occur between Months 42 and 96.

As of November 26, 2012, 30 of 1485 (2.0 %) subjects assigned to alemtuzumab in controlled trials had a serious thyroid AE, and 19 of 1485 (1.3%) required thyroidectomy.

The infant offspring of Subject 1018-3090 had a life-threatening SAE of thyroid storm from neonatal Graves' disease, which is caused by transfer of TSH receptor antibodies from mother to fetus. This raises a concern of possible transfer of other autoimmune antibodies from mother to fetus.

Associated with Graves' disease, Graves' ophthalmopathy was documented in 19 of 1485 (1.3%) alemtuzumab-treated subjects (Pool C). Graves' ophthalmopathy can cause functional eye impairment, including potential sight-threatening sequelae, as well as facial disfigurement with important psychosocial consequences.¹³ Two subjects have required surgical treatment for Graves' ophthalmopathy.

Autoimmune Coagulopathy: Acquired Hemophilia A (Factor VIII Inhibitor) (Section 7.3.5.1.4)

Acquired hemophilia A (AHA) is an autoimmune disease caused by an inhibitory antibody to coagulation factor VIII, a procoagulant component. Subjects with AHA are at risk for life-threatening bleeding. Management consists of rapid diagnosis, controlling bleeding, and immunosuppression to eradicate the inhibiting antibody.¹⁴

There were 3 reported cases of AHA in alemtuzumab-treated subjects: -- 1 in a CAMMS324 subject treated for MS and 2 cases in other indications. In MS studies, the incidence rate of AHA in alemtuzumab-treated subjects was 170 per million person-years.¹⁵ The general population incidence of AHA has been estimated to be 0.2–1.0 case per 1 million persons per year.¹⁶

Autoimmune (Type 1) Diabetes Mellitus

Two of 1485 (0.1%) Pool C subjects developed confirmed autoimmune (Type 1) diabetes mellitus:

- Subject 4701-5562: 37 year old non-obese (BMI 25) female with elevated levels of 3 types of antibodies to islet cells and islet autoantigens.
- Subject 6001-3188: 29 year old male from Russia (BMI 16.9); antibody testing was not performed.

¹³ Wiersinga WM. Best Pract Res Clin Endocrinol Metab. 2012 Jun;26(3):359-70.

¹⁴ Collins PW. J Thromb Haemost. 2011 Jul;9 Suppl 1:226-35.

¹⁵ As of April 20, 2013, the total number of person-years of follow-up in alemtuzumab-treated subjects was 5874.3. Information submitted to sBLA 103948 on May 14, 2013.

¹⁶ Franchini M, et al. Am J Hematol. 2005 Sep;80(1):55-63.

Autoimmune Diseases: Other

In Genzyme studies, 1 case of autoimmune retinopathy and 2 cases of undifferentiated connective tissue were reported. A case of autoimmune skin disease (pityriasis lichenoides chronicus) after alemtuzumab treatment for MS was described in a published report by Hirst.¹⁷

Autoimmune Disease: Conclusion

The wide range of autoimmune diseases seen after alemtuzumab treatment indicates the broad nature of the pathophysiologic process of altered immune reconstitution with alemtuzumab. Because of this broad process, it is likely that additional autoimmune diseases may be documented after alemtuzumab treatment.

Altered lymphocyte populations have been discussed as a potential basis for secondary autoimmune disease after alemtuzumab treatment.^{18 19} The anti-CD52 mechanism of action of alemtuzumab causes a rapid depletion of circulating lymphocytes. Differential depletion and repopulation lead to post-treatment shifts in the relative proportions of lymphocyte subsets.

There are no known ways to prevent secondary autoimmune disease with alemtuzumab. Efforts to mitigate the severity and sequelae of autoimmune events consist of monitoring to facilitate prompt identification and treatment.

Malignancy (Section 7.3.5.2)

In total, 22 of 1485 (1.5%) alemtuzumab-treated subjects (Pool C) had a treatment-emergent malignancy. In exploratory analyses of adverse events by demographic subgroup, subjects from the U.S. and female subjects had markedly higher incidences and incidence rates of treatment-emergent malignancy (see table below). All but 1 subject with a treatment-emergent malignancy was female.

¹⁷ Hirst CL, et al. Campath 1-H treatment in subjects with aggressive relapsing remitting multiple sclerosis.

¹⁸ Costelloe L, et al. Secondary autoimmune diseases following alemtuzumab therapy for multiple sclerosis. *Expert Rev. Neurother.* 12(3), 335–341 (2012).

¹⁹ Weetman A. Immune reconstitution syndrome and the thyroid. *Best Practice & Research Clinical Endocrinology & Metabolism* 23.6 (2009): 693-702.

Table 1. Incidence and incidence rate of treatment-emergent malignancy in female and U.S. demographic subgroups. All alemtuzumab subjects (Pool C)

	Incidence n/N (%)	Incidence rate (cases per 100,000 person-years)
All subjects	22/1485 (1.5%)	374.5 ^a
All female subjects	21/972 (2.2%)	544.2 ^b
U.S. subjects	15/555 (2.7%)	659.9 ^c
U.S. female subjects	15/397 (3.8%)	894.5 ^d

Corresponding data for male subjects and non-U.S. subjects is located in Table 52

Incidence rates as of April 20, 2013. Information on the total number of person-years of follow-up in alemtuzumab-treated subjects submitted to sBLA 103948 on May 14, 2013.

^a 5874 person-years of follow-up for all alemtuzumab-treated subjects

^b 3859 person-years of follow-up for all female alemtuzumab-treated subjects

^c 2273 person-years of follow-up for U.S. alemtuzumab-treated subjects

^d 1677 person-years of follow-up for female U.S. alemtuzumab-treated subjects

Malignancy: Thyroid Cancer

There were 6 (0.4%) cases of thyroid cancer in 1485 alemtuzumab-treated subjects (Pool C). In Pool E there were no cases in IFNB-1a subjects. The SEER reference rate for thyroid cancer (for all races) was 18.2 per 100,000 person-years for U.S. females.²⁰ The incidence rate in all female alemtuzumab subjects was 129.6 cases per 100,000 person-years.²¹ Four²² of five cases of thyroid cancer in female subjects occurred in subjects from the U.S. The incidence of thyroid cancer in U.S. females was 1.0% in alemtuzumab studies (4 cases in 397 U.S. Pool C female subjects).²³ The incidence rate in U.S. female alemtuzumab-treated subjects was 238.5 cases per 100,000 person-years.²⁴

The SEER reference rate for thyroid cancer (for all races) was 6.1 per 100,000 person-years for U.S. males.²⁵ The incidence rate in all male alemtuzumab subjects was 49.6 cases per 100,000 person-years.²⁶

²⁰ SEER Stat Fact Sheets: Thyroid. Accessed on 8/23/2013 at <http://seer.cancer.gov/statfacts/html/thyro.html>

²¹ 5 cases in 3859 person-years for all female alemtuzumab-treated subjects as of April 20, 2013. Information on the total number of person-years of follow-up in alemtuzumab-treated subjects submitted to sBLA 103948 on May 14, 2013.

²² U.S. alemtuzumab subjects who developed cancer were: 1001-3095, 1027-3419, 1041-5232, and 124-1080 (all female)

²³ Cancer statistics (Siegel et al., 2013, CA Cancer 63:11-30) reported that risk for thyroid cancer is 3 times higher in female than male in US population. The SEER data suggested that, in alemtuzumab treated population, the risk for thyroid cancer is 2.6 times higher for female than male worldwide. SEER data also indicated that, among alemtuzumab treated female subjects, the risk of thyroid cancer is 1.8 times higher in US than worldwide.

²⁴ 4 cases in 1677 person-years from U.S. female alemtuzumab-treated subjects as of April 20, 2013. Information on the total number of person-years of follow-up in alemtuzumab-treated subjects submitted to sBLA 103948 on May 14, 2013.

²⁵ SEER Stat Fact Sheets: Thyroid. Accessed on 8/23/2013 at <http://seer.cancer.gov/statfacts/html/thyro.html>

²⁶ 1 case (Subject 7101-3411 from Serbia) in 2015 person-years for all male alemtuzumab-treated subjects as of April 20, 2013. Information on the total number of person-years of follow-up in alemtuzumab-treated subjects submitted to sBLA 103948 on May 14, 2013.

Of note, one subject (1027-3419) had a whole body scan that was concerning for metastatic activity in the lower neck.

Malignancy: Melanoma

There have been 3 cases of melanoma in Genzyme clinical trials of alemtuzumab (all in extension trial CAMMS03409). In addition there was 1 case of atypical melanocytic tumor in CAMMS03409; based on pathology, a Mayo clinic physician said the atypical melanocytic tumor case should be treated like a malignant melanoma.

In a population-based study in Denmark, the incidence of melanoma in MS subjects from 1968 to 1997 was 18.8/100,000 subject-years.²⁷ The overall, age-adjusted incidence rate for the general population in the US was 21.0 per 100,000 per year (27.2 per 100,000 for men and 16.7 per 100,000 for women) from 2005 to 2009 in 18 SEER geographic areas. Age-Specific SEER incidence rates in the following age groups 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, and 50-54 were 1.55, 4.02, 6.99, 9.67, 13.03, 17.84, 23.12, and 29.0 per 100,000 person-years, respectively (Howlader, SEER Cancer Statistics Review, 2012). For all alemtuzumab-treated subjects in Genzyme trials, median and interquartile range age were 33 and 28 to 41, respectively.

Worldwide incidence rate for melanoma in Genzyme MS trials as of April 20, 2013: 3 cases in 5874 person-years = 51.0 cases per 100,000 person-years; this rate is approximately 3 times reference rates.

USA incidence rate for melanoma in Genzyme MS trials as of April 20, 2013: 2 cases in 2273 person-years = 88.0 cases per 100,000 person-years; this rate is approximately 5 times reference rates.

Additional safety issues with alemtuzumab

In addition to the safety concerns potentially preventing approvability of alemtuzumab listed above, the following safety issues of concern have been seen with alemtuzumab:

- Infusion reactions
- Serious infections
- Pneumonitis
- Lymphopenia
- Suicidal behavior and ideation

Infusion Reactions (Section 7.3.5.3)

Infusion of alemtuzumab is associated with a cytokine release syndrome. Infusion reactions were reported by 1360 of 1485 (91.6%) Pool C subjects. The most common infusion-associated

²⁷ Nielsen NM, et al. Int J Cancer: 118, 979-984 (2006)

reactions in alemtuzumab-treated subjects included fever, nausea, headache, rash, flushing, hypotension, and tachycardia.

In the ISS analysis, 37 of 1485 (2.5%) of all alemtuzumab-treated subjects (Pool C) had a serious infusion reaction. Serious infusion-related AEs included:

- Chest pain (5)
- Sinus bradycardia (heart rate in 30's-40's) (4)
- Headache (4)
- Atrial fibrillation (3)
- Hypotension (3)
- Anaphylactic shock (2)
- Hypertension (2)
- Sinus tachycardia (2)
- Increased liver transaminases (2)
- Rash (2)
- Brain stem syndrome (1)
- Angioedema (1)
- Pneumonitis (1)
- Pyrexia (1)
- Edema (1)
- Cellulitis (1)

This reviewer recommends that alemtuzumab be infused in a setting capable of treating acutely life-threatening medical emergencies, including anaphylactic shock and cardiac dysrhythmias. These capabilities include the ability to administer emergency cardiac medications, on-site professionals trained in Advanced Cardiovascular Life Support and management of anaphylaxis, and on-site cardiac monitoring. Alemtuzumab should be used with caution in patients with a history of cardiac disease.

In the Genzyme controlled trials, vital signs were not routinely measured during infusion or post-infusion. Thus, information that is essential for evaluating and mitigating risks of alemtuzumab during and after infusion is unavailable.

Infections (Section 7.3.5.4)

The incidence of infection AEs in controlled trials (Pool E) for the alemtuzumab 12 mg/day group was 71.8%, compared with 54.2% in the IFNB-1a group. Serious infections were reported for 27 (2.9%) subjects in the alemtuzumab 12 mg/day group and 6 (1.2%) subjects in the IFNB-1a group over 3 years of follow up. In the ISS analysis of all alemtuzumab subjects (Pool C), serious infections were reported for 46 (3.8%) subjects in the alemtuzumab 12 mg/day group.

Despite administration of acyclovir 200 mg twice daily beginning on the first day of any alemtuzumab treatment cycle and continuing for 28 days following the last infusion day of any cycle, in all active-controlled studies (Pool E), the overall incidence of herpes viral infection was

higher in the alemtuzumab 12 mg/day group (15.7%) than the IFN β -1a group (3.0%). Serious herpes infections in Pool C included herpes zoster, ophthalmic herpes, and herpes meningitis.

In controlled trials (Pool E), 31 of 1188 (2.6%) alemtuzumab-treated subjects had human papilloma virus (HPV) infection, compared to 7 of 496 (1.4%) of IFN β -1a subjects. There were 2 cases of HPV-related malignancies in subjects who received alemtuzumab 24 mg/day: vulval cancer (1025-5450) and cervical carcinoma (302-1224).

There was one serious adverse event of listeria meningitis in alemtuzumab-treated subjects (CAMMS223 Subject 201-1159, 36 year old female from the UK; Alemtuzumab 24 mg/day treatment group). No listeria infection was reported in subjects treated with IFN β -1a. The subject developed listeria meningitis after eating Brie cheese.

Reviewer comment: There is an increased risk of infection with alemtuzumab. Measures to address risks of specific types of infection are discussed in Section 7.3.5.4.

Pneumonitis (Section 7.3.5.5)

Cases of pneumonitis and potential pneumonitis have been reported with alemtuzumab use:

- 8 cases of pneumonitis and potential pneumonitis during and after controlled trials of alemtuzumab for MS
- 2 cases of hypersensitivity pneumonitis from a published post-study report of alemtuzumab in MS²⁸ with details obtained from an unpublished report.
- 1 published case of fatal pneumonitis after treatment with alemtuzumab for CLL²⁹
- 1 published case of diffuse alveolar hemorrhage after alemtuzumab for immunosuppression post-transplant³⁰

Hypersensitivity pneumonitis is described in multiple cases after alemtuzumab use; this condition can progress to fibrosis and end-stage lung disease. This reviewer recommends patient and healthcare provider education to facilitate prompt identification and treatment of these events.

Lymphopenia (Section 7.4.2.1)

A rapid depletion of circulating T and B lymphocytes, caused by the anti-CD52 mechanism of alemtuzumab action, results in nearly all subjects in MS clinical trials experiencing lymphopenia following treatment. In controlled trials (Pool E), 888/919 (96.6%) of subjects treated with alemtuzumab 12 mg/day had at least one lymphocyte count < 500 cells/ μ L (see Figure 6).

²⁸ Cossburn, et al. Autoimmune disease after alemtuzumab treatment for multiple sclerosis in a multicenter cohort. *Neurology* 2011;77:573–579

²⁹ Creelan, B and Ferber, A. A fatal case of almetuzumab-associated interstitial pneumonitis. *American Journal of Therapeutics* 15, 82-84 (2008).

³⁰ Sachdeva, A and Matuschak, G. Diffuse alveolar hemorrhage following alemtuzumab. *Chest*, 133: 6, June 2008.

Depletion of CD4+ lymphocytes was especially profound. Mean CD4+ counts were reduced to 40 cells/ μ L at Month 1³¹ from a baseline value of 960 cells/ μ L, and were 55% of the lower limit of normal by 12 months after Cycle 1 (270 cells/ μ L). Decreases in CD4+ lymphocytes to a count <200 cells/ μ L occurred in 1447 of 1485 alemtuzumab-treated subjects (Pool C). After a median of approximately 2 years of follow-up, 845 of 1447 subjects did not have a CD4+ lymphocyte count greater than that subjects baseline value or the LLN (whichever was lower).

Suicidal Behavior and Ideation (Section 7.3.5.6)

In controlled trials (Pool E) events of suicidal behavior or ideation included:

- Alemtuzumab
 - 3 of 1188 (0.3%) suicide attempts
 - 3 of 1188 (0.3%) suicidal ideation
 - 6 of 1188 (0.6%) total
- IFN β -1a
 - 3 of 496 (0.6%) suicidal ideation

There were 2 cases of suicide attempt and 3 cases of suicidal ideation in CAMMS03409. In all alemtuzumab studies (Pool C), 11 of 1496 (0.7%) experienced an event of suicidal attempt or ideation. Three of the 11 events were associated with thyroid abnormalities. Seven had a history of psychiatric illness prior to receiving alemtuzumab. (Of the 3 cases seen with IFN β -1a, 2 had a history of prior psychiatric illness.)

The first Warning in the Rebif (IFN β -1a) prescribing information is Depression and Suicide. Alemtuzumab had an equal incidence of suicide attempt or suicidal ideation as IFN β -1a, but the alemtuzumab events had a higher severity overall (3 events were suicide attempts). This reviewer recommends description of suicidal behavior and ideation with alemtuzumab in the Warnings and Precautions section of prescribing information, if alemtuzumab is approved.

1.2 Risk Benefit Assessment

For an assessment of efficacy, the reader is referred to the clinical review by John Marler, M.D..

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Genzyme has proposed Postmarket Risk Evaluation and Mitigation Strategies (REMS) with the following elements:

- Medication Guide
- Communication Plan (including Dear Healthcare Provider Letter)
- Elements to Assure Safe Use (including healthcare provider certification, certification for healthcare facilities that dispense and administer Lemtrada, enrollment and monitoring requirements for subjects)

³¹ Month 1 is the time of nadir median CD4+ lymphocyte count. No post-infusion laboratory measurements were routinely performed prior to 1 month, so the actual nadir value may have occurred prior to 1 month post-infusion.

- Implementation System: (including a restricted distribution system, a database of all healthcare providers to be maintained by Genzyme, facility and subject enrollment program, and a call center established by Genzyme)

Goals listed in the proposed REMS include: informing subjects and providers about the serious risks associated with use of alemtuzumab, including autoimmune conditions and serious infections; and to mitigate the severity and sequelae of incident autoimmune events and serious infections. This reviewer recommends that a REMS for alemtuzumab also seek to inform and mitigate risks of malignancies, infusion reactions, and pneumonitis.

1.4 Recommendations for Postmarket Requirements and Commitments

If alemtuzumab is approved for treatment of MS, this reviewer recommends postmarketing requirements to evaluate the occurrence of autoimmune conditions, serious infections, malignancies, infusion reactions, and pneumonitis to better characterize these events.

2 Introduction and Regulatory Background

2.1 Product Information

3. Chemical Name and Structure

Alemtuzumab is a genetically engineered human immunoglobulin subclass gamma 1 (IgG1) kappa monoclonal antibody containing 6 complementarity-determining regions derived from an IgG2a rat monoclonal antibody, specific for the cell surface glycoprotein, CD52. The 6 hypervariable complementarity determining regions of the heavy and light chain variable domains of the rat IgG2a monoclonal antibody were grafted into a human IgG1 kappa variable framework to produce a humanized antibody that binds the human CD52 antigen.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2. Disease-modifying medications approved for use in relapsing forms of multiple sclerosis

Brand Name	Generic Name	Year of FDA Approval	Incidence/Route of Delivery/Usual Dose
Avonex	Interferon beta-1a	1996	Once weekly; intramuscular injection; 30 mcg
Betaseron	Interferon beta-1b	1993	Every other day; subcutaneous injection; 250 mcg
Copaxone	Glatiramer acetate	1996	Every day; subcutaneous injection; 20 mg
Extavia	Interferon beta-1b	2009	Every other day; subcutaneous injection; 250 mcg
N/A	Mitoxantrone*	2000	Four times per year; intravenous infusion in a medical facility; lifetime cumulative dose limit of approximately 8-12 doses over 2-3 years (140 mg/m ²)
Rebif	Interferon beta-1a	2002	Three times per week; subcutaneous injection; 44 mcg
Tysabri	Natalizumab	2006	Every four weeks ; intravenous infusion in a registered infusion facility; 300 mg
Gilenya	Fingolimod	2010	Once daily; oral administration; 0.5 mg
Aubagio	Teriflunomide	2012	Once daily; oral administration; 7 or 14 mg
Tecfidera	Dimethyl fumarate	2013	Twice daily; oral administration; 120 mg for 7 days and then maintenance dose of 240 mg

*Mitoxantrone is only available as a generic drug.

2.3 Availability of Proposed Active Ingredient in the United States

Alemtuzumab was approved for use in B-CLL under the trade name Campath in 2001. Effective September 4, 2012 Campath was no longer available commercially. Campath is currently provided through the Campath Distribution Program free of charge. In order to receive Campath, the healthcare provider is required to document and comply with certain requirements.³² While these requirements are not specified, it has been reported that the distribution program allows access to subjects using alemtuzumab for oncologic indications³³ and MS subjects who need to complete an off-label course of alemtuzumab treatment.³⁴

Differences in Dose Regimen in Multiple Sclerosis versus B-CLL

According to Genzyme, Campath was removed from the commercial market “as part of the company’s plan for bringing alemtuzumab forward as a treatment for a new indication”³⁵ (i.e., MS). At the time of this review, it is unclear whether alemtuzumab will receive approval for treatment of MS in the U.S. A return of alemtuzumab to the U.S. market for treatment of B-CLL is possible, especially if approval for treatment of MS does not occur. If this happens, off-label use of alemtuzumab for MS, using a formulation intended for B-CLL, may occur.

³² Campath consumer website. Accessed September 5, 2013 at: <http://www.campath.com/>

³³ “Sanofi/Genzyme Primed Subject Community For Campath’s Removal From Commercial Distribution” *The Pink Sheet*. August 27, 2012.

³⁴ Laurance J. Company restores access to multiple sclerosis drug after pressure from neurologists. *BMJ* 2013;346:f703.

³⁵ “Sanofi/Genzyme Primed Subject Community For Campath’s Removal From Commercial Distribution” *The Pink Sheet*. August 27, 2012.

The commercial Campath product is a concentrate solution supplied in single use vials containing 30 mg/vial alemtuzumab. The dosing for Campath involves gradual escalation to a maximum dose of 30 mg administered 3 times per week for up to 12 weeks (total dose >1,000 mg). In contrast, the dosing regimen of alemtuzumab as used in clinical trials of MS, proposed for commercial use, involves 2 finite cycles (a 5-day cycle and a 3-day cycle) of alemtuzumab 12 mg/day, administered 12 months apart (total dose 96 mg). The differences between dosing regimens for subjects with B-CLL versus subjects with MS are shown in Table 3.

Table 3. Comparison of Dosing Regimens for Alemtuzumab in Multiple Sclerosis and B-CLL

Proposed Dosing Regimen for Alemtuzumab in MS	Approved Dosing Regimen for Campath in B-CLL
<p>Cycle 1: 12 mg/day administered by IV infusion for 5 consecutive days (60 mg total dose)</p> <p>Cycle 2: 12 mg/day administered by IV infusion for 3 consecutive days (36 mg total dose) 12 months following the initial treatment cycle</p>	<p><u>Recommended Dosing Regimen:</u></p> <ul style="list-style-type: none"> – Gradually escalate to the maximum recommended single dose of 30 mg. Escalation is required at initiation of dosing or if dosing is held ≥ 7 days during treatment. Escalation to 30 mg ordinarily can be accomplished in 3 – 7 days. <p><u>Escalation Strategy:</u></p> <ul style="list-style-type: none"> – Administer 3 mg daily until infusion reactions are \leq grade 2 – Administer 10 mg daily until infusion reactions are \leq grade 2 – Administer 30 mg/day 3 times per week on alternate days (e.g., Mon-Wed-Fri) – The total duration of therapy, including dose escalation, is 12 weeks (> 1,000 mg total dose)

Source: Pre-sBLA meeting background material. Table 1 on p. 17. Submitted to IND 010717 on 24 Oct 2011.

A comparison of the concentration and strength of the alemtuzumab drug products is shown in Table 4.

Table 4. Concentration and Strength of Alemtuzumab Drug Product as Used in MS and B-CLL

Product	Indication	Container	Fill Volume	Concentration	Strength	Packaging Configuration
Lemtrada ^a	MS (proposed)	2 mL glass vial	1.2 mL	10 mg/mL	12 mg/vial	1 vial/carton
Campath	B-CLL	2 mL glass vial	1 mL	30 mg/mL	30 mg/vial	1 or 3 vials/carton

^a Proposed trade name

Source: Pre-sBLA meeting background material. Table 2 on p. 17. Submitted to IND 010717 on 24 Oct 2011.

Reviewer comment: Depending on the intended indication, the dosage and strength of alemtuzumab drug products can vary. Use of alemtuzumab for an indication not intended may result in drug administration errors.

2.4 Important Safety Issues with Consideration to Related Drugs

Safety issues included as Boxed Warnings, Warnings, and/or Precautions in the Prescribing Information for disease-modifying medications approved for use in relapsing forms of MS are summarized below.

Table 5. Safety issues for disease-modifying medications approved for use in relapsing forms of multiple sclerosis

Brand Name	Generic Name	Safety Issues
Avonex	Interferon beta-1a	<p>Warnings:</p> <ul style="list-style-type: none"> • Depression and suicide • Anaphylaxis (rare) and other allergic reactions • Decreased peripheral blood counts in all cell lines, including rare pancytopenia and thrombocytopenia • Severe hepatic injury (rare), including hepatic failure, and asymptomatic transaminase elevation • Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD) <p>Precautions:</p> <ul style="list-style-type: none"> • Seizures – an increased rate of seizures was seen in Avonex-treated subjects in 2 placebo-controlled trials in MS • Cardiomyopathy and congestive heart failure – post-marketing cases were reported in subjects without known predisposition to these events • Autoimmune disorders – post-marketing cases of disorders including idiopathic thrombocytopenia, hyper- and hypothyroidism, and autoimmune hepatitis have been reported
Betaseron	Interferon beta-1b	<p>Warnings:</p> <ul style="list-style-type: none"> • Depression and suicide • Injection-site necrosis reported in 4% of subjects in controlled clinical trials • Anaphylaxis (rare) and other allergic reactions • Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD) <p>Precautions:</p> <ul style="list-style-type: none"> • Flu-like symptoms • Abortifacient potential

Brand Name	Generic Name	Safety Issues
Copaxone	Glatiramer acetate	<p>Warnings and Precautions:</p> <ul style="list-style-type: none"> • Immediate post-injection reaction in about 16% of exposed placebo-trial subjects (compared to 4% of placebo-treated subjects) with symptoms that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. These symptoms were generally transient and did not require treatment. • Chest pain (transient) • Lipoatrophy and skin necrosis at injection-sites • Potential effects on immune response
Extavia	Interferon beta-1b	<p>Warnings and Precautions:</p> <ul style="list-style-type: none"> • Depression and suicide • Injection-site necrosis reported in 4% of subjects in controlled clinical trials • Injection-site reactions (injection-site inflammation, pain, hypersensitivity, mass, or edema) in 78% of controlled clinical trial subjects • Anaphylaxis (rare) and other allergic reactions • Flu-like symptoms • Leukopenia • Hepatic enzyme elevation • Laboratory tests – in addition to tests normally required for monitoring subjects with MS, complete blood count and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests are recommended at regular intervals. Thyroid function tests are recommended every 6 months in subjects with thyroid dysfunction. • Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD)
N/A	Mitoxantrone*	<p>Boxed Warnings:</p> <ul style="list-style-type: none"> • May only be given into a freely flowing intravenous infusion. Severe injury may occur if there is extravasation during administration or if it is given subcutaneously, intramuscularly, intra-arterially, or intrathecally. • Bone marrow suppression, primarily nonlymphocytic leukopenia • Cardiotoxicity – potentially fatal congestive heart failure may occur during or after termination of therapy • Secondary acute myelogenous leukemia <p>Warnings:</p> <ul style="list-style-type: none"> • Safety in subjects with hepatic insufficiency has not been established • May cause fetal harm when given to pregnant women

Brand Name	Generic Name	Safety Issues
Rebif	Interferon beta-1a	<p>Warnings:</p> <ul style="list-style-type: none"> • Depression and suicide • Severe hepatic injury (rare), including hepatic failure, and asymptomatic transaminase elevation • Anaphylaxis (rare) and other allergic reactions • Albumin (a derivative of human blood) in lyophilized vials of Avonex carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease (CJD) <p>Precautions:</p> <ul style="list-style-type: none"> • Seizures – an increased rate of seizures has been seen with beta-interferons • Leukopenia • Worsening thyroid abnormalities • Possible abortifacient effects similar to other beta-interferons
Tysabri	Natalizumab	<p>Boxed Warning:</p> <ul style="list-style-type: none"> • Increased risk of Progressive Multifocal Leukoencephalopathy (PML) • Available only under a special restricted distribution program called the TOUCH Prescribing Program <p>Warnings and Precautions:</p> <ul style="list-style-type: none"> • Hypersensitivity reactions (including anaphylaxis) occurred at an incidence of <1% . Hypersensitivity reactions were more common in subjects with antibodies to Tysabri. • Immune system effects may increase the risk for infections. • Hepatotoxicity – clinically significant liver injury has been reported in the post-marketing setting. • Laboratory test abnormalities – Tysabri induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells.
Gilenya	Fingolimod	<p>Warnings and Precautions:</p> <ul style="list-style-type: none"> • Bradyarrhythmia and atrioventricular blocks following the first dose. • Dose-dependent reduction in peripheral lymphocyte count may increase risk of infections. • Macular edema • Respiratory Effects – dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) • Elevation of liver enzymes • Fetal harm - women of childbearing potential should use effective contraception during and for 2 months after stopping Gilenya treatment • Increase in blood pressure
Aubagio	Teriflunomide	Warnings and Precautions:

Brand Name	Generic Name	Safety Issues
		<ul style="list-style-type: none"> • Hepatotoxicity • Teratogenicity • Decreased white blood cell counts and increased risk of infection • Peripheral neuropathy • Acute renal failure and hyperkalemia • Rare skin reactions in leflunomide subjects • Blood pressure increase • Interstitial lung disease reported with leflunomide
Tecfidera	Dimethyl fumarate	Warnings and Precautions: <ul style="list-style-type: none"> • Lymphopenia • Flushing

*Mitoxantrone is only available in generic form.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The initial development of alemtuzumab was conducted under the sponsorship of Burroughs Wellcome (BW). BW developed the original manufacturing process and conducted early nonclinical toxicology studies in support of clinical studies in B-cell chronic lymphocytic leukemia (B-CLL). Eventually, BW (then Glaxo-Wellcome) chose to discontinue development of alemtuzumab and through various acquisitions the sponsorship of the program was finally transferred to Genzyme Corporation. Genzyme assumed sponsor responsibility of IND application 10717 from Ilex Oncology when Ilex was acquired in 2004.

Campath (alemtuzumab) was approved in the United States on May 7, 2001 under Biologics License Application (BLA) 103948 for the treatment of B-CLL. An IND application for alemtuzumab in the treatment of multiple sclerosis (MS) was submitted on October 8, 2002 (IND 10717).

In 2005, 3 cases of immune thrombocytic purpura (ITP), including a fatal index case, were identified during an interim data review of the Phase 2 study CAMMS223. Upon review of these events, the Data Safety Monitoring Committee recommended that dosing be suspended and Genzyme adopted this recommendation. The Food & Drug Administration (FDA) was immediately notified relative to the proposed dosing suspension and a clinical hold for IND 10717 was issued. With the submission of the randomized Phase 3 clinical study protocols (CAMMS323 and CAMMS32400507) under the SPA procedure, FDA lifted the clinical hold for IND 10717 (May 2007), after an ITP monitoring program was developed.

The efficacy supplement for the evaluation of alemtuzumab for MS was initially submitted May 30, 2012. Because of issues with the information provided and the data presentation, a refuse to file letter was issued August 27, 2013. The sBLA was resubmitted on November 27, 2012.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

After FDA issued a Refuse to File letter in response to the original May 30, 2012 submission for sBLA 103948, issues with the information provided and data presentation were addressed by Genzyme. The November 27, 2012 resubmission of sBLA 103948 was accepted for filing. During the course of reviewing the resubmission, some significant deficiencies became apparent. Discussion of autoimmune conditions in studies of MS was limited to the following topics: Thyroid disorders, Immune Thrombocytopenia (ITP), Other autoimmune cytopenias, and Nephropathies including Anti-Glomerular Basement Membrane Disease. Other autoimmune conditions, identified in the published literature, were not discussed in the submission. Also, information on vital sign measurements during and after alemtuzumab infusion was not routinely collected; this represented a lack of information necessary to assess potential morbidity and mortality related to infusion reactions in the postmarket setting.

3.2 Compliance with Good Clinical Practices

The FDA Division of Scientific Investigations consultation report (including reports on-site inspections) is pending at the time of this review.

3.3 Financial Disclosures

Discussion of financial disclosures is located in the review of clinical efficacy by John Marler, M.D..

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to the Chemistry review.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the pharmacology/toxicology review.

4.4 *Clinical Pharmacology*

For additional information on this topic, the reader is referred to the Clinical Pharmacology review.

4.4.1 *Mechanism of Action*

Alemtuzumab binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages. Alemtuzumab acts through antibody-dependent cellular cytotoxicity and complement-mediated lysis following cell surface binding to B and T lymphocytes. The mechanism by which alemtuzumab exerts its therapeutic effects in MS is unknown.

4.4.2 *Pharmacodynamics*

Alemtuzumab depletes circulating T and B lymphocytes after each treatment course with the lowest observed values occurring 1 month after a course of treatment (the earliest post-treatment time point of observation). Lymphocytes repopulate over time with B cell recovery usually completed within 6 months. T lymphocyte counts rise more slowly towards normal and generally do not return to baseline by 12 months post treatment. Approximately 40% of subjects had total lymphocyte counts reaching the lower limit of normal (LLN) by 6 months after each treatment course and approximately 80% of subjects had total lymphocyte counts reaching the LLN by 12 months after each course.

4.4.3 *Pharmacokinetics*

Information on pharmacokinetics listed below is obtained from the prescribing information proposed by the Sponsor, submitted November 27, 2013.

The pharmacokinetics of LEMTRADA were evaluated in a total of 216 subjects with RRMS who received either 12 mg/day or 24 mg/day for 5 consecutive days, followed by 3 consecutive days 12 months following the initial treatment course. Serum concentrations increased with each consecutive dose within a treatment course, with the highest observed concentrations occurring following the last infusion of a treatment course. Administration of 12 mg/day resulted in a mean C_{max} of 3014 ng/mL on Day 5 of the initial treatment course, and 2276 ng/mL on Day 3 of the second treatment course. The alpha half-life approximated 2 days and was comparable between courses leading to low or undetectable serum concentrations within approximately 30 days following each treatment course.

The population pharmacokinetics of LEMTRADA were best described by a linear, 2 compartment model. Systemic clearance decreased with lymphocyte count due to loss of CD52 antigen in the periphery; however, the decrease from Course 1 to Course 2 was less than 20%. The central volume of distribution was proportional to body weight, and approximated extracellular fluid volume (14.1

L), suggesting that LEMTRADA is largely confined to the blood and interstitial space. No effect of age, race, or gender on the pharmacokinetics of LEMTRADA was observed.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The table below lists clinical studies of in human subjects with MS. No studies of alemtuzumab performed on healthy human subjects were included in this sBLA.

Reviewer comment: The table below is an excerpt of Sponsor Table 1 in sBLA 103948 Section 5.2. While the table describes studies as rater-blinded, several factors contributed to unblinding of raters. Details are discussed in the review of clinical efficacy by John Marler, MD.

Table 6. Listing of clinical studies. (Excerpt of Sponsor Table 1 in Section 5.2)

Type of Study	Study Identifier	Location of Report	Objective(s) of Study	Study Design and Type of Control	Test product(s) Dosage regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Follow-up	Study Status; Type of Report
PK	Population Pharmacokinetic/ Pharmacodynamic Report for Alemtuzumab in Multiple Sclerosis Using Pooled Data from Selected Clinical Studies	5.3.3.5	Population PK/PD analysis	N/A	Alemtuzumab IV 12 mg/day or 24 mg/day for 5 consecutive days at Month 0 (60 mg or 120 mg total dose) -and- for 3 consecutive days at Month 12 (36 mg or 72 mg total dose) and optionally at Month 24 or thereafter for patients in CAMMS223 only	Subgroup of patients from CAMMS223, CAMMS323, and CAMMS324	Patients with RRMS (including naïve patients and those who have relapsed on prior MS therapy)	Phase 3 – 2 years follow-up; Phase 2 - 3 years follow-up (at time of primary analysis)	Population PK/PD Analysis Report

Type of Study	Study Identifier	Location of Report	Objective(s) of Study	Study Design and Type of Control	Test product(s) Dosage regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Follow-up	Study Status; Type of Report
Efficacy, safety, and PK	CAMMS223	5.3.5.1	Efficacy, safety, tolerability, and PK of 2 dose levels of alemtuzumab; dose selection; safety and efficacy of retreatment	Phase 2, randomized, rater-blinded, 3-arm, active-controlled	Alemtuzumab IV 12 mg/day or 24 mg/day for 5 consecutive days at Month 0 (60 mg or 120 mg total dose) and for 3 consecutive days at Month 12 (36 mg or 72 mg total dose) and optionally at Month 24 and during the retreatment period of the study.	334 randomized (223 alemtuzumab; 111 IFNB-1a)	Treatment-naïve patients with RRMS	3 years – primary analysis Up to 7 years total follow-up	Complete; Full CSR
Efficacy, safety, and PK	CAMMS323	5.3.5.1	Safety and efficacy	Phase 3, randomized, rater-blinded, 2-arm, active-controlled	Alemtuzumab IV 12 mg/day for 5 consecutive days at Month 0 (60 mg total dose) and for 3 consecutive days at Month 12 (36 mg total dose).	581 randomized (386 alemtuzumab; 195 IFNB-1a)	Treatment-naïve patients with RRMS	2 years	Complete; Full CSR

Type of Study	Study Identifier	Location of Report	Objective(s) of Study	Study Design and Type of Control	Test product(s) Dosage regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Follow-up	Study Status; Type of Report
Efficacy, safety, PK	CAMMS32400507 (CAMMS324)	5.3.5.1	Safety and efficacy	Phase 3, randomized, rater-blinded, 3-arm, active-controlled	Alemtuzumab IV 12 mg/day for 5 consecutive days at Month 0 (60 mg total dose) and for 3 consecutive days at Month 12 (36 mg total dose). or Alemtuzumab IV 24 mg/day for 5 consecutive days at Month 0 (120 mg total dose) and for 3 consecutive days at Month 12 (72 mg total dose).	840 randomized (609 alemtuzumab; 231 IFNB-1a)	Patients with RRMS who relapsed on prior MS therapy (IFNB-1a or glatiramer acetate)	2 years	Complete; Full CSR
Efficacy, safety	CAMMS03409	5.3.5.2	Safety and efficacy of alemtuzumab up to 5 years after first treatment	Open-label, rater-blinded, uncontrolled extension study	<u>Patients previously treated with alemtuzumab:</u> Alemtuzumab IV 12 mg/day for 3 consecutive days (36 mg total	1320 enrolled as of 31 December 2011	Eligible patients from CAMMS223, CAMMS323, and CAMMS324	Up to 3 years	Ongoing; Study protocol included

Type of Study	Study Identifier	Location of Report	Objective(s) of Study	Study Design and Type of Control	Test product(s) Dosage regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Follow-up	Study Status; Type of Report
					dose) as needed (i.e., upon documented evidence of resumed disease activity). <u>Patients previously treated with IFNB-1a:</u> Alemtuzumab IV 12 mg/day for 5 consecutive days (60 mg total dose) at study entry and for 3 consecutive days (36 mg total dose) 12 months later and for any subsequent as-needed treatment.				

Type of Study	Study Identifier	Location of Report	Objective(s) of Study	Study Design and Type of Control	Test product(s) Dosage regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Follow-up	Study Status; Type of Report
Semen Substudy	CARE-MS Semen Substudy of CAMMS323 and CAMMS32400507	5.3.5.3	Analysis of sperm count, motility, morphology, agglutination, and anti-sperm antibodies in a subgroup of male patients participating in CAMMS323 or CAMMS324	N/A	Alemtuzumab IV 12 mg/day for 5 consecutive days at Month 0 (60 mg total dose) and for 3 consecutive days at Month 12 (36 mg total dose) for patients participating in CAMMS323 and CAMMS324 or Alemtuzumab IV 24 mg/day for 5 consecutive days at Month 0 (120 mg total dose) and for 3 consecutive days at Month 12 (72 mg total dose) for patients participating in CAMMS324	16 enrolled (13 alemtuzumab, 3 IFNB-1a)	Subgroup of male patients with RRMS who were treatment naïve or who relapsed on prior MS therapy (IFNB-1a or glatiramer acetate)	2 years	Complete; Full substudy report

Source: Table 1 in Section 5.2 Tabular listing of clinical studies. Submitted to sBLA 10394 on November 27, 2013.

5.2 *Review Strategy*

The clinical review of sBLA 103948 evaluating alemtuzumab for treatment of MS is divided into a review of clinical efficacy (by John Marler, MD) and this review of clinical safety.

Information submitted as part of sBLA 103948, as well as information on postmarketing safety reports and relevant published literature, are discussed in this review.

5.3 *Discussion of Individual Studies/Clinical Trials*

Please refer to Section 5.1 for a summary of individual trials.

6 **Review of Efficacy**

Please refer to the review of clinical efficacy by John Marler, M.D..

7 **Review of Safety**

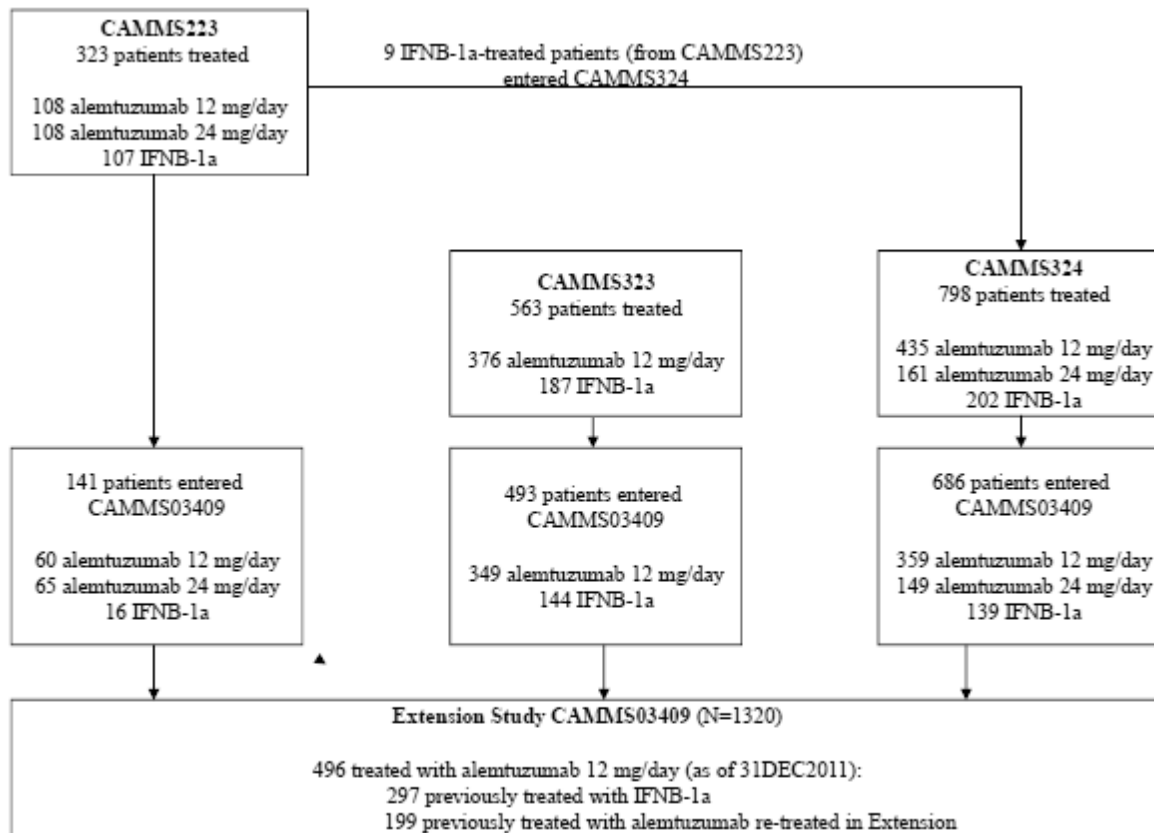
7.1 *Methods*

7.1.1 *Studies/Clinical Trials Used to Evaluate Safety*

The safety database supporting this application contains data from 1,684 subjects with relapsing remitting multiple sclerosis (RRMS) who received IV alemtuzumab or subcutaneous (SC) IFNB-1a as an active control in Genzyme-sponsored clinical studies. This includes 323 subjects treated in the completed Phase 2 study (CAMMS223) and 1,361 subjects treated in the completed Phase 3 studies (CAMMS323 and CAMMS324). Nine subjects treated with IFNB-1a in CAMMS223 who met study eligibility criteria subsequently enrolled and received treatment in CAMMS324.

The alemtuzumab safety database contains data from 1,485 alemtuzumab-treated subjects: 972 subjects in the Phase 3 studies, 216 subjects in the Phase 2 study, and 297 subjects who had received IFNB-1a in a prior study and then received alemtuzumab in the Extension Study (CAMMS03409). As of 31 December 2011 (the data cutoff date for ISS analyses), 1,320 subjects from the 3 completed studies were enrolled in the ongoing Extension Study to receive further follow-up, with or without treatment/re-treatment with alemtuzumab. A schematic illustrating the numbers of subjects treated by study in the clinical development program is provided in Sponsor Figure 3-1.

Figure 1. Sponsor Figure 3-1. Schematic of Alemtuzumab Treatment in Clinical Studies



Source: Tables 4.1.1 and 4.2.2, CAMMS223 CSR Table 14.1.2.1, CAMMS323 CSR Table 14.1.1.1.1, and CAMMS324 CSR Table 14.1.1.1.1

The majority of subjects (824 of 1320; 62.4%) in Extension Study CAMMS03409 received no alemtuzumab treatment and only received follow-up.

Reviewer comment: Because the majority of extension study subjects did not receive alemtuzumab treatment, the cumulative number of person-years of follow-up in Genzyme trials differs from the cumulative number of person-years of treatment. In this review, the incidence of adverse events is described in terms of the number of person-years of follow-up.

Table 7 lists the total number of cumulative person-years of follow-up and the number of alemtuzumab treatment cycles as of April 20, 2013.

Table 7. Total Number of Person-Years of Follow-up and number of Alemtuzumab Treatment Cycles. All alemtuzumab-treated subjects (Pool C) as of April 20, 2013

	Alemtuzumab 12 mg/day (N=1217)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1486)
All Alemtuzumab-Treated Subjects	1217	269	1486
Total Number of Person-Years	4519.5	1354.9	5874.3
Total Number of Alemtuzumab Treatment Cycles	2740	664	3404
All U.S. Alemtuzumab-Treated Subjects	420	135	555
Total Number of Person-Years	1608.0	665.2	2273.2
Total Number of Alemtuzumab Treatment Cycles	945	328	1273

Source: Table 3.2.4.2.1 in Appendix 13 submitted to sBLA 103948 on May 14, 2013.

Details on the individual studies are provided in Sponsor Table 3-1.

Reviewer comment: While Sponsor Table 3-1 describes studies as rater-blinded, several factors contributed to unblinding of raters. Details are discussed in the review of clinical efficacy by John Marler, MD.

Table 8. Sponsor Table3-1. Genzyme-Sponsored Clinical Studies of Alemtuzumab in Multiple Sclerosis

Protocol No. (Status)	Study Population	Total Number of Patients	Study Design and Key Objective	Test Product(s), Dosage Regimen(s), Route of Administration	Number of Patients Treated by Arm	Duration of Follow Up
Phase 2 Study						
CAMMS223 (completed)	Treatment-naïve patients with early, active RRMS	333	Randomized, open-label, rater-blinded, parallel-group to evaluate safety and efficacy	Alemtuzumab IV 12 mg/day for 5 consecutive days (60 mg total dose) at Month 0 and for 3 consecutive days (36 mg total dose) at Month 12 and per Investigator's discretion at Month 24 or later	108	Up to 7 years for alemtuzumab- treated patients;
				Alemtuzumab IV 24 mg/day for 5 consecutive days (120 mg total dose) at Month 0 and for 3 consecutive days (72 mg total dose) at Month 12 and per Investigator's discretion at Month 24 or later. Some patients received a third cycle of 12 mg/day for 3 consecutive days (36 mg total dose) instead. ^a	108	
				IFNB-1a SC 3 times weekly (sponsor supplied study drug for 3 years)	107	

Protocol No. (Status)	Study Population	Total Number of Patients	Study Design and Key Objective	Test Product(s), Dosage Regimen(s), Route of Administration	Number of Patients Treated by Arm	Duration of Follow Up
Phase 3 Studies						
CAMMS323 (completed)	Treatment-naïve patients with RRMS	563	Rater-blinded, randomized, parallel-group, pivotal study to evaluate safety and efficacy	Alemtuzumab IV 12 mg/day for 5 consecutive days (60 mg total dose) at Month 0 and for 3 consecutive days (36 mg total dose) at Month 12	376	2 years from start of study treatment
				IFNB-1a SC 3 times weekly	187	
CAMMS324 (completed)	Patients with RRMS who had experienced an inadequate response to prior MS therapy (IFNB-1a or glatiramer acetate)	798 (includes 9 patients who had received IFNB-1a in CAMMS223; see Appendix 14.1)	Rater-blinded, randomized, parallel-group, pivotal study to evaluate safety and efficacy	Alemtuzumab IV 12 mg/day for 5 consecutive days (60 mg total dose) at Month 0 and for 3 consecutive days (36 mg total dose) at Month 12	435	2 years from start of study treatment
				Alemtuzumab IV 24 mg/day for 5 consecutive days (120 mg total dose) at Month 0 and for 3 consecutive days (72 mg total dose) at Month 12 ^b	161	
				IFNB-1a SC 3 times weekly	202	
Extension Study						
CAMMS03409 (ongoing)	Eligible patients from studies CAMMS223, CAMMS323, and CAMMS324	1320 ^c	Open-label, rater-blinded, uncontrolled to evaluate long-term safety and efficacy	Patients previously treated with IFNB-1a: Alemtuzumab IV 12 mg/day for 5 consecutive days (60 mg total dose) at study entry and for 3 consecutive days (36 mg total dose) 12 months later and for any subsequent as-needed treatment	297 treated of 1320 enrolled ^c (Patients previously treated with IFNB-1a)	4 years from enrollment
				Patients previously treated with alemtuzumab: Alemtuzumab IV 12 mg/day for 3 consecutive days (36 mg total dose) as needed (i.e., only in the setting of resumed disease activity).	199 re-treated of 1320 enrolled ^c (Patients previously treated with alemtuzumab)	

a. With Amendment 8 to CAMMS223, the 24 mg/day dose was no longer used, so patients in the 24 mg/day alemtuzumab treatment group who were to be re-treated received 12 mg/day alemtuzumab.

b. With Amendment 2 to CAMMS324, the 24 mg/day alemtuzumab treatment group was closed to newly-enrolling patients.

c. Enrollment in CAMMS03409 as of 31 December 2011.

No. = number; RRMS = relapsing-remitting multiple sclerosis; IFNB-1a = interferon beta-1a; IV = intravenous; MS = multiple sclerosis

Source: CAMMS223 CSR; CAMMS323 CSR; CAMMS324 CSR, CAMMS03409 Protocol; and Table 4.2.2.

Source: Table 3-1, ISS pp. 39-41

7.1.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 12.1 was used for coding AEs in CAMMS223, whereas the MedDRA version 13.1 was used for coding AEs in the ISS. Consequently, the results might be slightly different between the CAMMS223 Final CSR analysis and the CAMMS223 ISS analysis. MedDRA version 13.1 was used for coding AEs in CAMMS323 and CAMMS324.

Verbatim terms provided by investigators and subjects were compared to Preferred Terms coded by the Sponsor. Notable cases in which this reviewer disagreed with the Sponsor's Preferred Term mapping will be discussed in each relevant section in this review.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Table 9 describes the Integrated Summary of Safety subject pools analyzed by the Sponsor. This review focuses on Pool C (all alemtuzumab-treated subjects), because it is the most inclusive pool which includes controlled trial data and extension study data. This review also focuses on Pool E (all active-controlled studies), because it includes all of the active-controlled data and allows for comparisons between alemtuzumab and IFN β -1a.

Table 9. Sponsor ISS Table 3-6. Studies Contributing Safety Data and Analysis Pools

Phase	Protocol Number	Title	Total Treated	All Active-Controlled Studies (Pools A / E) (N=1684)	Phase 3 Studies (Pool B) (N=1361)	Treatment-Naïve Patients (Pools D / F) (N=886)	All Alemtuzumab Treated Patients (Pool C) (N=1485)
2	CAMMS223	A Phase 2, Randomized, Open-Label, Three-Arm Study Comparing Low- and High-Dose Alemtuzumab and High-Dose Subcutaneous Interferon Beta-1a (Rebif®) in Patients With Early, Active Relapsing-Remitting Multiple Sclerosis	323	X		X	X
3	CAMMS323	A Phase 3 Randomized, Rater-Blinded Study Comparing Two Annual Cycles of Intravenous Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif®) in Treatment-Naïve Patients with Relapsing-Remitting Multiple Sclerosis	563	X	X	X	X
3	CAMMS324	A Phase 3, Randomized, Rater- and Dose-Blinded Study Comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif®) in Patients with Relapsing-Remitting Multiple Sclerosis Who Have Relapsed on Therapy	798 ^a	X	X		X
Extension	CAMMS03409	An Extension Protocol for Multiple Sclerosis Patients who Participated in Genzyme-Sponsored Studies of Alemtuzumab	496				X

a. Nine (9) patients who received IFNB-1a in study CAMMS223 subsequently enrolled in study CAMMS324 and were randomized to either alemtuzumab (5 patients) or IFNB-1a (4 patients) (see Appendix 14.1).

Source: Sponsor Table 3-6, ISS p. 126-127.

Pools A and D include only 2-year data and omit year 3 data from CAMMS323 and CAMMS324; due to the post-hoc nature of the Pool A and Pool D data and their omission of important year 3 safety data, analyses of Pools A and D are not covered in this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Adequacy of Overall Clinical Experience

Sponsor Table 13.2.4 summarizes exposure to alemtuzumab in all active-controlled studies (Pool E). A total of 1188 subjects were exposed to alemtuzumab in these studies. A total of 919 and 874 subjects completed 1 and 2 annual cycles of alemtuzumab 12 mg/day, respectively.

Table 10. Sponsor Table 13.2.4. Exposure to Alemtuzumab (Pool E)

TABLE 13.2.4
 Exposure to Alemtuzumab
 Alemtuzumab-Treated Patients
 Pool E

	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
Cycle 1 (Month 0), n(%)	919 (100.0)	269 (100.0)	1188 (100.0)
Complete	907 (98.7)	261 (97.0)	1168 (98.3)
Partial	12 (1.3)	8 (3.0)	20 (1.7)
5 infusions in 5 calendar days	878 (95.5)	253 (94.1)	1131 (95.2)
5 infusions in 5-7 calendar days	886 (96.4)	254 (94.4)	1140 (96.0)
Cycle 2 (Month 12), n(%)	891 (97.0)	260 (96.7)	1151 (96.9)
Complete	874 (98.1)	257 (98.8)	1131 (98.3)
Partial	17 (1.9)	3 (1.2)	20 (1.7)
3 infusions in 3 calendar days	861 (96.6)	253 (97.3)	1114 (96.8)
3 infusions in 3-5 calendar days	869 (97.5)	254 (97.7)	1123 (97.6)
Cycle 3 (Month 24), n(%)	24 (2.6)	22 (8.2)	46 (3.9)
Complete	24 (100.0)	21 (95.5)	45 (97.8)
Partial	0	1 (4.5)	1 (2.2)
3 infusions in 3 calendar days	24 (100.0)	21 (95.5)	45 (97.8)
3 infusions in 3-5 calendar days	24 (100.0)	21 (95.5)	45 (97.8)

Source: P. 174 of ISS Appendix 14.4.10. Link to table located on ISS p. 157.

Sponsor Table 13.2.1 summarizes the follow-up duration in all active-controlled studies (Pool E). A total of 910 subjects had ≥ 18 months of follow-up.

Table 11. Sponsor Table 13.2.1. Follow-Up Duration (Pool E)

TABLE 13.2.1
Follow-Up Duration
Pool E

	SC IFNB-1a	Alemtuzumab 12 mg/day	Alemtuzumab 24 mg/day	Alemtuzumab Pooled	Total
Patients treated	496	919	269	1188	1684
Months of follow-up					
Mean (SD)	24.4 (6.97)	25.3 (3.98)	28.7 (6.15)	26.1 (4.77)	25.6 (5.56)
Median	24.0	24.1	24.4	24.2	24.1
Min, Max	0.1, 39.1	8.9, 38.5	10.0, 37.6	8.9, 38.5	0.1, 39.1
Q1, Q3	23.8, 24.5	24.0, 24.4	24.0, 36.0	24.0, 24.5	24.0, 24.5
Months of follow-up, n(%)					
0 - <6	17 (3.4)	0	0	0	17 (1.0)
6 - <12	19 (3.8)	1 (0.1)	2 (0.7)	3 (0.3)	22 (1.3)
12 - <18	17 (3.4)	8 (0.9)	1 (0.4)	9 (0.8)	26 (1.5)
≥18	443 (89.3)	910 (99.0)	266 (98.9)	1176 (99.0)	1619 (96.1)
Completed CAMMS323/324 or initial 3 years on CAMMS223	398 (80.2)	878 (95.5)	251 (93.3)	1129 (95.0)	1527 (90.7)
Total Person-years	1007.57	1938.21	642.25	2580.46	3588.03

Source: P. 14 of ISS Appendix 14.4.10. Link to table located on ISS p. 157.

Reviewer comment: In the opinion of this reviewer, the doses and duration of exposure were adequate to assess most safety issues. Long-term safety issues, including risk of malignancy, will require additional follow-up for more complete assessment.

Inclusion and Exclusion Criteria

Table 12 lists the eligibility criteria used in the CAMMS studies (Genzyme studies of alemtuzumab for treatment of MS).

Tables 13 and 14 list the number of subjects who failed screening and the reasons for screening failure for CAMMS323 and CAMMS324, respectively. Information on screened subjects was not recorded on the CAMMS223 study case report form; therefore, the Sponsor was unable to provide reasons for screen failure.

In CAMMS323, 152 of 733 (20.7%) of screened subjects failed screening. In CAMMS324, 206 of 1046 (19.7%) of screened subjects failed screening. The most common reasons for failing screening in both studies were: 1) B or T cell counts below acceptable limits (6.7% of screened subjects); and 2) past or present hepatitis infection (3.8% of screened subjects).³⁶

³⁶ Percentages refer to the percentage of screened subjects in CAMMS323 and CAMMS324 combined.

Table 12. Inclusion and Exclusion criteria for CAMMS studies

Inclusion Criteria	CAMMS223	CAMMS323	CAMMS324	CAMMS03409
Signed informed consent form (ICF)	X	X	X	
Age: <ul style="list-style-type: none"> Male or non-pregnant, non-lactating female patients, 18 to 50 years of age (inclusive) as of signing the ICD^a Age 18 to 50 years old (inclusive) as of the date the ICF is signed Age 18 to 55 years old (inclusive) as of the date the ICF is signed^b 	X	X	X	
Diagnosis of MS: <ul style="list-style-type: none"> Diagnosis of MS per McDonald's update of the Poser criteria, including cranial MRI consistent with those criteria Diagnosis of MS per update of McDonald criteria, and cranial MRI scan demonstrating white matter lesions attributable to MS within 5 years of Screening Diagnosis of MS per update of McDonald criteria 	X	X	X	
Onset of MS symptoms: <ul style="list-style-type: none"> Onset of first MS symptoms within 3 years prior to screening as of signing the ICD^a Onset of MS symptoms (as determined by a neurologist, either at present or retrospectively) within 5 years of the date the ICF is signed^c Onset of MS symptoms (as determined by a neurologist, at present or retrospectively) within 10 years of the date the ICF is signed^d 	X	X	X	
EDSS score: <ul style="list-style-type: none"> EDSS score 0.0 to 3.0 (inclusive) at Screening^{a,f} EDSS score 0.0 to 5.0 (inclusive) at Screening^f 	X	X	X	
Prior clinical episodes or MS attacks: <ul style="list-style-type: none"> At least 2 completed clinical episodes of MS in the 2 years prior to study entry (ie, the initial event if within 2 years of study entry plus ≥ 1 relapse, or ≥ 2 relapses if the initial event was between 2 and 3 years prior to study entry)^g ≥ 2 MS attacks (first episode or relapse) occurring in the 24 months prior to the date the ICF is signed, with ≥ 1 attack in the 12 months prior to the date the ICF is signed, with objective neurological signs confirmed by a physician, nurse practitioner, or other Genzyme-approved health-care provider. The objective signs may be identified retrospectively.^{h,i} ≥ 1 MS attack (relapse) during treatment with a beta interferon therapy or glatiramer acetate after having been on that therapy for ≥ 6 months within 10 years of the date the ICF is signed^j 	X	X	X	

MRI: <ul style="list-style-type: none"> • ≥ 1 enhancing lesion on any 1 of the up to 4 screening gadolinium-enhanced MRI brain scans during a maximum 3-month run-in period (inclusive of the Month 0 baseline scan)^k • MRI scan demonstrating white matter lesions attributable to MS and meeting at least 1 of the following criteria, as determined by the neurologist or a radiologist^l <ul style="list-style-type: none"> ○ ≥ 9 T2 lesions at least 3 mm in any axis ○ a gadolinium-enhancing lesion at least 3 mm in any axis plus ≥ 1 brain T2 lesions ○ a spinal cord lesion consistent with MS plus ≥ 1 brain T2 lesions 	X		X	
Received alemtuzumab in CAMMS323 or CAMMS324, completed the 2-year study period, and have NOT subsequently received DMTs (other than glatiramer acetate or interferon beta) ^{m,n} OR Received SC IFNB-1a in CAMMS323 or CAMMS324, completed the 2-year study period, and have NOT subsequently received alternative DMTs (other than glatiramer acetate or another interferon beta) ^{m,n} OR Participated in CAMMS223				X

^a In CAMMS223-A2 added "as of signing ICD".

^b In CAMMS324-A1 changed "50" to "55".

^c In CAMMS323-A2 added "either at present or retrospectively" and changed "within 5 years of screening" to "within 5 years of the date the ICF is signed".

^d In CAMMS324-A1 added "at present or retrospectively" and changed "within 5 years of screening" to "within 10 years of the date the ICF is signed".

^e CAMMS223: EDSS score at screening and baseline visits. "Baseline visits" added to inclusion criteria in CAMMS223-A1.

^f In CAMMS323-A2 and CAMMS324-A1 added "at screening".

^g In CAMMS223-A2 added "completed" prior to "clinical episodes".

^h In CAMMS323-A1 added "(first episode or relapse)" after " ≥ 2 MS attacks".

ⁱ In CAMMS323-A2 and CAMMS324-A1 changed "prior to screening" to "prior to the date the ICF is signed" and added "nurse practitioner, or other Genzyme-approved health-care provider. The objective signs may be identified retrospectively".

^j In CAMMS324-A1 changed "at least 6 months; relapses that occur within 6 months of initiating treatment with interferon beta or glatiramer acetate do not qualify as a relapse during treatment" to " ≥ 6 months within 10 years of the date the ICF is signed".

^k In CAMMS223-A1 added "brain" after "MRI" and "a maximum" prior to "3-month run in period".

^l In CAMMS324-A1 deleted "treating" before "neurologist" and added "or a radiologist".

^m Criteria mean that patients who were enrolled in CAMMS323 or CAMMS324 but either did not complete the 2-year study period or went on to receive non-study drug DMTs (other than glatiramer acetate or interferon beta) after randomization are not eligible for inclusion in the Extension Study (CAMMS03409). This clarification included in CAMMS03409-A1.

^a Patients who enrolled in CAMMS324 after participation in CAMMS223 must meet either inclusion criteria to be eligible for inclusion in the Extension Study (CAMMS03409). This clarification included in CAMMS03409-A1.

Note: In CAMMS323-A2 and CAMMS324-A1 an additional inclusion criterion was added ["Neurologically stable for the 30 days prior to the date of the ICF is signed (eg, no relapse)"]. This criterion was subsequently deleted in CAMMS323-A3 and CAMMS324-A2.

Exclusion Criteria	CAMMS223	CAMMS323	CAMMS324	CAMMS03409
Participation in another clinical study/trial: <ul style="list-style-type: none"> Patients currently participating in a clinical trial of an experimental or unapproved/unlicensed therapy^a Current participation in another clinical study Current participation in another clinical study or previous participation in CAMMS323^b Ongoing participation in any other investigational study, unless approved by Genzyme^{c,d,e} 	X	X	X	X
Previous treatment: <ul style="list-style-type: none"> Previous immunotherapy for MS other than steroids, including treatment with interferons, IV immunoglobulin, glatiramer acetate, and mitoxantrone^f Previous treatment with mitoxantrone, cyclophosphamide, cladribine, rituximab or any other immunosuppressant or cytotoxic therapy (other than steroids)^g Exposure to azathioprine, cladribine, cyclophosphamide, cyclosporine A, methotrexate, or any other immunosuppressive agent other than systemic corticosteroid treatment Treatment with natalizumab, methotrexate, azathioprine, or cyclosporine in the past 6 months. Patients who received one of these medications more than 6 months before the date the ICF is signed may be eligible for study entry if approval is granted by Genzyme^g Received treatment with a monoclonal antibody for any reason^h Previous treatment with any investigational medication, ie drug has not been approved at any dose or for any indication (Prior treatment with herbal medications or nutritional supplements is permitted)ⁱ 	X	X (including alemtuzumab and natalizumab) X X X	X X X (unless approval granted by Genzyme and patient completes any required washout) ^j	

Other forms of MS: <ul style="list-style-type: none"> Patients who, in the opinion of the Investigator, have any form of MS other than relapsing-remitting^a Any progressive form of MS 	X		X	
History of malignancy: <ul style="list-style-type: none"> History of thyroid carcinoma (previous thyroid adenoma is acceptable and is not to be considered an exclusion criterion) History of malignancy, except basal skin cell carcinoma^{d,k} 	X X (in which situation the patient is eligible only if disease-free for ≥5 years)	X	X	X
Disability or other illness: <ul style="list-style-type: none"> Any disability acquired from trauma or another illness that, in the opinion of the Investigator, could interfere with evaluation of disability due to MS Any other illness or infection (latent or active) that, in the Investigator's opinion, could be exacerbated by either study medication^l 	X	X	X	
<ul style="list-style-type: none"> Medical, psychiatric, cognitive, or other conditions that, in the Investigator's opinion, compromise the patient's ability to understand the patient information, to give informed consent, to comply with the trial protocol, or to complete the study 		X	X	
<ul style="list-style-type: none"> Epileptic seizures that are not adequately controlled by treatment^d 	X	X	X	X
Allergies/Hypersensitivity: <ul style="list-style-type: none"> History of anaphylaxis following exposure to humanized monoclonal antibodies Previous hypersensitivity reaction to any immunoglobulin product^m Known allergy or intolerance to interferon beta, human albumin, or mannitol Intolerance of pulsed corticosteroids, especially a history of steroid psychosis^d 	X X	X X X	X X X	X

Laboratory tests: <ul style="list-style-type: none"> Confirmed platelet count <LLN of the evaluating laboratory at Screening or documented at <100,000/μL within the past year on a sample without platelet clumping^a Abnormal CD4 count or significantly abnormal thyroid function; presence of anti-TSH receptor antibodies Presence of anti-thyroid stimulating hormone (TSH) receptor (TSHR) antibodies (ie, above LLN)^o CD4+ cell count (absolute CD3+CD4+) < lower limit of normal (LLN) at Screening^p CD8+ cell count (absolute CD3+CD8+) <LLN at Screening^q B-cell count (absolute CD19+) <LLN at Screeningⁱ CD4+, CD8+, or CD19+ (ie, absolute CD3+CD4+, CD3+CD8+, or CD19+/mm³) count <LLN at Screening; if abnormal cell count(s) return to within normal limits, eligibility may be reassessed^f Absolute neutrophil count <LLN at Screening^{is} 	X	X	X	
Presence of a monoclonal paraprotein Seropositive for Trypanosoma cruzi or the Human T-lymphotropic virus type I or type II (HTLV-I/II) (testing required in endemic regions only). Guidance on region-specific testing recommendations and patient eligibility is provided in the SOM	X	X	X	
Bleeding disorders: <ul style="list-style-type: none"> Known bleeding disorder (eg, dysfibrinogenemia, factor IX deficiency, hemophilia, Von Willebrand's disease, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency)^t or therapeutic anticoagulation (CAMMS03409 ONLY)^d 		X	X	X
Autoimmune disease: <ul style="list-style-type: none"> Personal history of clinically significant autoimmune disease (eg, inflammatory bowel disease, diabetes, lupus, severe asthma) Personal history of thyroid autoimmune disease 	X			
	X			

<ul style="list-style-type: none"> Significant autoimmune disease including but not limited to: immune cytopenias, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease, severe psoriasis^{d,t} 		X	X	X (or anti-GBM disease [also known as Goodpasture's disease])
Infection: <ul style="list-style-type: none"> Active infection, eg, deep-tissue infection, that the Investigator considers sufficiently serious to preclude study participation In the Investigator's opinion, is at high risk for infection (eg, indwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent urinary tract infection)ⁱ Prior history of invasive fungal infections^d 		X	X	
<ul style="list-style-type: none"> Seropositivity for human immunodeficiency virus (HIV)^d 	X	X	X	X
Tuberculosis: <ul style="list-style-type: none"> Latent tuberculosis unless effective anti-tuberculosis therapy has been completed, or active tuberculosis. More specific guidance on tuberculosis testing and patient eligibility is provided in the Study Operations Manual (SOM)^u 		X	X	
Hepatitis: <ul style="list-style-type: none"> Infection with hepatitis C virus^v Past or present hepatitis B infection (positive hepatitis B serology)^h Known infection with hepatitis B or C virus^d 		X X	X X	X
Childbearing potential: <ul style="list-style-type: none"> Female patients with childbearing potential with a positive serum pregnancy test at screening or baseline. (Note: Serum pregnancy testing will be performed on each occasion.)^w Of childbearing potential with a positive serum pregnancy test, pregnant, or lactating^x 	X	X	X	
Unwilling to use contraceptive methods: <ul style="list-style-type: none"> Male and female patients who do not agree to use effective contraceptive method(s) during the study 	X			

<ul style="list-style-type: none"> Unwilling to agree to use a reliable and acceptable contraceptive method throughout the study period (fertile patients only). Reliable and effective contraceptive method(s) include: intrauterine device (IUD), hormonal-based contraception, surgical sterilization, abstinence, or double-barrier contraception (condom and occlusive cap (diaphragm or cervical cap with spermicide).^{dy} 		X	X	X (and for at least 6 months following each alemtuzumab treatment cycle)
Depression/psychiatric disorders: <ul style="list-style-type: none"> Untreated, major depressive disorder (MDD) Suicidal ideation Major psychiatric disorder that is not adequately controlled by treatment^d 	X X	X	X	X
Major systemic disease: <ul style="list-style-type: none"> Major systemic disease or other illness that would, in the opinion of the Investigator, compromise patient safety or interfere with the interpretation of study results Major systemic disease or other illness that would, in the opinion of the Investigator, compromise patient safety or interfere with the interpretation of study results, eg, current peptic ulcer disease, or other conditions that may predispose to hemorrhage^z 	X	X	X	
HPV: <ul style="list-style-type: none"> Cervical high risk human papillomavirus (HPV) positivity or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS)ⁱ Cervical high risk human papillomavirus (HPV) positivity or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS). The patient may be eligible after the condition has resolved (eg, follow-up HPV test is negative or cervical abnormality has been effectively treated).^{aa} 		X	X	
Hepatic/renal function: <ul style="list-style-type: none"> Impaired renal function (ie, serum creatinine ≥ 2 times the Institutional upper limit of normal [ULN]) 	X			

<ul style="list-style-type: none">Any hepatic or renal function value grade 2 or higher at Screening, with the exception of hyperbilirubinemia due to Gilbert's syndrome. See Table below, drawn from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE), published 09 August 2006. <table><tr><th colspan="2">Hepatic</th></tr><tr><td>Bilirubin</td><td>>1.5 × ULN</td></tr><tr><td>SGOT/AST</td><td>>2.5 × ULN</td></tr><tr><td>SGPT/ALT</td><td>>2.5 × ULN</td></tr><tr><td>Alkaline phosphatase</td><td>>2.5 × ULN</td></tr><tr><th colspan="2">Renal</th></tr><tr><td>Creatinine</td><td>>1.5 × ULN</td></tr></table> <ul style="list-style-type: none">Note: Patients will be considered screen failures if they do not meet all of the eligibility criteria within 35 days of the date they sign the ICF, or within 56 days for patients who relapse or develop an infection during Screening unless approval to extend the Screening period is granted by Genzyme. Screen failures may be rescreened with prior approval from Genzyme.^{bb}	Hepatic		Bilirubin	>1.5 × ULN	SGOT/AST	>2.5 × ULN	SGPT/ALT	>2.5 × ULN	Alkaline phosphatase	>2.5 × ULN	Renal		Creatinine	>1.5 × ULN		X	X (unless, in the Investigator's opinion, the abnormality is due to a condition that has resolved [eg, recent interferon treatment subsequently discontinued] and levels return to within normal limits) (Note: Or patients must complete the washout period unless approval to extend Screening period granted by Genzyme. Medication washout may be deferred until eligibility is determined) ^{cc}	
Hepatic																		
Bilirubin	>1.5 × ULN																	
SGOT/AST	>2.5 × ULN																	
SGPT/ALT	>2.5 × ULN																	
Alkaline phosphatase	>2.5 × ULN																	
Renal																		
Creatinine	>1.5 × ULN																	
Alemtuzumab use: <ul style="list-style-type: none">Previous treatment with alemtuzumab^{dd}Does not wish to receive alemtuzumab^dAny patient who has received alemtuzumab off-label (ie, outside of one of the prior Genzyme studies) will be excluded from participating in this study^{c,d}	X	X	X	X X														
ITP: <ul style="list-style-type: none">Diagnosis of ITP, or other autoimmune hematologic abnormality. Patients who were diagnosed with ITP per the protocol definition in one of the prior studies can still be considered for the extension study if the ITP was not considered to be autoimmune. Such situations require prior approval by Genzyme^d				X														
Inability to self-administer SC injections or receive SC injections from caregiver		X	X															

Inability to undergo MRI with gadolinium administration	X	X	X	
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^a New criteria added in CAMMS223-A1.

^b In CAMMS324-A1 deleted “or any other investigational drug for MS” from criterion on “previous treatment with alemtuzumab” and added this new criterion on participation in another study or previous participation in CAMMS323.

^c Exclusion criteria for alemtuzumab patients from CAMMS223, CAMMS323, and CAMMS324 in the Extension Study (CAMMS03409).

^d Exclusion criteria for SC IFNB-1a patients from CAMMS223, CAMMS323, and CAMMS324 in the Extension Study (CAMMS03409).

^e In CAMMS03409-A1 added “unless approved by Genzyme”.

^f In CAMMS223-A2 added “intravenous immunoglobulin”.

^g In CAMMS324: Original protocol included criteria for “Previous treatment with mitoxantrone or natalizumab” and “Exposure to azathioprine, cladribine, cyclophosphamide, cyclosporine A, methotrexate, or any other immunosuppressive agent other than systemic corticosteroid treatment”. In CAMMS324-A1 these criteria were updated to the current criteria listed.

^h This criterion was included in the original CAMMS324 protocol, but was deleted in CAMMS324-A1.

ⁱ New criteria added in CAMMS323-A2 and CAMMS324-A1.

^j In CAMMS324-A2 added unless approval granted by Genzyme and patient completes any required washout.

^k In CAMMS323-A2 and CAMMS324-A1 deleted “if disease free for ≥5 years” after “basal cell skin carcinoma”.

^l In CAMMS323-A2 and CAMMS324-A1 deleted “alemtuzumab treatment” and added “either study medication”.

^m In CAMMS323-A2 and CAMMS324-A1 changed “other immunoglobulin” to “any immunoglobulin”.

ⁿ In CAMMS323-A1 changed “<150,000/μL within the past year” to “< the lower limit of normal (LLN) of the evaluating laboratory at Screening or documented at <100,000/μL within the past year on a sample without platelet clumping”. In CAMMS323-A2 added “platelet” before “clumping”. In CAMMS324-A1 changed “<130,000/μL at Screening or documented at <100,000/μL within the past year on a sample without platelet clumping” to “< the lower limit of normal (LLN) of the evaluating laboratory at Screening or documented at <100,000/μL within the past year on a sample without platelet clumping”.

^o New criterion added in CAMMS323-A1. In CAMMS323-A2 and CAMMS324-A1 added “(ie, above LLN)”.

^p In CAMMS323-A2 changed “Documented CD4+ cell count <490/mm³ within the past year” to “CD4+ cell count (absolute CD3+CD4+) < lower limit of normal (LLN) at Screening”.

^q In CAMMS323-A2 changed “Documented CD8+ cell count <200/mm³ within the past year” to “CD8+ cell count (absolute CD3+CD8+) <LLN at Screening”.

^r In CAMMS324: Original protocol included separate criteria for CD4+, CD8+ and platelet counts. In CAMMS324-A1 these criteria were updated and new criterion of B-cell (CD19+) was added. As part of the CAMMS324-A1 update, added “unless, in the Investigator’s opinion, the abnormality is due to the patient’s recent MS treatment and CD4+/CD8+/B-cell count levels return to within normal limits after washout”. In CAMMS324-A2 combined CD4+, CD8+ and CD19+ into one criterion and deleted “after washout” after “within normal limits”.

^s In CAMMS324-A2 deleted “unless, in the Investigator’s opinion, the abnormality is due to the patient’s recent MS treatment and the absolute neutrophil count returns to within normal limits after washout” and added “if abnormal cell count returns to within normal limits, eligibility may be reassessed”.

^t In CAMMS323-A2 and CAMMS324-A1 changed “eg” to “including but not limited to”.

^u In CAMMS323-A1 changed “has been initiated” to “has been completed”.

^v In CAMMS323-A2 and CAMMS324-A1 deleted “hepatitis B virus” as it became a separate exclusion criterion.

^w In CAMMS223-A2 added “at screening or baseline”.

^x In CAMMS223-A2 added “pregnant, or lactating”.

^y In CAMMS323-A2 deleted “condoms (male or female) with or without a spermicidal agent, diaphragm with spermicide or cervical cap” and added “surgical sterilization, abstinence, or double-barrier contraception (condom and occlusive cap (diaphragm or cervical cap with spermicide))”.

^z In CAMMS223-A2 and CAMMS324-A1 added “eg, current peptic ulcer disease, or other conditions that may predispose to hemorrhage”.

^{aa} In CAMMS324-A2 added “The patient may be eligible after the condition has resolved (eg, follow-up HPV test is negative or cervical abnormality has been effectively treated)”.

^{bb} In CAMMS223-A2 added the Note under the table on screen failures.

^{cc} In CAMMS324-A2 added unless, in the Investigator’s opinion, the abnormality is due to a condition that has resolved and levels return to within normal limits. In addition, changed “28 day washout” to “complete the washout” and added “Medication washout may be deferred until eligibility is determined”.

^{dd} In CAMMS323-A2 added “alemtuzumab”, so that prior therapy with alemtuzumab became an exclusion criterion.

Note: The criterion “History of untreated cervical dysplasia or intraepithelial neoplasia (CIN)” was deleted in CAMMS323-A2 and CAMMS324-A1.
Source: ISS Appendix 14.5. Submitted to sBLA 103948 on November 27, 2012.

Table 13. Screening failure -- reasons and numbers of subjects. CAMMS323.

	Number of Subjects
Total screened	733
Total Number of Subjects who Failed Screening	152
Abnormal laboratory assessments	1
Active infection, eg, deep-tissue infection, that the Investigator considers sufficiently serious to preclude study participation	1
Any hepatic or renal function value grade 2 or higher at screening, with the exception of hyperbilirubinemia due to Gilbert's syndrome	2
Any other illness or infection that, in the Investigator's opinion, could be exacerbated by alemtuzumab treatment	2
B or T cell counts below acceptable limits	49
Cervical high risk human papillomavirus (HPV) positivity or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS)	1
HCV antibodies detected at screening	1
Hepatitis B and low CD19+	1
High level of bilirubin	1
History of malignancy	1
Major systemic disease or other illness that would, in the opinion of the Investigator, compromise patient safety or interfere with the interpretation of study results	3
Not stable for the 30 days before signing the ICF	1
Of childbearing potential with a positive serum pregnancy test, pregnant or lactating	1
Past or present hepatitis infection	32
Positive anti-TPO antibodies	1
Presence of anti-thyroid stimulating hormone (TSH) receptor (TSHR) antibodies	6
Previous treatment with any investigational medication, ie drug has not been approved at any dose or for any indication	1
Seropositivity for Trypanosoma cruzi or the human T-lymphotropic virus type I or type II (HTLV-I/II)	1
Seropositivity for human immunodeficiency virus (HIV)	1
Significant autoimmune disease (eg, immune cytopenias, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders; vasculitis; inflammatory bowel disease; severe psoriasis)	3
Tuberculosis, treatment not meeting protocol requirements	2

Note: Screen failures attributed to the "other" category were for reasons not recorded as a violation of a specific study eligibility criterion as listed above. Such reasons for screen failure may include, but are not limited to, patient withdrawal of consent, patient lost to follow-up, study site closed, exceeded protocol defined time period for screening.

	Number of Subjects
≥2 MS attacks occurring in the 24 months prior to screening/ICF signature	5
Age 18 to 50 years old (inclusive) as of signing informed consent form (ICF)	1
Diagnosis of MS per update of McDonald criteria, and cranial MRI scan demonstrating white matter lesions attributable to MS within 5 years prior to screening	3
EDSS score 0.0 to 3.0 (inclusive)	24
Signed, informed consent form	1
Time since onset of MS symptoms exceeds allowable limit	3
Other	20

Note: Screen failures attributed to the "other" category were for reasons not recorded as a violation of a specific study eligibility criterion as listed above. Such reasons for screen failure may include, but are not limited to, patient withdrawal of consent, patient lost to follow-up, study site closed, exceeded protocol defined time period for screening.

Source: Sponsor response submitted to sBLA 103948 on August 21, 2013

Table 14. Screening failure -- reasons and numbers of subjects. CAMMS324

	Number of Subjects
Total screened	1046
Total Number of Subjects who Failed Screening	206
Absolute neutrophil count < LLN at screening	3
Any disability acquired from trauma or another illness that, in the opinion of the Investigator, could interfere with evaluation of disability due to MS	3
Any hepatic or renal function value grade 2 or higher at screening, with the exception of hyperbilirubinemia due to Gilbert's syndrome	5
Any other illness or infection that, in the Investigator's opinion, could be exacerbated by alemtuzumab treatment	5
B or T cell counts below acceptable limits	70
Disease duration was out of window	2
Exclusionary treatment history	1
Hepatitis and B or T cell counts below acceptable limits	2
History of malignancy	3
Intolerance to rebif	1
Known allergy or intolerance to interferon beta, human albumin, or mannitol	1
Known bleeding disorder	2
MS relapse	2
Major psychiatric disorder that is not adequately controlled by treatment	1
Major systemic disease or other illness	3
Medical, psychiatric, cognitive or other conditions that compromise the patient's ability to understand the patient information, give informed consent, comply with trial protocol or complete the study	7
Past or present hepatitis infection	35
Platelets below acceptable limits	3
Positive HPV history	1
Presence of anti-thyroid stimulating hormone (TSH) receptor (TSHR) antibodies	6
Previous treatment with mitoxantrone or natalizumab	1

Note: Screen failures attributed to the "other" category were for reasons not recorded as a violation of a specific study eligibility criterion as listed above. Such reasons for screen failure may include, but are not limited to, patient withdrawal of consent, patient lost to follow-up, study site closed, exceeded protocol defined time period for screening.

	Number of Subjects
Previous treatment with mitoxantrone, cyclophosphamide, cladribine, rituximab or any other immunosuppressant or cytotoxic therapy (other than steroids)	1
Seropositivity for human immunodeficiency virus (HIV)	1
Significant autoimmune disease	2
Treatment with natalizumab, methotrexate, azathioprine or cyclosporine in the past 6 months	3
Tuberculosis, treatment not meeting protocol requirements	3
>6 months continuous treatment with beta interferon or glatiramer acetate during the past 5 years prior to screening.	1
≥2 MS attacks occurring in the 24 months prior to screening/ICF signature	10
Age 18 to 50 years old (inclusive) as of signing informed consent form (ICF)	1
At least 1 MS attack (relapse) during treatment with a beta interferon therapy or glatiramer acetate after having been on that therapy for ≥6 months within 10 years of the date the ICF is signed	11
Diagnosis of MS per update of McDonald criteria	2
EDSS score 0.0 to 5.0 (inclusive)	8
MRI scan demonstrating white matter lesions due to MS and additional criteria	3
Neurologically stable for the 30 days prior to the date the ICF is signed (eg, no relapse)	2
Time since onset of MS symptoms exceeds allowable limit	21
Other	24

Note: Screen failures attributed to the "other" category were for reasons not recorded as a violation of a specific study eligibility criterion as listed above. Such reasons for screen failure may include, but are not limited to, patient withdrawal of consent, patient lost to follow-up, study site closed, exceeded protocol defined time period for screening.

Source: Sponsor response submitted to sBLA 103948 on August 21, 2013

Demographics

Table 15 displays demographics for subjects in controlled studies (Pool E). The mean age of subjects in Pool E was 34 years. In Pool E 698 of 1684 (41.4%) subjects were from the USA.

Table 15. Demographic and baseline characteristics in all controlled studies (Pool E)

Parameter	IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Total (N=1684)
Age (years)				
N	496	919	269	1684
Mean (SD)	34.2 (8.78)	33.8 (8.23)	34.1 (8.70)	33.9 (8.47)
Median	34.0	33.0	33.0	33.0
Min, Max	18.0, 60.0	18.0, 55.0	18.0, 54.0	18.0, 60.0
Q1, Q3	27.0, 40.0	27.0, 40.0	28.0, 40.0	27.0, 40.0
Sex, n (%)				
Male	173 (34.9)	319 (34.7)	86 (32.0)	578 (34.3)
Female	323 (65.1)	600 (65.3)	183 (68.0)	1106 (65.7)
Ethnicity, n (%)				
Hispanic/Latino	35 (7.1)	79 (8.6)	35 (13.0)	149 (8.8)
Non-Hispanic/Latino	461 (92.9)	839 (91.3)	234 (87.0)	1534 (91.1)
Race, n (%)				
White	463 (93.3)	841 (91.5)	231 (85.9)	1535 (91.2)
Black	14 (2.8)	41 (4.5)	15 (5.6)	70 (4.2)
Asian	1 (0.2)	7 (0.8)	1 (0.4)	9 (0.5)
American Indian or Alaska Native	0	4 (0.4)	3 (1.1)	7 (0.4)
Other	18 (3.6)	26 (2.8)	19 (7.1)	63 (3.7)
Weight (kg)				
N	493	917	268	1678
Mean (SD)	76.3 (19.64)	75.0 (17.89)	76.2 (20.07)	75.5 (18.77)
Median	72.6	72.0	72.0	72.1
Min, Max	44.0, 166.7	40.0, 157.4	42.0, 188.2	40.0, 188.2
Q1, Q3	62.0, 85.0	62.0, 85.0	62.0, 85.0	62.0, 85.0
BMI (kg/m ²)				
N	491	914	268	1673
Mean (SD)	26.4 (6.42)	25.8 (5.84)	26.3 (6.09)	26.1 (6.06)
Median	24.5	24.6	24.8	24.6
Min, Max	16.2, 54.4	16.0, 56.4	14.2, 59.5	14.2, 59.5
Q1, Q3	22.1, 29.6	21.7, 28.7	22.4, 29.3	21.9, 29.0

Parameter	IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Total (N=1684)
Geographic Region, n (%)				
USA/Canada/Australia	212 (42.7)	381 (41.5)	151 (56.1)	744 (44.2)
Latin America	17 (3.4)	38 (4.1)	7 (2.6)	62 (3.7)
EU	102 (20.6)	197 (21.4)	53 (19.7)	352 (20.9)
Non-EU Europe and Israel	165 (33.3)	303 (33.0)	58 (21.6)	526 (31.2)

SC = subcutaneous; IFNB-1a = interferon beta-1a; SD = standard deviation; Min = minimum; Max = maximum; Q = quartile; BMI = body mass index; USA = United States of America; EU = European Union

Source: ISS Table 5-1, p. 143-144

Sponsor-defined geographic regions are listed below:

- United States/Canada/Australia
- Latin America (Mexico, Brazil, Argentina)
- EU (Germany, France, UK, Sweden, Poland, Czech Republic)
- Non-EU Europe and Israel (Serbia, Croatia, Israel, Russia, Ukraine)

There were 555 subjects from the USA. The Non-EU Europe and Israel region 503 subjects from non-EU Europe and 23 subjects from Israel.

7.2.2 Explorations for Dose Response

In CAMMS223 subjects were randomly assigned at baseline 1:1:1 to receive low-dose (12 mg/day) alemtuzumab, high-dose (24 mg/day) alemtuzumab, or IFNB-1a (44 µg 3 times per week [after initial titration]).

Under the original protocol for CAMMS324, approximately 1200 subjects were to be randomized in a 2:2:1 ratio to receive 2 annual cycles of alemtuzumab 12 mg/day or 24 mg/day, or 3-times weekly IFNB-1a. Beginning with Amendment 2, the alemtuzumab 24 mg/day group was closed to newly enrolling subjects, and all subjects enrolled after approval of Amendment 2 were randomized in a 2:1 ratio to receive alemtuzumab 12 mg/day or IFNB-1a.

In CAMMS323 alemtuzumab-treated subjects received only the 12 mg/day dose.

A single dosing regimen -- an initial treatment course of 12 mg/day for 5 consecutive days (60 mg total dose) and a second treatment course of 12 mg/day for 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course -- has been proposed by Genzyme for marketing approval. Reasons for proposing only the 12 mg/day dose are likely related to safety concerns with the 24 mg/day dose. (These reasons are not specifically discussed in the sBLA submission.)

7.2.3 *Special Animal and/or In Vitro Testing*

Please refer to the pharmacology toxicology review.

7.2.4 *Routine Clinical Testing*

In CAMMS223, vital signs (blood pressure, pulse, respiration, weight, and temperature) were recorded at baseline, every 3 months, and 1 month after the start of study drug through end of study. In addition, these were performed at Months 13 and 25 for alemtuzumab-treated subjects. In the CAMMS223 study report, there was no description of a standard physical examination performed at regular intervals. According to the CAMMS223 study report, “Any clinically significant changes from baseline were documented as AEs and followed accordingly.”³⁷

In CAMMS323 and CAMMS324, physical examinations were performed and vital signs were measured at each quarterly visit.

Table 16 lists the clinical laboratory assessments evaluated in the ISS.

³⁷ CAMMS223 study report. Section 8.5.1.2.3 p. 61.

Table 16. Sponsor ISS Table 7-1. List of Clinical Laboratory Assessments Evaluated in ISS

Hematology^a	Clinical Chemistry^b	Urinalysis^c
CBCs with WBC differential: •Neutrophils •Eosinophils •Basophils •Lymphocytes •Monocytes RBC Hemoglobin Hematocrit Platelets	Sodium Potassium Chloride CO ₂ (Phase 3 Only) T3 T4 TSH Creatinine BUN ALT AST Gamma Glutamyl Transferase (GGT) (Phase 2 only) Alkaline Phosphatase Bilirubin Total Bilirubin C-Reactive Protein (CRP) (Phase 2 only) Glucose Calcium Phosphate Albumin Total Protein (Phase 3 only)	Specific Gravity pH Occult Blood RBC Protein

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBCs = complete blood counts; CO₂ = carbon dioxide; T3 = triiodothyronine (liothyronine); T4 = thyroxine; TSH = thyroid-stimulating hormone; RBC = red blood cells; WBC = white blood cells.

^a Monthly for all patients in CAMMS323, CAMMS324 and CAMMS03409; monthly in CAMMS223 for alemtuzumab patients after Amendment 3.

^b Quarterly for all patients. Additional chemistry evaluations at Month 1 for IFNB-1a patients in the Phase 3 studies. Additional monthly serum creatinine testing for alemtuzumab patients in CAMMS03409 and starting with CAMMS323 Amendment 3, CAMMS324 Amendment 2, and CAMMS223 Amendment 10. T3 and T4 are assessed following an abnormal TSH result in CAMMS03409.

^c Quarterly for all patients and monthly for alemtuzumab patients starting with CAMMS323 Amendment 3, CAMMS324 Amendment 2, and CAMMS223 Amendment 10. Urinalysis performed on a monthly basis in CAMMS03409

Source: ISS Table 7-1, p. 440.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the clinical pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Deib provides a review of monoclonal antibodies used or being studied for use in treatment for MS,³⁸ including adverse effects seen with alemtuzumab, natalizumab, daclizumab, ocrelizumab, and ofatumumab. Natalizumab is the only monoclonal antibody currently approved for MS. Major safety issues of natalizumab are listed in Table 5.

7.3 Major Safety Results

7.3.1 Deaths

In controlled trials (Pool E), 5 of 1188 (0.4%) of alemtuzumab-treated subjects died, compared to 1 of 496 (0.2%) IFN β -1a-treated subjects. A total of 8 of 1496 (0.5%) subjects in Pool C (all alemtuzumab-treated subjects) died during the study period. After reviewing the deaths, this reviewer considered 3 deaths in alemtuzumab-treated subjects and 1 death in an IFN β -1a subject to be unrelated to treatment. See Table 17, which lists the deaths in the ISS analysis (7 alemtuzumab-treated and 1 IFN β -1a-treated).

One additional alemtuzumab-treated subject died after the ISS analysis data cut-off date. Subject 6010-3077 was found in his apartment 4-5 days after his death at age 52. He was a CAMMS323 treated with IFN β -1a, and he received 2 cycles of alemtuzumab in CAMMS03409. His death occurred 2 years after his first alemtuzumab cycle and 1 year after his last alemtuzumab cycle. An autopsy was performed, but the cause of death could not be established due to body decomposition.

Brief summary narratives for deaths assessed by this reviewer as related or possibly related to alemtuzumab treatment are presented below:

- A 45-year-old female subject enrolled in CAMMS223 (Subject 114-1027) died from cardiovascular disorder 2 months after receiving the third annual cycle of alemtuzumab 12 mg/day. The subject had a medical history of cardiac risk factors including obesity, hypertension, smoking, and estrogen therapy. The coroner ruled the death a result of cardiovascular disorder. In the opinion of the site investigator, the cause of death was unknown. *Because the cause of death is unclear, this reviewer assesses this death as possibly related to alemtuzumab. Cardiac toxicity after alemtuzumab treatment has been reported in a subject with peripheral T cell lymphoma³⁹ and in a case series of subjects with mycosis fungoides.⁴⁰*
- A 46-year-old male subject enrolled in CAMMS03409 (Subject 7105-3488) died from sepsis a year and a half after the second annual cycle of alemtuzumab 12

³⁸ Beib a, et al. Treating multiple sclerosis with monoclonal antibodies: a 2013 update. Expert Rev. Neurother. 13(3), 313–335 (2013)

³⁹ Damaj, et al. Eur J Haematol 2002;68:324

⁴⁰ Lenihan, et al. Blood. 2004; 104:655-658

mg/day. The subject was hospitalized for autoimmune pancytopenia, febrile neutropenia, and sepsis. A bone marrow biopsy revealed non-specific morphological findings corresponding to immune mediated bone marrow impairment. There was no other potential cause for pancytopenia reported. He died from sepsis 2 days after his hospitalization. *Reviewer comment: Section 7.3.5.1.3 discusses the increased incidence of autoimmune cytopenias with alemtuzumab. This reviewer assesses this fatal event as related to the study drug.*

- A 39-year-old male subject enrolled in CAMMS223 (Subject 113-1125) died from idiopathic thrombocytopenic purpura (ITP) and a cerebral hemorrhage 7 months after the second annual cycle of alemtuzumab 24 mg/day. The subject's relevant recent medical history included diffuse petechiae and easy bruising of approximately 2 weeks duration and right-sided weakness for a few days before admission. A computed tomography (CT)-scan of the head showed a large extensive intracranial haemorrhage. The platelet count was $4 \times 10^9/L$. There was no evidence of any non-autoimmune cause for thrombocytopenia. The subject died 1 day after admission. A serum sample taken 3 months prior to alemtuzumab treatment was negative for antiplatelet antibody and positive 1.5 months prior to the event and at the time of the event. The investigator assessed these events as related to the study drug. *Reviewer comment: Section 7.3.5.1.3 discusses the increased incidence of ITP with alemtuzumab. This reviewer assesses this fatal event as related to the study drug.*
- A 28 year old male (Subject 404-1334) died after injuring his arm on broken glass and sustaining an injury to the deep left brachial vein. The wound was surgically sealed in the hospital, but he died later that day. *Reviewer comment: This reviewer assesses this event as possibly related to alemtuzumab. In the active-controlled studies over 3 years of follow up, the incidence of AEs in the MedDRA Hemorrhages SMQ was higher in the alemtuzumab 12 mg/day group (29.8%) compared to the IFN β -1a group (19.4%).⁴¹ However, in controlled trials (Pool E), SAEs in the MedDRA Hemorrhages SMQ occurred at comparable frequencies in alemtuzumab subjects (11 of 1188; 0.9%) and IFN β -1a subjects (5 of 496; 1.0%).*

A post-study death from Burkitt's lymphoma was reported after an alemtuzumab-treated Subject 201-1012 had completed Study CAMMS223 which was reported to the Genzyme Safety database. Forty months after the third annual cycle of alemtuzumab, the subject died from sepsis following chemotherapy.

Reviewer comment: This reviewer thinks there is a possible relationship between this subject's development of Burkitt's lymphoma and subsequent death (see Section 7.3.5.2).

⁴¹ Table 13.3.18.3.1 in ISS Appendix 14-4-5. Link on ISS p. 338.

Table 17. Listing of deaths. All studies. ISS analysis

Study / Patient ID (sex)	Age at Death (years)	Treatment Group	Number of Cycles or Weeks (Total Dose)	Preferred Term for Cause of Death	Days (Months) From First Dose to Death	Days (Months) From Last Dose to Death	Relatedness*
Treatment: Alemtuzumab 12 mg							
CAMMS223 / 114-1027 (female)	45	12 mg/day	3 Cycles (132 mg)	Cardiovascular disorder	830 days (27 months)	72 days (2 months)	Possible
CAMMS323 / 7101-3128 (male)	32	12 mg/day	2 Cycles (96 mg)	Road traffic accident	670 days (22 months)	281 days (9 months)	Not related
CAMMS324 / 1095-5592 (female)	28	12 mg/day	2 Cycles (96 mg)	Death (auto-pedestrian accident)	589 days (19 months)	228 (7 months)	Not related
CAMMS324 / 4008-5485 (male)	30	12 mg/day	2 Cycles (96 mg)	Pneumonia aspiration	701 days (23 months)	312 days (10 months)	Not related
CAMMS03409 / 404-1334 (male)	28	12 mg/day	4 Cycles (168 mg)	Wound	2378 days (78 months)	100 days (3 months)	Possible
CAMMS03409 / 7105-3488 (male)	46	12 mg/day	2 Cycles (96 mg)	Sepsis	957 days (32 months)	590 days (19 months)	Related
Treatment: Alemtuzumab 24 mg							
CAMMS223 / 113-1125 (male)	39	24 mg/day	2 Cycles (192 mg)	Idiopathic thrombocytopenic purpura and cerebral haemorrhage	585 days (19 months)	220 days (7 months)	Related
Treatment: IFNB-1a							
CAMMS223 / 403-1269 (male)	32	IFNB-1a	156 weeks	Death (train accident)	1609 days (53 months)	521 days (17 months)	Not related

* Relatedness in the opinion of this FDA reviewer Source: ISS Table 16-8 Data as of December 31, 2011
ID = identification ; IFNB-1a = interferon beta-1a

CAMMS324 Subject 4008-5485 died of aspiration pneumonia related to MS. He had pre-existing brainstem MS lesions prior to alemtuzumab treatment. One year after his first cycle of MS, he had a brainstem relapse of MS, which lead to poor bulbar function and aspiration pneumonia. He was documented as “not for resuscitation” and died from aspiration pneumonia. *Reviewer comment: This reviewer considers this death not related to alemtuzumab.*

Reviewer comment: The deaths in Subjects 113-1125 and 7105-3488 exemplify the life-threatening nature of autoimmune disease with alemtuzumab. Additional cases of autoimmune disease are discussed in Section 7.3.5.1.

In summary, 2 of 1188 (0.2%) alemtuzumab-treated subjects in controlled trials (Pool E) died for reasons related or possibly related to treatment, compared to 0 of 496 IFNB-1a

subjects. Five⁴² of 1496 (0.4%) alemtuzumab-treated subjects in all studies (Pool C) have died for reasons related or possibly related to alemtuzumab treatment.

7.3.2. Nonfatal Serious Adverse Events

Serious adverse events (SAEs) by MedDRA System Organ Class (SOC) from the ISS analysis are reported in Table 18. SAEs from the Safety Update Report⁴³ and 4-Month Safety Update Report⁴⁴ have been reviewed. Notable SAEs from these update reports are discussed below or in the sections referenced below.

Table 18. Serious Adverse Events in All Active-Controlled Studies by MedDRA System Organ Class (SOC) (Pool E)

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Any Event	96 (19.4)	177 (19.3)	228 (19.2)
Blood and lymphatic system disorders	0 (0.0)	10 (1.1)	18 (1.5)
Cardiac disorders	2 (0.4)	13 (1.4)	16 (1.3)
Endocrine disorders	0 (0.0)	7 (0.8)	11 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.6)	8 (0.9)	14 (1.2)
Immune system disorders	0 (0.0)	1 (0.1)	2 (0.2)
Eye disorders	1 (0.2)	3 (0.3)	3 (0.3)
Infections and infestations	6 (1.2)	27 (2.9)	37 (3.1)
Skin and subcutaneous tissue disorders	0 (0.0)	6 (0.7)	9 (0.8)
General disorders and administration site conditions	3 (0.6)	12 (1.3)	14 (1.2)
Psychiatric disorders	2 (0.4)	6 (0.7)	9 (0.8)
Renal and urinary disorders	2 (0.4)	4 (0.4)	5 (0.4)
Respiratory, thoracic and mediastinal disorders	5 (1.0)	10 (1.1)	16 (1.3)
Reproductive system and breast disorders	5 (1.0)	8 (0.9)	13 (1.1)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	5 (1.0)	5 (0.5)	6 (0.5)
Nervous system disorders	54 (10.9)	72 (7.8)	84 (7.1)
Hepatobiliary disorders	8 (1.6)	4 (0.4)	5 (0.4)
Gastrointestinal disorders	9 (1.8)	12 (1.3)	17 (1.4)

⁴² The six subjects are: 114-1027, 404-1334, 7105-3488, 113-1125, and 201-1012.

⁴³ ISS Appendix 14.6 submitted to sBLA 103948 27 November 2012.

⁴⁴ Submitted to sBLA103948 on 3/19/2013

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Injury, poisoning and procedural complications	13 (2.6)	13 (1.4)	14 (1.2)

-MedDRA version 13.1 was used for coding.

-Percentages are based on the number of treated subjects in the corresponding treatment group.

-A subject is counted only once within each SOC/PT.

-SOCs are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

SC = subcutaneous; IFNB-1a = interferon beta-1a; SOC = system organ class; PT = preferred term

Source: Sponsor ISS Table 6-10

Reviewer comment: Recommended dosing for alemtuzumab occurs in yearly cycles. Individual treatment intervals varied between subjects. In most cases, the second cycle of treatment occurred in Year 2. In the ISS analysis of controlled trial (Pool E) subjects, 1151 of 1188 (96.9%) and 46 of 1188 (3.9%) received second and third alemtuzumab cycles, respectively.

7.3.2.1. Serious Adverse Events: Blood and lymphatic system disorders SOC

Fourteen of 1188 (1.2%) alemtuzumab-treated subjects in controlled trials (Pool E) had SAEs coded to the Blood and lymphatic system disorders SOC, compared to 0 of 496 IFN β -1a subjects. Of all alemtuzumab-treated subjects (Pool C), 23 of 1485 (1.5%) had a total of 25 SAEs in this SOC.

Table 19. Serious Adverse Events. Blood and lymphatic system disorders SOC. All alemtuzumab-treated subjects (Pool C). Integrated Summary of Safety analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	23 (1.5)	4 (0.3)	10 (0.8)	9 (0.8)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Autoimmune thrombocytopenia	8 (0.5)	0 (0.0)	5 (0.4)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Agranulocytosis	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Idiopathic thrombocytopenic purpura	4 (0.3)	1 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia haemolytic autoimmune	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Autoimmune pancytopenia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Febrile neutropenia	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancytopenia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	3 (0.2)	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.

- Years defined by calendar time.

Serious adverse events with the following Preferred Terms are discussed in Section 7.3.5.1, which discusses secondary autoimmunity after alemtuzumab treatment: Autoimmune thrombocytopenia, Idiopathic thrombocytopenic purpura, Anaemia haemolytic autoimmune, Autoimmune pancytopenia, Febrile neutropenia (7105-3488 only), and Thrombocytopenia (Subjects 7102-5804 and 113-1102 only). A third Thrombocytopenia SAE (Subject 1046-5011) involved a nadir platelet count of

103,000/ μ L of unclear etiology during hospitalization for herpes zoster; the thrombocytopenia resolved after 1 day, when the subject had a platelet count of 217,000/ μ L. Brief narratives for other SAEs in this SOC are reported in the table below.

Table 20. Description of Serious Adverse Events. Blood and lymphatic system disorders SOC (excluding autoimmunity and thrombocytopenia SAEs). Integrated Summary of Safety analysis.

Subject Study	Treatment	Age Sex Country	Preferred Term	Description/Comment												
1018-3090 CAMMS323	Alemtuzumab 12 mg/day	32 F USA	Agranulocytosis	Agranulocytosis after receiving propylthiouracil (PTU) for treatment of Graves' Disease after alemtuzumab treatment. <i>Reviewer comment: Agranulocytosis is described in the prescribing information for PTU. Thioamides (including PTU and methimazole) are frequently used antithyroid drugs. Given the frequency of thyroid disorders with alemtuzumab, a large proportion of alemtuzumab-treated patients will be exposed to this risk of agranulocytosis.</i>												
4507-3204 CAMMS323	Alemtuzumab 12 mg/day	32 F France	Agranulocytosis	First alemtuzumab was in July 2008. 1 month later, she developed agranulocytosis. Nadir hematologic values from 8/25/2008 are listed below: <table><tr><th>Parameter</th><th>Value</th></tr><tr><td>hemoglobin</td><td>11.8 g/dL</td></tr><tr><td>WBC</td><td>0.5 x 10⁹/L</td></tr><tr><td>neutrophils</td><td>0.23 x 10⁹/L</td></tr><tr><td>lymphocytes</td><td>0.13 x 10⁹/L</td></tr><tr><td>monocytes</td><td>0.13 x 10⁹/L</td></tr></table> CMV PCR on Day 38 (27 Aug 2008) showed <500 copies/mL, so there was no clear evidence of CMV infection. The investigator judged this event as definitely related to study drug and the subject was treated with lenograstim.	Parameter	Value	hemoglobin	11.8 g/dL	WBC	0.5 x 10 ⁹ /L	neutrophils	0.23 x 10 ⁹ /L	lymphocytes	0.13 x 10 ⁹ /L	monocytes	0.13 x 10 ⁹ /L
Parameter	Value															
hemoglobin	11.8 g/dL															
WBC	0.5 x 10 ⁹ /L															
neutrophils	0.23 x 10 ⁹ /L															
lymphocytes	0.13 x 10 ⁹ /L															
monocytes	0.13 x 10 ⁹ /L															
1027-3096 CAMMS03409	Alemtuzumab 12 mg/day in CAMMS323	40 F USA	Anaemia	First alemtuzumab was in May 2008. In May 2011 subject had iron deficiency anemia related to upper gastrointestinal hemorrhage. (Prior to May 2011 hemoglobin measurements were normal.) Nadir hematocrit was 20%. She was diagnosed with gastritis. At last follow-up hemoglobin was normal. <i>Reviewer comment: Given the description of events, there is no evidence of a relationship between alemtuzumab and this subject's anemia. However, in analysis of the MedDRA Hemorrhages SMQ, 29.8% of alemtuzumab-treated subjects had an adverse event, compared to 19.4% of IFNβ-1a</i>												

Subject Study	Treatment	Age Sex Country	Preferred Term	Description/Comment
				<i>subjects.⁴⁵ Alemtuzumab-treated subjects had a higher incidence of adverse events in the Gastrointestinal disorders SOC within the Hemorrhages SMQ – 5.9% in alemtuzumab subjects, compared to 3.6% in IFNβ-1a subjects. Thus, this reviewer thinks this adverse event is possibly related to alemtuzumab.</i>
3208-5531 CAMMS324	Alemtuzumab 24 mg/day	36 F Argentina	Anaemia	Subject had a history of hereditary spherocytosis. First alemtuzumab was in April 2009. Hemoglobin level was low at screening prior to alemtuzumab treatment (115g/L). Nadir hemoglobin 34 g/L in February 2011. After evaluation, which included a bone marrow biopsy which showed erythroid hyperplasia, the hematologist and investigator attributed the anemia to hemolytic crisis related to hereditary spherocytosis. <i>Reviewer comment: SAE not related to alemtuzumab.</i>
1039-5419 CAMMS324	Alemtuzumab 24 mg/day	50 F USA	Febrile neutropenia	Received alemtuzumab 24 mg/day mar 30 2009 to April 3, 2009. On May 20, 2009 (Day 52) she had nausea, vomiting, oral blisters, and inability to walk. She was diagnosed with febrile neutropenia. Nadir neutrophil count was $0.43 \times 10^3/\text{mm}^3$. She was treated with amoxicillin / clavulanic acid, famciclovir, loratadine, lidocaine, and ceftazidime. Fever abated by (b) (6) and subject was discharged.
134-1241 CAMMS223	Alemtuzumab 12 mg/day	47 F USA	Neutropenia	Grade 3 neutropenia and sepsis requiring hospitalization 2 years after last alemtuzumab and 29 months after treatment with mitoxantrone. <i>Reviewer comment: Event possibly related to alemtuzumab. Because it can cause bone marrow suppression, treatment with mitoxantrone is a confounding factor.</i>

Reviewer comment: Alemtuzumab-treated subjects had an increased frequency of SAEs in the Blood and lymphatic system disorders SOC. These SAEs included autoimmune disease-related events and SAEs without a reported autoimmune component.

⁴⁵ Table 13.3.18.3.1, p. 4568-4577 in ISS Appendix 14-4-5.

7.3.2.2. Serious Adverse Events: Cardiac disorders SOC

In controlled trials (Pool E), 16 of 1188 (1.3%) of alemtuzumab-treated subjects had an SAE in the Cardiac disorders SOC, compared to 2 of 496 (0.4%) IFN β -1a subjects (Table 21). Of all alemtuzumab-treated subjects (Pool C), 19⁴⁶ of 1485 (1.3%) had an SAE in this SOC (Table 22); in 10 of these 19 subjects, the Cardiac Disorders SOC SAE was part of an infusion reaction. Infusion reaction SAEs are discussed in Section 7.3.5.3. In controlled trials, the incidence of SAEs in the Ischaemic coronary artery disorders High Level Term group was similar in alemtuzumab subjects (5 of 1188; 0.4%) compared to IFN β -1a subjects (4 of 496; 0.8%).

Table 21. Serious Adverse Events. Cardiac disorders SOC. Controlled trials (Pool E). Integrated Summary of Safety analysis.

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Cardiac disorders	2 (0.4)	13 (1.4)	16 (1.3)
Atrial fibrillation	0 (0.0)	2 (0.2)	2 (0.2)
Sinus tachycardia	0 (0.0)	2 (0.2)	3 (0.3)
Tachycardia	0 (0.0)	2 (0.2)	2 (0.2)
Acute myocardial infarction	0 (0.0)	1 (0.1)	1 (0.1)
Angina pectoris	0 (0.0)	1 (0.1)	2 (0.2)
Bradycardia	0 (0.0)	1 (0.1)	2 (0.2)
Cardiovascular disorder	0 (0.0)	1 (0.1)	1 (0.1)
Coronary artery disease	0 (0.0)	1 (0.1)	1 (0.1)
Myocardial infarction	1 (0.2)	1 (0.1)	1 (0.1)
Sick sinus syndrome	0 (0.0)	1 (0.1)	1 (0.1)
Sinus bradycardia	0 (0.0)	1 (0.1)	1 (0.1)
Arrhythmia	1 (0.2)	0 (0.0)	0 (0.0)

Source: ISS Table 6-10

⁴⁶ SAEs of Cardiac failure acute and Cardiomyopathy occurred in Subject 1039-3030.

Table 22. Serious Adverse Events. Cardiac disorders SOC. All alemtuzumab-treated subjects (Pool C). Integrated Summary of Safety analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	20 (1.3)	8 (0.5)	7 (0.5)	3 (0.3)	0 (0.0)	1 (0.6)	1 (0.7)	0 (0.0)	0 (0.0)
Atrial fibrillation	3 (0.2)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Acute myocardial infarction	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus tachycardia	3 (0.2)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	2 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angina pectoris	2 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bradycardia	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure acute	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiomyopathy	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular disorder	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery disease	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sick sinus syndrome	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus bradycardia	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pericarditis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.

- Years defined by calendar time.

Brief narratives for selected SAEs in this SOC are reported in the table below.

Table 23. Description of selected Serious Adverse Events (non-infusion-related). Cardiac disorders SOC. Integrated Summary of Safety analysis.

Subject Study	Treatment	Age Sex Country	Preferred Term	Description/Comment
1039-5025 CAMMS324	Alemtuzumab 12 mg/d	45 F USA	Tachycardia (Verbatim Term: Wide complex tachycardia)	Subject had sustained monomorphic ventricular tachycardia. No reported history of cardiac disease. First alemtuzumab was in March 2008. In December 2009 she underwent an exercise cardiac stress test to evaluate chest pain (date of chest pain onset not reported). While exercising, she had a sustained monomorphic ventricular tachycardia and lost consciousness. She was treated with lidocaine and was successfully cardioverted. An electrophysiology study with induction of arrhythmias performed on Day 1103 (01 Apr 2011) suggested the possibility of atrial fibrillation being the cause of all related events. A looping event monitor was implanted but results of this test were not reported.
4801-5565 CAMMS324	Alemtuzumab 12 mg/d	40 M Czech Republic	Sick sinus syndrome	First alemtuzumab was in April 2009. In August 2009 he had irregular heart beat, palpitations, dyspnea, and chest pain. He was diagnosed with sick sinus syndrome and treated with metoprolol, amantadine, and omeprazole. Event reported as resolved December 2010.
1039-3030 CAMMS03409	Alemtuzumab 12 mg/day (IFN β -1a in CAMMS323)	25 F USA	Cardiac failure acute Cardiomyopathy	Subject had peripartum cardiomyopathy. She received one cycle of alemtuzumab in February 2010. She became pregnant and delivered a healthy infant on (b) (6). On (b) (6) she was hospitalized for shortness of breath and diagnosed with peripartum cardiomyopathy. An echocardiogram revealed moderately dilated left ventricle, severely reduced left ventricular systolic function, calculated ejection fraction at 18%, impaired left ventricle relaxation, and severe global hypokinesis of the left ventricle. ANA and anti-DNA screen were negative. The events of dyspnea and cardiac failure acute were reported as resolved on August 3, 2011.

Reviewer comment: There is evidence that peripartum cardiomyopathy is an autoimmune disease.⁴⁷ It is a rare condition, which occurred in 1 of 4025 deliveries in a U.S. population-based study.⁴⁸ This reviewer thinks that the event is possibly related to

⁴⁷ Sundstrom JB. Is peripartum cardiomyopathy an organ-specific autoimmune disease? Autoimmunity Reviews 1 (2002) 73–77.

⁴⁸ Brar SS. Incidence, Mortality, and Racial Differences in Peripartum Cardiomyopathy. Am J Cardiol 2007;100:302–304

alemtuzumab. If alemtuzumab is approved, I recommend that this SAE be described in the prescribing information. I also recommend that events of peripartum cardiomyopathy be reported in the postmarketing period.

Regarding the SAEs in Subject 1039-5025 (ventricular tachycardia) and 4801-5565(sick sinus syndrome), this reviewer considers these events possibly related to alemtuzumab. There was no evidence indicating that these events were related to alemtuzumab. However, no similar events occurred in controlled trial subjects treated with IFN β -1a.⁴⁹ Cardiac disorders after alemtuzumab treatment (infusion-related and non-infusion-related) have been reported in the published literature.^{50,51, 52} In a report by Lenihan, 4 of 8 patients with mycosis fungoides/Sézary syndrome, with no prior cardiac history, developed arrhythmias or congestive heart failure. It is unclear whether these findings may have been specific to patients with mycosis fungoides/Sézary syndrome via targeting of disease-related T-lymphocytes infiltrating the heart. If alemtuzumab is approved, postmarketing reports will need to be monitored for a possible increased frequency of cardiac disorders.

7.3.2.3. Serious Adverse Events: Eye disorders SOC

Three of 1188 (0.3%) alemtuzumab-treated subjects in controlled trials had SAEs coded to the Eye disorders SOC, compared to 1 of 496 (0.2%) IFN β -1a subjects (Table 24). Of all alemtuzumab-treated subjects, 7 of 1485 (0.5%) had an SAE in this SOC (Table 24).

⁴⁹ The SAE coded to the PT of 'Arrhythmia,' originally considered to be palpitations, was deemed to be a non-cardiac sensory manifestation of an MS exacerbation by the cardiology consultation.

⁵⁰ Lenihan DJ, Alencar AJ, Yang D, Kurzrock R, Keating MJ, Duvic M. Cardiac toxicity of alemtuzumab in patients with mycosis fungoides/Sezary syndrome. *Blood* 104, 655–658 (2004).

⁵¹ Basquiera AL, Berretta AR, Garcia JJ, Palazzo ED. Coronary ischemia related to alemtuzumab therapy. *Ann. Oncol.* 15, 539–540 (2004)

⁵² Damaj G, Rubio MT, Audard V, Hermine O. Severe cardiac toxicity after monoclonal antibody therapy. *Eur. J. Haematol.* 68, 324 (2002).

Table 24. Serious Adverse Events. Eye disorders SOC. Controlled trials (Pool E). Integrated Summary of Safety analysis.

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Eye disorders	1 (0.2)	3 (0.3)	3 (0.3)
Eye pain	0 (0.0)	1 (0.1)	1 (0.1)
Retinal pigment epitheliopathy	0 (0.0)	1 (0.1)	1 (0.1)
Visual acuity reduced	0 (0.0)	1 (0.1)	1 (0.1)
Diplopia	1 (0.2)	0 (0.0)	0 (0.0)

Source: ISS Table 6-10

Table 25. Serious Adverse Events. Eye disorders SOC. All alemtuzumab-treated subjects (Pool C). ISS analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	7 (0.5)	2 (0.1)	1 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.7)	1 (0.8)	0 (0.0)
Endocrine ophthalmopathy	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Exophthalmos	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye pain	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal pigment epitheliopathy	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Visual acuity reduced	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vision blurred	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.
- Years defined by calendar time.

Three SAEs of endocrine ophthalmopathy (coded to Preferred Terms 'Endocrine ophthalmopathy' and 'Exophthalmos') are included in a discussion of all documented cases of endocrine ophthalmopathy in Section 7.3.5.1.2.

Table 26. Description of Serious Adverse Events. Eye disorders SOC (excluding endocrine ophthalmopathy cases). Integrated Summary of Safety analysis.

Subject Study	Treatment	Age Sex Country	Preferred Term	Description/Comment
4001-6041 CAMMS324	Alemtuzumab 12 mg/d	34 M Great Britain	Retinal pigment epitheliopathy	Hospitalized for scotomata with headache. Diagnosed with acute multifocal placoid pigment epitheliopathy (AMPPE). Judged to be autoimmune in origin by ophthalmologist. <i>Reviewer comment: this case is likely related to alemtuzumab. Case discussed in detail in Section 7.3.5.1.8.</i>
404-1333 CAMMS223	Alemtuzumab 12 mg/d	42 F Poland	Visual acuity reduced	Reduced visual acuity during an MS exacerbation. <i>Reviewer comment: SAE unlikely related to alemtuzumab.</i>
205-1167 CAMMS223	Alemtuzumab 24 mg/d	47 F Croatia	Vision blurred	The last dose of study drug prior to the event was 29 Dec 2004. In August 2009 the subject developed visual blurring of the left eye field. (b) (6) nearly 6 years after starting alemtuzumab, the subject was hospitalized for a diagnostic evaluation of the transient visual blurring. Approximately 20 years prior, the subject experienced a trauma to the left eye which resulted in transient visual impairment. An MRI of the brain performed on (b) (6) showed one heterointense pontine lesion (T2) and multiple hyperintense periventricular lesions (T2, FLAIR). On (b) (6), visual evoked potentials showed conduction impairment of the left visual pathway. Brain stem auditory evoked potentials and somatosensory evoked potentials (median nerve) were within acceptable parameters. The ongoing event of vision blurred was reported as resolved on an unspecified day in December 2009. <i>Reviewer comment: Unable to determine a specific cause of this adverse event from the information provided. Multiple sclerosis is a possible cause of this adverse event. This subject did not have any documented thyroid abnormality, so endocrine ophthalmopathy is an unlikely diagnosis.</i>
1041-5071 CAMMS324	Alemtuzumab 12 mg/d	45 F USA	Eye pain	The last dose of study drug prior to the event was 26 Jul 2008. On Day 175 (b) (6), the subject was unable to open her right eye and was hospitalized for grade 3 eye pain (right eye pain). Pain resolved on 14 Jan 2009 after treatment with methylprednisolone. <i>Reviewer comment: Etiology of this SAE of eye pain is unclear from the information provided.</i>

Subject Study	Treatment	Age Sex Country	Preferred Term	Description/Comment
IFNβ-1a SAE				
120-1225 CAMMS223	IFNβ-1a	39 F USA	Diplopia	Subject was hospitalized with diplopia and symptoms consistent with MS relapse. A new enhancing lesion was seen on MRI. Treated with methylprednisolone. <i>Reviewer comment: Related to MS relapse and unlikely related to IFNβ-1a</i>

7.3.2.4. Serious Adverse Events: Infections and infestations

Thirty seven of 1188 (3.1%) alemtuzumab-treated subjects in controlled trials had SAEs coded to the Infections and infestations SOC, compared to 6 of 496 (1.2%) IFNβ-1a subjects. There were 66 (4.4%) SAEs coded to the Immune system disorders SOC in all alemtuzumab-treated subjects (Pool C). Section 7.3.5.4 describes infections after alemtuzumab treatment.

7.3.2.5. Serious Adverse Events: Skin and subcutaneous tissue disorders

Nine of 1188 (0.8%) alemtuzumab-treated subjects in controlled trials had SAEs coded to the Skin and subcutaneous tissue disorders SOC, compared to 0 of 496 IFNβ-1a subjects (Table 27). Ten of 1496 (0.7%) of subjects in all alemtuzumab studies (pool C) had SAEs coded to this SOC (Table 27). Seven of 10 were infusion-associated reactions.⁵³

Brief descriptions of non-infusion reaction events in this SOC are listed below:

- Subject 7003-3435 had an SAE coded to the PT ‘Urticaria’. One month after his second alemtuzumab cycle (CAMMS323; 12 mg/day), he had urticaria of both hands. He was hospitalized and treated with loratadine. The event resolved in 2 days.
- Subject 1040-5309 had an SAE coded to the PT ‘Urticaria’. Three months after her third cycle of alemtuzumab, she developed a rash that was most consistent with a spongiotic drug reaction, according to biopsy results. She was treated with prednisone, and the rash resolved after 1 month.
- Subject 6001-5557 had an SAE coded to the PT ‘Urticaria’. Seven weeks after her first cycle of alemtuzumab, she developed urticaria and was hospitalized. She was treated with corticosteroids, and the rash resolved after 2 weeks.

⁵³ Skin disorder SAEs in Subjects 1055-5753 (Angioedema) and 2001-5657 (Rash) were not categorized as infusion-related in ISS dataset ADAE, but were considered infusion reactions in narratives.

Reviewer comment: In the opinion of this reviewer, these 3 cases of urticaria are likely related to alemtuzumab, because urticaria occurred more frequently in alemtuzumab subjects, compared to IFNB-1a subjects. (In controlled trials (Pool E), urticaria was reported as an AE in 237 of 1188 (19.9%) alemtuzumab subjects, compared to 9 of 496 (1.8%) IFNB-1a subjects; 44 of 1188 (3.7%) alemtuzumab subjects had an AE of urticaria that was not an infusion reaction.) No other possible causes for the urticaria SAEs were discussed in the narratives.

Table 27. Serious Adverse Events. Skin and subcutaneous tissue disorders SOC. Controlled trials (Pool E). ISS Analysis.

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Skin and subcutaneous tissue disorders	0 (0.0)	6 (0.7)	9 (0.8)
Urticaria	0 (0.0)	4 (0.4)	5 (0.4)
Angioedema	0 (0.0)	2 (0.2)	2 (0.2)
Increased tendency to bruise	0 (0.0)	1 (0.1)	1 (0.1)
Rash	0 (0.0)	0 (0.0)	2 (0.2)

Source: ISS Table 6-10

Table 28. Serious Adverse Events. Skin and subcutaneous tissue disorders SOC. All alemtuzumab-treated subjects (Pool C). Integrated Summary of Safety analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	10 (0.7)	6 (0.4)	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria	6 (0.4)	4 (0.3)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Angioedema	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increased tendency to bruise	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.
- Years defined by calendar time.

7.3.2.6. Serious Adverse Events: Musculoskeletal and connective tissue disorders SOC

Six of 1188 (1.5%) alemtuzumab-treated subjects in controlled trials had SAEs coded to the Musculoskeletal and connective tissue disorders SOC, compared to 5 of 496 (1.0%) IFN β -1a subjects. There were 14 (0.9%) SAEs coded to this SOC in all alemtuzumab-treated subjects (Table 29).

Table 29. Serious Adverse Events. Skin and subcutaneous tissue disorders SOC. Controlled trials (Pool E). ISS Analysis.

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Musculoskeletal and connective tissue disorders	5 (1.0)	5 (0.5)	6 (0.5)
Intervertebral disc protrusion	1 (0.2)	1 (0.1)	1 (0.1)
Muscular weakness	2 (0.4)	1 (0.1)	1 (0.1)
Myalgia	0 (0.0)	1 (0.1)	1 (0.1)
Plantar fasciitis	0 (0.0)	1 (0.1)	1 (0.1)
Rotator cuff syndrome	0 (0.0)	1 (0.1)	1 (0.1)
Osteitis	1 (0.2)	0 (0.0)	0 (0.0)
Osteoarthritis	1 (0.2)	0 (0.0)	0 (0.0)
Polyarthritis	0 (0.0)	0 (0.0)	1 (0.1)

Source: ISS Table 6-10

Table 30. Serious Adverse Events. Musculoskeletal and connective tissue disorders SOC. All alemtuzumab-treated subjects (Pool C). Integrated Summary of Safety analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	14 (0.9)	2 (0.1)	4 (0.3)	5 (0.4)	3(0.6)	1 (0.6)	0 (0.0)	1 (0.8)	0 (0.0)
Costochondritis	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscular weakness	3 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back disorder	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Intervertebral disc protrusion	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal chest pain	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoarthritis	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Plantar fasciitis	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rotator cuff syndrome	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAPHO syndrome	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Back pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pain in extremity	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Polyarthritis	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.
- Years defined by calendar time.

- The event of synovitis, acne, palmoplantar pustulosis, hyperostosis, and osteitis (SAPHO) syndrome (Subject 104-171) was an exacerbation of SAPHO syndrome that was diagnosed prior to alemtuzumab treatment. This reviewer considers this adverse event unlikely to be related to alemtuzumab.
- The event of polyarthritis (Subject 207-1239) resolved after 10 days after hospitalization and antibiotic treatment. Etiology was unclear. Blood and urine cultures were sterile.

7.3.2.7. Serious Adverse Events: Nervous system disorders SOC

In controlled trials, (Pool E), 84 of 1188 (7.1%) alemtuzumab-treated subjects in controlled trials had SAEs coded to the Nervous system disorders SOC, compared to 54 of 496 (10.9%) IFN β -1a subjects (Table 31). Multiple sclerosis relapse was the most common SAE in both groups (5.4% alemtuzumab subjects and 10.3% IFN β -1a subjects). SAEs other than multiple sclerosis relapse were more common in alemtuzumab-treated subjects (20 of 1188; 1.7%), compared to IFN β -1a subjects (3 of 496; 0.6%). There were 106 SAEs coded to this SOC in all alemtuzumab-treated subjects (Table 32); 81 were Multiple sclerosis relapse SAEs, and 25 were not MS relapses.

Table 31. Serious Adverse Events. Nervous system disorders SOC. Controlled trials (Pool E). ISS analysis.

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Nervous system disorders	54 (10.9)	72 (7.8)	84 (7.1)
Multiple sclerosis relapse	51 (10.3)	57 (6.2)	64 (5.4)
Syncope	0 (0.0)	3 (0.3)	3 (0.3)
Headache	1 (0.2)	2 (0.2)	4 (0.3)
Migraine	0 (0.0)	2 (0.2)	3 (0.3)
Brain stem syndrome	0 (0.0)	1 (0.1)	1 (0.1)
Cerebrovascular accident	0 (0.0)	1 (0.1)	1 (0.1)
Cerebrovascular insufficiency	0 (0.0)	1 (0.1)	1 (0.1)
Convulsion	0 (0.0)	1 (0.1)	1 (0.1)
Hemiparesis	0 (0.0)	1 (0.1)	1 (0.1)
Hypoxic-ischaemic encephalopathy	0 (0.0)	1 (0.1)	1 (0.1)
Intracranial hypotension	0 (0.0)	1 (0.1)	2 (0.2)
Multiple sclerosis	0 (0.0)	1 (0.1)	2 (0.2)
Myelitis	0 (0.0)	1 (0.1)	1 (0.1)
Paraparesis	0 (0.0)	1 (0.1)	2 (0.2)
Sensory loss	0 (0.0)	1 (0.1)	1 (0.1)
Spinal cord compression	0 (0.0)	1 (0.1)	1 (0.1)
Status migrainosus	0 (0.0)	1 (0.1)	1 (0.1)
Ataxia	2 (0.4)	0 (0.0)	1 (0.1)
Balance disorder	0 (0.0)	0 (0.0)	1 (0.1)

Carpal tunnel syndrome	1 (0.2)	0 (0.0)	0 (0.0)
Cerebellar ataxia	1 (0.2)	0 (0.0)	0 (0.0)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	1 (0.1)
Dizziness	1 (0.2)	0 (0.0)	0 (0.0)
Hypoaesthesia	1 (0.2)	0 (0.0)	1 (0.1)
Monoparesis	1 (0.2)	0 (0.0)	0 (0.0)
Paraesthesia	1 (0.2)	0 (0.0)	0 (0.0)
Post herpetic neuralgia	0 (0.0)	0 (0.0)	1 (0.1)
Sensory disturbance	1 (0.2)	0 (0.0)	0 (0.0)

Source: ISS Table 6-10

Table 32. Serious Adverse Events. Nervous system disorders SOC. All alemtuzumab-treated subjects (Pool C). ISS analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	106 (7.1)	51 (3.4)	39 (3.0)	25 (2.2)	10 (1.9)	7 (4.2)	4 (2.8)	4 (3.4)	3 (2.5)
Multiple sclerosis relapse	81 (5.5)	41 (2.8)	31 (2.4)	15 (1.3)	7 (1.3)	6 (3.6)	4 (2.8)	4 (3.4)	3 (2.5)
Syncope	6 (0.4)	1 (0.1)	1 (0.1)	3 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	6 (0.4)	1 (0.1)	2 (0.2)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Convulsion	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Migraine	3 (0.2)	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Brain stem syndrome	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular accident	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular insufficiency	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depressed level of consciousness	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemiparesis	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoxic-ischaemic encephalopathy	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intracranial hypotension	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple sclerosis	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Myelitis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paraparesis	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sensory loss	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal cord compression	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Status epilepticus	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Status migrainosus	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Trigeminal neuralgia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ataxia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Balance disorder	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebral haemorrhage	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoaesthesia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Loss of consciousness	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Post herpetic neuralgia	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.
- Years defined by calendar time.

Reviewer comment: The incidence of events with the Preferred Term ‘Syncope’ was similar between treatment groups. In controlled trials, 22 of 1188 (1.9%) of alemtuzumab subjects had a treatment-emergent adverse event (serious and non-serious events) with the Preferred Term ‘Syncope’, compared to 10 of 496 (2.0%) of INFβ-1a-treated subjects. The incidence of convulsions was also similar. In controlled trials, 7 of 1188 (0.6%) of subjects had a treatment-emergent adverse event in the MedDRA Convulsions SMQ, compared to 2 of 496 (0.4%) of INFβ-1a-treated subjects).⁵⁴

Six neurologic disorder SAEs were infusion-associated reactions: Headache (2), Migraine (2), Status migrainosus (1), and Brain stem syndrome (1).

Information regarding selected Neurologic SAEs in alemtuzumab-treated subjects is listed below:

- Subject 1090-5393 had an SAE coded to Preferred Term ‘Depressed level of consciousness’ during an accidental overdose of an unspecified medication.

⁵⁴ Table 13.3.13.1, p. 4481 ISS Appendix 14-4-5.

- Subject 4005-3056 had an SAE coded to Preferred Term ‘Brain stem syndrome’ as part of a cytokine release syndrome during alemtuzumab infusion. Details of this SAE are discussed in Section 7.3.5.3, which discussed infusion reactions.
- Subject 134-1089 had an SAEs coded to Preferred Term ‘Cerebrovascular accident’ and ‘Hemiparesis.’ The subject had a positive test for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome in 2004 (after her first cycle of alemtuzumab).⁵⁵ The cause of this SAE was unclear. Differential for these radiographic findings included vasculitis and demyelinating disease. Treatment included prednisone, methylprednisolone, clopidogrel, and aspirin. She was transferred to the rehabilitation unit, and the event is reported as resolved.

Reviewer comment: This subject had a cerebrovascular accident with radiologic changes possibly consistent with vasculitis. The event improved after treatment that included corticosteroids. This reviewer considers this a case of possible vasculitis. Another case of possible vasculitis occurred in CAMMS324 Subject 3006-5762; this subject had an event categorized as systemic vasculitis in Medwatch report 7154140.⁵⁶ The report describes cutaneous vasculitis, polyarthritis, hematuria, confusional state. This AE was coded to the PT ‘Erythema nodosum’ in the ISS submission. However, there was no diagnosis of erythema nodosum seen upon review of the medical records. Also, the confusion described in this subject is unexplained by a diagnosis of erythema nodosum. No biopsy was performed. The subject improved after treatment with corticosteroids.

- Subject 7003-3605, a 33 year old male from Croatia had an SAE coded to Preferred Term ‘cerebrovascular insufficiency’ (verbatim term ‘Chronic cerebro-spinal venous insufficiency’). He underwent balloon catheter angioplasty of both jugular veins. *Reviewer comment: This condition has been associated with multiple sclerosis.⁵⁷ This event is unlikely related to alemtuzumab.*
- Subject 113-1125 had an SAE coded to the PT ‘Cerebral haemorrhage.’ This adverse event was part of the fatal index case of ITP.

Reviewer comment: Multiple sclerosis relapse SAEs were more common in IFNβ-1a subjects (5.4% alemtuzumab subjects and 10.3% IFNβ-1a subjects), but Nervous system disorder SOC SAEs other than multiple sclerosis relapse were more common in alemtuzumab-treated subjects (20 of 1188; 1.7%), compared to IFNβ-1a subjects (3 of 496; 0.6%). The incidence of adverse events of syncope and adverse events of convulsions was similar in alemtuzumab subjects and IFNβ-1a subjects.

⁵⁵ It was determined that the subject was not qualified to participate in the study due to the fact that at baseline she had been misdiagnosed with MS. It was determined that the correct diagnosis was CADASIL syndrome. Safety follow-up continued for the subject and she was not included in the Full Analysis data set due to her misdiagnosis.

⁵⁶ See Appendix Section 9.1 for a copy of Medwatch case 7154140 reporting systemic vasculitis (Subject 3006-5762)

⁵⁷ Khan O, et al. Chronic cerebrospinal venous insufficiency and multiple sclerosis. *Annals of Neurology*. Volume 67, Issue 3, pages 286–290, March 2010

7.3.2.8. Serious Adverse Events: Psychiatric disorders SOC

Nine of 1188 (0.8 %) alemtuzumab-treated subjects in controlled trials (Pool E) had SAEs coded to the Psychiatric disorders SOC, compared to 0 of 496 IFN β -1a subjects (Table 33). There were 16 SAEs in this SOC in all alemtuzumab-treated subjects (Pool C; N=1485) (Table 34). A discussion of adverse events of suicidal behavior or ideation in subjects treated with alemtuzumab for multiple sclerosis is located in Section 7.3.5.6.

Table 33. Serious Adverse Events. Psychiatric disorders SOC. Controlled trials (Pool E). ISS Analysis.

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Psychiatric disorders	2 (0.4)	6 (0.7)	9 (0.8)
Bipolar disorder	0 (0.0)	1 (0.1)	1 (0.1)
Drug dependence	0 (0.0)	1 (0.1)	1 (0.1)
Insomnia	0 (0.0)	1 (0.1)	1 (0.1)
Major depression	0 (0.0)	1 (0.1)	2 (0.2)
Mania	0 (0.0)	1 (0.1)	1 (0.1)
Suicidal ideation	0 (0.0)	1 (0.1)	2 (0.2)
Suicide attempt	0 (0.0)	1 (0.1)	3 (0.3)
Anxiety	1 (0.2)	0 (0.0)	0 (0.0)
Mood altered	1 (0.2)	0 (0.0)	0 (0.0)

Source: ISS Table 6-10

Table 34. Serious Adverse Events. Psychiatric disorders SOC. All alemtuzumab-treated subjects (Pool C). ISS analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	16 (1.1)	7 (0.5)	2 (0.2)	8 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal ideation	5 (0.3)	3 (0.2)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mental status changes	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bipolar II disorder	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bipolar disorder	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug dependence	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Major depression	3 (0.2)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mania	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Schizoaffective disorder bipolar type	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicide attempt	3 (0.2)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychotic disorder	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.

- Years defined by calendar time.

7.3.2.9. Serious Adverse Events: Vascular disorders SOC

Seven of 1188 (0.6%) alemtuzumab-treated subjects in controlled trials had SAEs coded to the Vascular disorders SOC, compared to 0 of 496 IFN β -1a subjects (Table 35). Twelve of 1496 (0.8%) of subjects in all alemtuzumab studies (Pool C) had SAEs coded to this SOC (Table 36).

Table 35. Serious Adverse Events. Vascular disorders SOC. Controlled trials (Pool E). ISS Analysis.

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Vascular disorders	0 (0.0)	6 (0.7)	7 (0.6)
Hypotension	0 (0.0)	2 (0.2)	2 (0.2)
Hypertension	0 (0.0)	1 (0.1)	2 (0.2)
Thrombophlebitis	0 (0.0)	1 (0.1)	1 (0.1)
Thrombosis	0 (0.0)	1 (0.1)	1 (0.1)
Venous thrombosis limb	0 (0.0)	1 (0.1)	1 (0.1)

Source: ISS Table 6-10

Table 36. Serious Adverse Events. Vascular disorders disorders SOC. All alemtuzumab-treated subjects (Pool C). ISS analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	12 (0.8)	7 (0.5)	1 (0.1)	2 (0.2)	1 (0.2)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hypotension	3 (0.2)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Deep vein thrombosis	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	3 (0.2)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertensive crisis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombophlebitis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombosis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Venous thrombosis limb	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.
- Years defined by calendar time.

Five of 12 Pool C SAEs were infusion-associated reactions: Hypotension (Subjects 404-1334, 3006-3281, and 4006-3074); and Hypertension (Subjects 122-1319 and 1009-5030). Non-infusion reaction vascular disorder SAEs are discussed below:

- Venous thrombosis limb: Subject 1009-5034 (36 year old female from USA; CAMMS324 alemtuzumab 12 mg/day) was diagnosed with extensive thrombus in the basilic vein 4 days after the last dose of her first alemtuzumab cycle. The thrombosis occurred in the same arm used for intravenous infusion of alemtuzumab and methylprednisolone. *Reviewer comment: Intravenous catheters cause endothelial trauma and inflammation, which can lead to venous thrombosis.*
- Thrombophlebitis: Subject 1081-5578 (38 year old female from USA; CAMMS324 alemtuzumab 12 mg/day) had a lower extremity DVT 10 months after the first alemtuzumab cycle. No risk factors for DVT were described.
- Deep vein thrombosis (DVT): Subject 4001-3019 (26 year old female from UK; CAMMS323) had a right leg DVT while 28 weeks pregnant. *Reviewer comment: Pregnancy is a risk factor for DVT.*
- Deep vein thrombosis (DVT): Subject 1001-3727 (47 year old female from USA; CAMMS323 alemtuzumab 12 mg/day) developed left lower extremity DVT 16 months after her second cycle of alemtuzumab. She had risk factors for thrombosis of hyperhomocysteinemia and Factor V Leiden gene mutation.
- Thrombosis: Subject 1039-5350 (46 year old male from USA; CAMMS324 alemtuzumab 12 mg/day) had a right lower extremity blood clot 4 days after arthroscopic surgery to the right knee. *Reviewer comment: Event is unlikely related to alemtuzumab.*
- Hypertension: Subject 3006-5807 had hypertension (blood pressure measurement not provided) during hospitalization for autoimmune pancytopenia and sepsis.
- Hypertensive crisis: Subject 6010-3077 (48 year old male from Russia assigned to IFN β -1a in CAMMS323; SAE occurred in CAMMS03409 9 months after the first alemtuzumab cycle) had a medical history of hypertension upon entry to CAMMS323. He had a hypertensive crisis after undergoing bronchoscopy for a COPD exacerbation. *Reviewer comment: Event is unlikely related to alemtuzumab.*

Reviewer comment: Of the five SAEs of venous thrombosis in all alemtuzumab studies (Pool C), 4 had documented risk factors for thrombosis.

7.3.2.10. Serious Adverse Events: Immune system disorders SOC

Two of 1188 (0.2%) alemtuzumab-treated subjects in controlled trials had SAEs coded to the Immune system disorders SOC, compared to 0 of 496 IFN β -1a subjects. There were 3 SAEs coded to the Immune system disorders SOC in all alemtuzumab-treated subjects (Table 37).

Table 37. Serious Adverse Events. Immune system disorders SOC. All alemtuzumab-treated subjects (Pool C). ISS analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	3 (0.2)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaphylactic shock	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergy to arthropod	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaphylactoid reaction	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.

- Years defined by calendar time.

The SAEs coded to Preferred Terms Anaphylactic shock and Anaphylactoid reaction are infusion reactions discussed in Section 7.3.5.3, which discusses infusion reactions.

7.3.2.11. Serious Adverse Events: Endocrine disorders SOC

All SAEs in the Endocrine disorders SOC in alemtuzumab-treated subjects were thyroid-related. An analysis of thyroid disorders is located in Section 7.3.5.1.1.

7.3.2.12. Serious Adverse Events: Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC

In controlled trials, (Pool E), 14 of 1188 (1.2%) alemtuzumab-treated subjects in controlled trials had SAEs coded to the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC, compared to 3 of 496 (0.6%) IFN β -1a subjects. A discussion of malignancies in subjects treated with alemtuzumab for multiple sclerosis is located in Section 7.3.5.2.

7.3.2.13. Serious Adverse Events: Hepatobiliary disorders SOC

Hepatobiliary disorders are reviewed in Submission Specific Primary Safety Concerns Section 7.3.5.7.

7.3.3 Dropouts and/or Discontinuations

Sponsor ISE Table 3-3 (below) provides subject disposition for randomized subjects in CAMMS trials.

Reviewer comment: The CAMMS trials were open label trials. There are notable findings in subject disposition seen in ISE Table 3-3. Percentages of subjects completing treatment and completing the study were substantially lower in IFN β -1a subjects compared to alemtuzumab subjects. Also, randomized subjects in CAMMS324 were required to have experienced an inadequate response to prior MS therapy with IFN β -1a or glatiramer acetate. Therefore, it is understandable that in this open-label trial, 11.7% of subjects assigned to IFN β -1a (a drug with which many subjects already had an inadequate treatment response) discontinued prior to treatment, compared to 1.6% of alemtuzumab-assigned subjects.

Table 38. Sponsor ISE Table 3-3. Subject disposition. Randomized subjects.

Table 3-3: Patient Disposition: Randomized Patients

	CAMMS324		CAMMS323		CAMMS223	
	SC IFNB-1a (N=231)	Alem 12 mg/day (N=436)	SC IFNB-1a (N=195)	Alem 12 mg/day (N=386)	SC IFNB-1a (N=111)	Alem 12 mg/day (N=113)
Patients Randomized	231	436	195	386	111	113
Discontinued Prior to Treatment, n (%)	29 (12.6)	10 (2.3)	8 (4.1)	10 (2.6)	4 (3.6)	5 (4.4)
Investigator decision	0	2 (0.5)	0	0	0	1 (0.9)
Withdrawal by patient	27 (11.7)	7 (1.6)	7 (3.6)	8 (2.1)	1 (0.9)	0
Other	2 (0.8)	1 (0.2)	1 (0.5)	2 (0.6)	3 (2.7)	4 (3.6)
Patients Treated, n (%)	202 (87.4)	435 ^a	187 (95.9)	376 (97.4)	107 (96.4)	108 (95.6)
Completed Treatment^b, n (%)	158 (78.2)	404 (92.9)	164 (87.7)	360 (95.7)	56 (52.3)	102 (94.4)
Discontinued Treatment, n (%)	44 (21.8)	31 (7.1)	23 (12.3)	16 (4.3)	51 (47.7)	6 ^c (5.6)
Completed Study^d, n (%)	175 (75.8)	416 (95.4)	173 (88.7)	367 (95.1)	66 (59.5)	92 (81.4)
Discontinued Study ^d , n (%)	56 (24.2)	20 (4.6)	22 (11.3)	19 (4.9)	41 (36.9)	16 (14.2)
AE	6 (2.6)	2 (0.5)	5 (2.6)	1 (0.3)	13 (11.7)	3 (2.7)
Lack of efficacy	6 (2.6)	0	2 (1.0)	0	16 (14.4)	2 (1.8)
Investigator decision	3 (1.3)	4 (0.9)	1 (0.5)	2 (0.5)	3 (2.7)	0
Withdrew consent/Patient refused further treatment	36 (15.6)	11 (2.5)	12 (6.2)	12 (3.1)	4 (3.6)	8 (7.1)
Death	0	1 (0.2)	0	1 (0.3)	0	1 (0.9)
Protocol violation	1 (0.4)	0	0	0	2 (1.8)	0
Lost to follow up	1 (0.4)	1 (0.2)	0	1 (0.3)	0	2 (1.8)
Pregnancy	1 (0.4)	0	1 (0.5)	0	0	0
Other	2 (0.9)	1 (0.2)	1 (0.5)	2 (0.5)	3 (2.7)	0

^a Includes 426 patients randomized to alemtuzumab 12 mg/day plus 9 patients randomized to alemtuzumab 24 mg/day who received alemtuzumab 12 mg/day.

^b Percentages of patients who completed or discontinued treatment are of the number of patients treated. Completed alemtuzumab treatment in CAMMS324 and CAMMS323 includes patients who received the full planned dose of alemtuzumab (2 cycles); discontinued treatment includes all patients who did not receive the full planned dose of alemtuzumab. Completed treatment in CAMMS223 includes patients who completed 2 cycles of alemtuzumab 12 mg/day during the original 3-year study period.

^c Includes 2 patients who did not receive Cycle 2 in CAMMS223 due to the dosing suspension.

^d In CAMMS223, the numbers of patients who completed or discontinued the study are based on the original 3-year study period and percentages are of the number of treated patients.

Source: CAMMS223 Final CSR Table 9-1, Table 14.1.2.1, Table 9-8, Table 9-9; CAMMS323 CSR Figure 9-1, Table 14.1.1.1.1, Table 14.1.1.1.2, Table 9-6, Table 9-7; CAMMS324 CSR Figure 9-1; Table 14.1.1.1.1; Table 14.1.1.1.2, Table 9-8, Table 9-9.

Source: Sponsor Table 3-3 on p. 91 of the ISE; submitted to NDA 103948 on November 27, 2012

Adverse Events Associated with Discontinuation

In controlled trials, adverse events leading to treatment discontinuation occurred most frequently in the following System Organ Classes: Blood and lymphatic system

disorders; Cardiac disorders; Respiratory, thoracic and mediastinal disorders; and Skin and subcutaneous tissue disorders (Table 39). (In each listed SOC, there were 4 adverse events leading to treatment discontinuation in the alemtuzumab pooled dose group).

Table 39. MedDRA SOC with Most Frequent Incidence of Treatment-Emergent Adverse Events Leading to Treatment Withdrawal by MedDRA SOC and Preferred Term. Controlled Trials (Pool E)

System Organ Class Preferred Term	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)
	n (%)	n (%)	n (%)
Any Event	39 (7.9)	22 (2.4)	7 (2.6)
Blood and lymphatic system disorders	5 (1.0)	3 (0.3)	1 (0.4)
Autoimmune thrombocytopenia	0 (0.0)	1 (0.1)	0 (0.0)
Idiopathic thrombocytopenic purpura	0 (0.0)	1 (0.1)	1 (0.4)
Lymphopenia	2 (0.4)	1 (0.1)	0 (0.0)
Neutropenia	1 (0.2)	0 (0.0)	0 (0.0)
Thrombocytopenia	2 (0.4)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	3 (0.3)	1 (0.4)
Cardiovascular disorder	0 (0.0)	1 (0.1)	0 (0.0)
Coronary artery disease	0 (0.0)	1 (0.1)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.1)	0 (0.0)
Tachycardia	0 (0.0)	1 (0.1)	0 (0.0)
Sinus tachycardia	0 (0.0)	0 (0.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	3 (0.3)	1 (0.4)
Dyspnoea	0 (0.0)	2 (0.2)	0 (0.0)
Pharyngeal oedema	0 (0.0)	1 (0.1)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	1 (0.4)
Pulmonary embolism	1 (0.2)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.4)	4 (0.4)	0 (0.0)
Dermatitis allergic	0 (0.0)	1 (0.1)	0 (0.0)
Purpura	0 (0.0)	1 (0.1)	0 (0.0)
Rash	0 (0.0)	1 (0.1)	0 (0.0)
Urticaria	1 (0.2)	1 (0.1)	0 (0.0)
Alopecia	1 (0.2)	0 (0.0)	0 (0.0)

-Percentages are based on the number of treated subjects in the corresponding treatment group.

-A subject is counted only once within each SOC/PT.

Source: Table 13.3.3.7 ISS Appendix 14-4-5, p. 3240-3244

Adverse events leading to treatment discontinuation represented topics of overall concern in the safety profile for alemtuzumab. Appendix 9.2 of this review lists the incidence of all treatment-emergent adverse events leading to treatment withdrawal by MedDRA SOC and Preferred Term in controlled trials.

Reviewer comment: Notable adverse events leading to discontinuation are discussed elsewhere in this review, including Section 7.3.2 (Nonfatal Serious Adverse Events) and Section 7.3.5 (Submission Specific Primary Safety Concerns).

Also, errors were seen in Sponsor ISS Table 6-11 (p. 222-225), titled “Incidence of Adverse Events Leading to Treatment Discontinuation in All Active-Controlled Studies.

(Some adverse events listed for the alemtuzumab 12 mg/day dose group were not listed for the alemtuzumab pooled dose group.)

7.3.4 Significant Adverse Events

Significant adverse events will be discussed in Section 7.3.5. Submission-Specific Primary Safety Concerns.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Submission Specific Primary Safety Concerns: Autoimmune Diseases

Autoimmune Diseases: Introduction

In Phase 2 Study CAMMS223, secondary autoimmunity emerged as an important group of adverse events after alemtuzumab treatment. This section describes autoimmune disorders seen after alemtuzumab treatment in Genzyme clinical trials of MS, as well as published cases and postmarketing cases.

Alemtuzumab is a monoclonal antibody that depletes cells carrying CD52. In expanded lymphocyte phenotyping sub-studies conducted in CAMMS323 and CAMMS324, naïve T and B cells were depleted by alemtuzumab to a relatively greater extent than Memory T and B cells.⁵⁸ Altered immune reconstitution is a likely underlying mechanism of autoimmunity with alemtuzumab.

Autoimmune disorders discussed in this section are:

- Thyroid disorders (including Graves' disease and thyroiditis)
- Endocrine ophthalmopathy
- Immune cytopenias
 - Immune thrombocytopenia
 - Autoimmune hemolytic anemia
 - Immune pancytopenia
- Acquired hemophilia A (anti-Factor VIII antibodies)
- Autoimmune kidney diseases
 - Anti-glomerular basement membrane (Anti-GBM) disease
 - Membranous glomerulonephritis
- Type 1 diabetes mellitus
- Acute epitheliopathy of the retina
- Autoimmune skin disease
- Undifferentiated connective tissue disorders

⁵⁸ ISS Appendix 14-7. Lymphocyte phenotyping report, p. 29.

7.3.5.1.1. Autoimmune Diseases: Thyroid Disorders

Incidence and Rate

In the active-controlled studies, the incidence of thyroid AEs was higher in the alemtuzumab 12 mg/day group (18.3%) than in the IFNB-1a group (5.4%) (see table below). Similarly, the rate of thyroid AEs over the 3-year follow-up period was also higher for the 12 mg/day group (0.122 per person year) compared to the IFNB-1a group (0.034 per person year).⁵⁹ The most commonly reported adverse event Preferred Terms were Hypothyroidism, Hyperthyroidism, and Basedow's disease (also known as Graves' disease).

Reviewer comment: The reported number of Graves' disease adverse events (using the Preferred Term Basedow's disease) likely does not include all Graves' disease cases. This reviewer has noted subjects who had an adverse event of 'Hyperthyroidism' and an abnormal level of anti-thyroid stimulating hormone (anti-TSH) receptor antibodies, which are the pathogenic entity for Graves' disease.⁶⁰ This reviewer has also noted subjects without an adverse event coded as Basedow's disease who had coexisting thyrotoxicosis, goiter and ocular signs. (This combination is the basis of clinical diagnosis of Graves' disease.)⁶¹

⁵⁹ Sponsor Table 13.3.6.2 on p. 4375-4376 of ISS Appendix 14-4-5.

⁶⁰ Weetman AP. Graves' Disease. N Engl J Med 2000; 343:1236-1248

⁶¹ Ginsberg J. Diagnosis and management of Graves' disease. CMAJ. 2003 March 4; 168(5): 575-585.

Table 40. Sponsor Table 6-21. Incidence of Thyroid Adverse Events in All Active-Controlled Studies (Pool E)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)
Any Event	27 (5.4)	168 (18.3)	220 (18.5)
Endocrine disorders	13 (2.6)	134 (14.6)	175 (14.7)
Hypothyroidism	8 (1.6)	46 (5.0)	59 (5.0)
Hyperthyroidism	4 (0.8)	38 (4.1)	55 (4.6)
Basedow's disease	0 (0.0)	29 (3.2)	42 (3.5)
Autoimmune thyroiditis	2 (0.4)	16 (1.7)	21 (1.8)
Goitre	2 (0.4)	13 (1.4)	19 (1.6)
Thyroiditis	1 (0.2)	5 (0.5)	7 (0.6)
Thyroiditis subacute	0 (0.0)	2 (0.2)	3 (0.3)
Primary hypothyroidism	0 (0.0)	1 (0.1)	1 (0.1)
Thyroid cyst	0 (0.0)	1 (0.1)	1 (0.1)
Thyroid mass	0 (0.0)	1 (0.1)	1 (0.1)
Thyrotoxic crisis	0 (0.0)	1 (0.1)	1 (0.1)
Investigations	14 (2.8)	47 (5.1)	62 (5.2)
Blood thyroid stimulating hormone decreased	5 (1.0)	22 (2.4)	30 (2.5)
Blood thyroid stimulating hormone increased	5 (1.0)	11 (1.2)	14 (1.2)
Anti-thyroid antibody positive	0 (0.0)	10 (1.1)	12 (1.0)
Thyroxine free decreased	0 (0.0)	6 (0.7)	8 (0.7)
Tri-iodothyronine free increased	1 (0.2)	4 (0.4)	7 (0.6)
Thyroid function test abnormal	0 (0.0)	3 (0.3)	3 (0.3)
Tri-iodothyronine free decreased	0 (0.0)	3 (0.3)	4 (0.3)
Thyroxine free increased	0 (0.0)	2 (0.2)	2 (0.2)
Thyroxine decreased	1 (0.2)	1 (0.1)	3 (0.3)
Thyroxine increased	1 (0.2)	1 (0.1)	2 (0.2)
Tri-iodothyronine increased	0 (0.0)	1 (0.1)	1 (0.1)
Blood thyroid stimulating hormone abnormal	1 (0.2)	0 (0.0)	0 (0.0)
Thyroxin binding globulin increased	0 (0.0)	0 (0.0)	1 (0.1)
Tri-iodothyronine decreased	0 (0.0)	0 (0.0)	2 (0.2)
Surgical and medical procedures	0 (0.0)	2 (0.2)	3 (0.3)
Thyroidectomy	0 (0.0)	2 (0.2)	3 (0.3)

Thyroid disorders refers to AEs with HLGT = Thyroid gland disorders or HLT=Thyroid analyses or PT=Blood thyroid stimulating hormone abnormal, Blood thyroid stimulating hormone increased, or Blood thyroid stimulating hormone decreased.

SC = subcutaneous; IFNB-1a = interferon beta-1a; HLGT = high level group term; HLT = high level term; PT = preferred term

Source: ISS Table 6-21 p. 290

Thyroid disorders were defined as a thyroid AE and/or a thyroid laboratory abnormality. Thyroid disorders occurred in 38.6% of subjects in the alemtuzumab 12 mg/day group compared to 28.2% in the IFNB-1a group (see table below).

Table 41. Sponsor Table 6-22: Incidence of Treatment-Emergent Thyroid Disorders in All Active-Controlled Studies (Pool E)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled (N=1188)
	n/N (%)	n/N (%)	n/N (%)
Abnormal TSH	115/491 (23.4)	302/919 (32.9)	380/1188 (32.0)
TSH < LLN	79/491 (16.1)	232/919 (25.2)	304/1188 (25.6)
TSH > ULN	43/491 (8.8)	147/919 (16.0)	178/1188 (15.0)
Abnormal FT4	46/477 (9.6)	202/896 (22.5)	264/1155 (22.9)
Any thyroid lab abnormality (defined as abnormal TSH or FT4)	139/491 (28.3)	344/919 (37.4)	441/1188 (37.1)
Patients with thyroid AEs	27/496 (5.4)	168/919 (18.3)	220/1188 (18.5)
Abnormal TSH and thyroid AE	24/491 (4.9)	153/919 (16.6)	196/1188 (16.5)
Abnormal FT4 and thyroid AE	11/477 (2.3)	117/896 (13.1)	154/1155 (13.3)
Any thyroid lab abnormality and thyroid AE	26/491 (5.3)	157/919 (17.1)	220/1188 (18.5)
Any thyroid lab abnormality or thyroid AE	140/496 (28.2)	355/919 (38.6)	458/1188 (38.6)

Thyroid AEs refer to AEs coded to MedDRA HLGT 'Thyroid gland disorders', or coded to HLT 'Thyroid analyses', 'Thyroid radiotherapies', 'Thyroid therapeutic procedures', 'Thyroid histopathology procedures', or coded to PT 'Blood thyroid stimulating hormone abnormal', 'Blood thyroid stimulating hormone increased', 'Blood thyroid stimulating hormone decreased'.

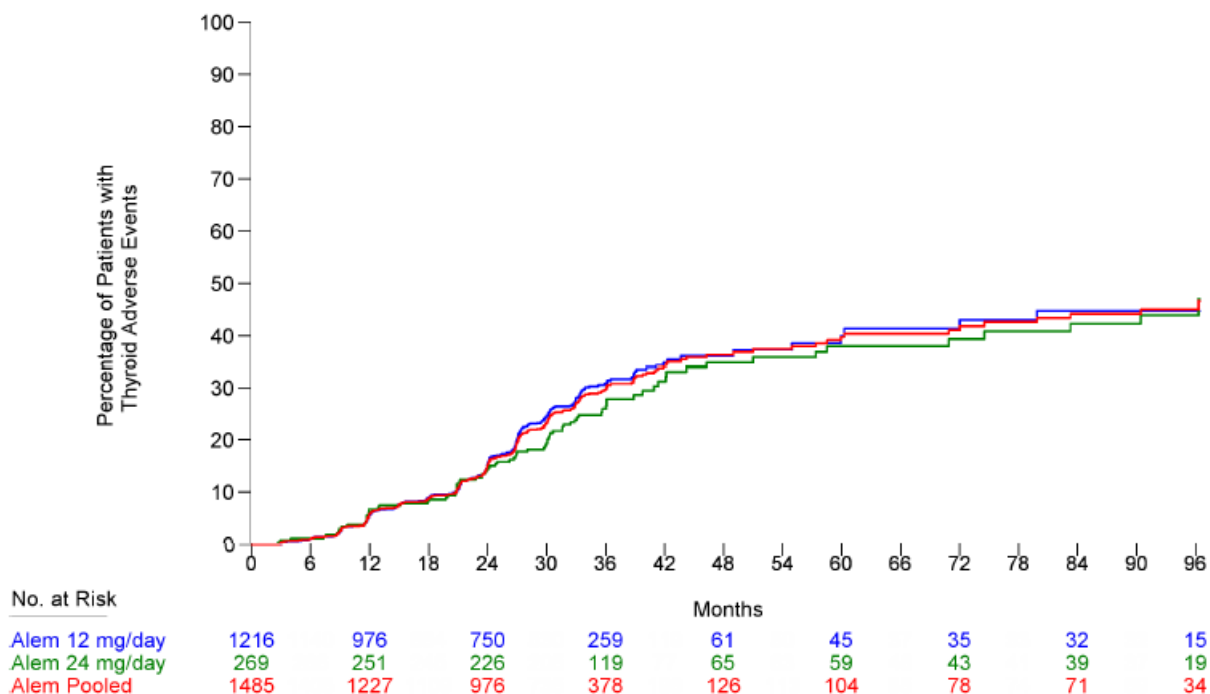
SC = subcutaneous; IFNB-1a = interferon beta-1a; TSH = Thyroid Stimulating Hormone, LLN = Lower Limit of Normal, ULN = Upper Limit of Normal, FT4 = Free levothyroxine.

Source: Table 6-22. ISS p. 295.

Time to First Thyroid Adverse Event

The risk of experiencing a first thyroid AE was most increased between Months 6 and 42. First thyroid AEs continued to occur between Months 42 and 96 at a lower incidence; fewer subjects participated in studies between Months 42 and 96 (see figure below).

Figure 2. Sponsor Figure 6-2. Time to First Thyroid Adverse Event in All Alemtuzumab-Treated Subjects (All Alemtuzumab-Treated Subjects, Pool C)



Source: Figure 3.3.6.1

Note: Percentages of patients with event are based on Kaplan-Meier estimation.

No. = number; Alem = alemtuzumab

Source: Sponsor Figure 6-2 ISS p. 279.

Thyroid Serious Adverse Events

In controlled trials (Pool E), serious thyroid AEs were reported in 12 of 1188 (0.9%) of alemtuzumab-treated subjects. In controlled trials, 4 of 1188 (0.3%) of alemtuzumab-treated subjects required thyroidectomy. None of the 496 subjects assigned IFN β -1a in controlled trials had a thyroid SAE in controlled trials.

In follow-up including the extension study (Pool C; cut-off date November 26, 2012), 30 of 1485 (2.0 %) alemtuzumab-treated had a serious thyroid AE, and 19 of 1485 (1.3%) required thyroidectomy (Table 42). Serious thyroid adverse event occurred in 23 of 972 (2.4%) female subjects, compared to 7 of 513 (1.4%) male subjects (Pool C).

Table 42. Listing of Thyroid SAEs for All Alemtuzumab-Treated Subjects (Pool C)

Subject	Study	Age Sex Country	Number of Cycles (Total Dose)	Thyroid-ectomy	Preferred Term	Description/Comment
Controlled trial treatment: alemtuzumab 12 mg/day						
202-1312 (7003-1312)	CAMMS 03409	34 F Croatia	2 Cycles (96 mg)	Y	Hyperthyroidism	First dose May 2004. Diagnosed with hyperthyroidism Dec 2005. Treatment-emergent TSH antibody, likely diagnosis is Graves' Disease. Underwent thyroidectomy (b) (6).
302-1187	CAMMS 03409	30 M Russia	3 Cycles (132 mg)	Y	Basedow's Disease	Hospitalized (b) (6) 23 months after the last dose of study drug for Basedow's disease (Graves' disease) and underwent thyroidectomy. Diagnosed with endocrine ophthalmopathy. Had sinus rhythm with partial block of right atrioventricular bundle and signs of cardiofibrosis in interventricular septum area. Also diagnosed with Hashimoto's thyroiditis.
302-1203	CAMMS 03409	41 F Russia		Y	Autoimmune thyroiditis	Required thyroidectomy. Diagnosed with ophthalmopathy. Had tachycardia with heart rate in the 120's.
302-1308	CAMMS 03409	32 M Russia	3 Cycles (132 mg)	Y	Basedow's disease	First dose of Alemtuzumab was in May 2004. Diagnosed with Graves' disease and endocrine ophthalmopathy September 2006. Thyroidectomy in (b) (6).
1009-3025	CAMMS 03409	33 F USA	2 Cycles (96 mg)	Y	Basedow's disease	First Alemtuzumab in Jan 2008. In Jul 2010 diagnosed with Basedow's disease (Graves disease). Failed thiamazole treatment. Thyroidectomy (b) (6).
1018-3090	CAMMS 323	32 F USA	1 Cycle (60 mg)	Y	Basedow's disease Thyrotoxic crisis SAE in infant offspring: Thyrotoxic crisis (thyroid storm)	First alemtuzumab 12 May 2008. Pregnancy was reported Sept 2008. Laboratory results consistent with Graves' Disease in November 2008. She was treated with propylthiouracil (PTU) and metoprolol. Had tachycardia in the 160's. Male infant born by cesarean section at 38 2/7 weeks gestation on (b) (6). The infant was discharged, but had neonatal Graves' disease with life-threatening thyroid storm 21 days after birth. He experienced intermittent apnea and decreases in heart rate but recovered. He was treated with PTU, which was discontinued after thyroid hormone levels fell in hypothyroid range. According to a Genzyme response dated December 13, 2012, the investigator said on 07 Dec 2012: "We just re-confirmed that the infant of subject 1018-3090 has experienced

Subject	Study	Age Sex Country	Number of Cycles (Total Dose)	Thyroid- ectomy	Preferred Term	Description/Comment
						<p>no further adverse events since the resolution of the grade 4 thyroid storm in (b) (6) and has not been followed by any physician regarding this event since the infant's discharge in (b) (6). No laboratory testing has been performed since the infant's discharge. All medical records concerning this event were forwarded to Genzyme PV in June 2009. No further records are available or are expected. Subject 1018-3090 reports no further related adverse events experienced by her son since event resolution in 2009.'</p> <p>On 17-19 Aug 2009, the subject received alemtuzumab cycle 2. On (b) (6) after an elective hysterectomy, she experienced grade 3 thyroid storm with tachycardia (HR 120's) and fever (over 38.3C). She underwent thyroidectomy in (b) (6)</p> <p>On (b) (6) she was hospitalized for grade 3 agranulocytosis. Between Day 720 (b) (6) and Day 730 (b) (6), subject's WBC and ANC remained low, with results ranging from 0.9 x 103/mm3 to 4.2 x 103/mm3 and from 0.0 x 103/mm3 to 0.1 x 103/mm3, respectively. A bone marrow aspiration and biopsy performed on Day 724 (b) (6) revealed normocellular marrow with granulocyte aplasia. She received therapeutic plasma exchange. Neutrophils started to be detectable on Day 730 (b) (6). During hospital stay, the subject had neutropenic fever and was treated with broad spectrum antibiotics. The subject's blood cultures, urine cultures, and HIV test were all negative.</p> <p><i>Reviewer comment: The subject experienced agranulocytosis while taking PTU to treat Graves' disease; agranulocytosis is described in the Warnings section of the prescribing information for PTU.</i></p> <p>The subject was diagnosed with endocrine ophthalmopathy in</p>

Subject	Study	Age Sex Country	Number of Cycles (Total Dose)	Thyroid-ectomy	Preferred Term	Description/Comment
						Apr 2010. In (b) (6) she was hospitalized for endocrine ophthalmopathy and underwent endoscopic facial decompression. In (b) (6) she was hospitalized, because of ongoing thyroid orbitopathy, including headaches and vision disturbances. This issue is still ongoing as of last report.
1039-3028	CAMMS 03409	24 F USA	2 Cycles (96 mg) at time of AE, 3 Cycles (132 mg) total	N	Hyperthyroidism	Hospitalized for thyrotoxicosis with HR 161 BPM. Diagnosed with Graves' disease.
1101-3515	CAMMS 03409	33 F Canada	2 Cycles (96 mg)	N	Hyperthyroidism	Hyperthyroidism with hospitalization for depression. She had suicidal ideation and attempted suicide via an overdose of quetiapine (50 tablets 25 mg strength).
3102-3735	CAMMS 03409	48 F Mexico	2 Cycles (96 mg)	Y	Hypothyroidism	Autoimmune hypothyroidism requiring thyroidectomy.
4007-3635	CAMMS 03409	41 F UK	2 Cycles (96 mg)	N	Basedow's disease	Hospitalized for palpitations and Basedow's disease, as well as autoimmune hemolytic anemia.
4634-3725	CAMMS 03409	39 M Germany	3 Cycles (132 mg)	N	Basedow's disease	Basedow's disease requiring hospitalized for radioiodine therapy.
4701-3701	CAMMS 323	27 F Sweden	1 Cycle (60 mg) at AE, 2 Cycles (96 mg) total	Y	Basedow's disease	Basedow's disease requiring thyroidectomy.
6001-3586	CAMMS 03409	25 F Russia	1 Cycle (60 mg)	Y	Basedow's disease Goitre	Basedow's disease requiring thyroidectomy.
1059-5028	CAMMS 03409	40 F USA	3 Cycles (132 mg)	Y	Basedow's disease	Basedow's disease requiring thyroidectomy.
4106-5472	CAMMS 03409	29 F Italy	2 Cycles (96 mg)	N	Hyperthyroidism Hypothyroidism	Thyroiditis treated with thiamazole, which resulted in hypothyroidism
5302-5300	CAMMS 324	50 F Denmark	2 Cycles (96 mg)	N	Hypothyroidism	Hypothyroidism requiring hospitalization for peripheral edema.
6002-5241	CAMMS	23 F	2 Cycles	Y	Basedow's	Basedow's disease requiring thyroidectomy.

Subject	Study	Age Sex Country	Number of Cycles (Total Dose)	Thyroid-ectomy	Preferred Term	Description/Comment
	03409	Russia	(96 mg)		disease	
4607-5413*	CAMMS 03409	33 F Germany	2 Cycles (96 mg)	Y	Basedow's disease	Graves' disease with nervousness, sweating, rapid pulse, increased bowel movements and hair loss. Underwent thyroidectomy. (Manufacturer report CAMP 1002409 Follow-up report #2 submitted to IND 010717 on 07 Nov 2012.)
2005-5724*	CAMMS 324	46 F Australia	2 Cycles (96 mg)	Y	Basedow's disease	Basedow's disease requiring thyroidectomy (Manufacturer report CAMP 1002581 Follow-up #1 entered to IND 010717 13 Dec 2012.)
7002-3476*	CAMMS 03409	34 F Croatia	2 Cycles (96 mg)	Y	Hyperthyroidism	Hyperthyroidism requiring thyroidectomy. (Manufacturer report CAMP 1002102 on p. 692 of ISS Appendix 14-3-2-4)
1053-5726*	CAMMS 03409	37 F USA	3 cycles (132 mg)	N	Hyperthyroidism	Hyperthyroidism secondary to thyroiditis. Had sinus bradycardia and change in mental status. Hyperthyroidism treated medically (treatment not specified). (ISS Appendix 16-6 p. 76)
1037-5653*	CAMMS 324	32 F USA	2 Cycles (96 mg)	Y	Basedow's disease	Graves' disease requiring thyroidectomy. Thyroid cancer found on pathology. (ISS Appendix 14-6 p. 76)
Controlled trial treatment: alemtuzumab 24 mg/day						
104-1124	CAMMS 223	29 F USA	2 Cycles (192 mg)	Y	Basedow's disease	Basedow's disease requiring thyroidectomy.
107-1057	CAMMS 223	34 M USA	3 Cycles (238 mg)	N	Thyroiditis subacute	Subacute thyroiditis treated with propylthiouracil
305-1192	CAMMS 03409	43 M Russia	3 Cycles (228 mg)	N	Basedow's disease	Basedow's disease prolonging hospitalization for acute gastric ulcer
1046-5011	CAMMS 324	36 F USA	2 Cycles (156 mg)	N	Hypothyroidism	Hypothyroidism with positive anti-nuclear antibodies (ANA) and microglobulin antibodies.
1046-5047	CAMMS 324	34 F USA	1 Cycles (120 mg at time of AE, 156 mg total)	Y	Goitre	Multinodular goiter with Hurthle cell follicular epithelial change
6001-5153	CAMMS	36 F	2 Cycles	Y	Autoimmune	Autoimmune thyroiditis requiring thyroidectomy.

Subject	Study	Age Sex Country	Number of Cycles (Total Dose)	Thyroid- ectomy	Preferred Term	Description/Comment
	03409	Russia	(192 mg)		thyroiditis	
2009-5598*	CAMMS0 3409	38 F Australia	2 Cycles (192 mg)	Y	Hyperthyroidism Hypomania	<p>On (b) (6) the subject experienced hyperthyroidism associated with hypomanic episode. The discharge summary mentions the subject had attempted suicide the week prior to this hospital admission (she took an impulse overdose of her son's methylphenidate). The Investigator indicated that the subject's suicide attempt was likely misreported by a junior physician and after speaking with the subject's psychiatrist it was felt the subject had more likely overdosed to 'get high' while hypomanic.</p> <p>Subject required thyroidectomy.</p> <p><i>Reviewer note: As described above, there was disagreement on whether this subject had a suicide attempt. The treating physician classified the event as a suicide attempt, while the investigator did not classify this event as a suicide attempt. Based on the investigator's opinion, the adverse event of suicide attempt was deleted from the adverse event database by Genzyme.</i></p> <p>(Manufacturer report CAMP 1002403. Follow-up #3 entered to IND 010717 on 27 Nov 2012.)</p>

Data as of November 26, 2012. Sources: ISS, ISS Appendix 14-6, 4-month safety update, narratives, and manufacturer safety reports.

Reviewer comment: The infant offspring of Subject 1018-3090 had a SAE of neonatal Graves' disease, which is caused by transfer of TSH receptor antibodies from mother to fetus. This raises a concern of possible transfer of other autoimmune antibodies from mother to fetus.

Thyroid Events by Baseline Anti-Thyroid Peroxidase (Anti-TPO) Receptor Antibody Status

The presence of baseline anti-TPO antibodies was associated with higher incidences of thyroid AEs and thyroid laboratory abnormalities across all treatment groups, including the IFNB-1a group. In the alemtuzumab 12 mg/day group, 30/67(44.8%) subjects with positive anti-TPO antibodies at baseline had a thyroid AE compared with 136/842 (16.2%) for subjects with a negative anti-TPO test, with similar results for the alemtuzumab pooled dose group. In the IFNB-1a group, 6/36 (16.7%) subjects with positive anti-TPO antibodies at baseline had a thyroid AE compared with 20/451 (4.4%) for subjects with a negative baseline anti-TPO.

An abnormal level of anti-thyroid stimulating hormone (anti-TSH) receptor antibodies at baseline was an exclusion criterion in Phase 2-3 Genzyme trials of alemtuzumab for MS. Analyses of the association between baseline anti-TSH receptor antibodies and post-treatment thyroid AEs could not be performed.

Thyroid Disorders: Reviewer Conclusion and Recommendations

In the active-controlled studies, the incidence of thyroid AEs was higher in the alemtuzumab 12 mg/day group (18.3%) than in the IFNB-1a group (5.4%). The risk of experiencing a first thyroid AE was greatest between Months 6 and 42. First thyroid AEs continued to occur between Months 42 and 96 at a lower incidence; fewer subjects participated in studies between Months 42 and 96.

Genzyme proposes obtaining tests of thyroid function (e.g., TSH) prior to initiation of treatment and every 3 months until 48 months after the last infusion. The incidence of thyroid disorders more than 4 years after the last dose of alemtuzumab is not clear, given the small number of subjects with follow-up in that time period.

If alemtuzumab is approved for marketing this reviewer recommends:

- Discussion of thyroid disorders in the Warnings and Precautions Section of prescribing information
- Obtaining tests of thyroid function (e.g., TSH) prior to initiation of treatment and every 3 months until 48 months after the last infusion
- Obtaining tests of thyroid function (e.g., TSH) yearly beyond 48 months after the last infusion
- Evaluation of thyroid disorders in alemtuzumab-treated subjects in the postmarketing period through a post-marketing requirement to better characterize long-term sequelae.

7.3.5.1.2. Autoimmune Diseases: Graves' Ophthalmopathy

In Graves' disease, anti-thyrotropin-receptor antibodies can trigger the proliferation of orbital fibroblasts, leading to increased retroorbital fat and enlarged extraocular muscles (i.e., Graves' ophthalmopathy). Clinically apparent Graves' ophthalmopathy occurs in 30-50% of subjects with Graves' disease.⁶² Common clinical features include upper eyelid retraction, exophthalmos, edema, and erythema of the periorbital tissues and conjunctivae. Severe disease can result in intense pain, inflammation, and sight-threatening corneal ulceration or compressive optic neuropathy; severe disease occurs in 3-5% of subjects with Graves' ophthalmopathy. In addition to functional eye impairment, Graves' ophthalmopathy can cause facial disfigurement with important psychosocial consequences.⁶³

19 of 1485 (1.3%) alemtuzumab-treated subjects (Pool C) had documented Graves' ophthalmopathy.⁶⁴ Two subjects have received surgical treatment (Subjects 1018-3090 and 134-1053). There were no protocol predefined procedures to assess the occurrence of ocular manifestations of Graves' disease in the alemtuzumab clinical studies. Since the manifestations of Graves' ophthalmopathy are often nonspecific, the incidence of Graves' ophthalmopathy in alemtuzumab-treated subjects likely has not been fully measured.

If alemtuzumab is approved for marketing this reviewer recommends:

- Discussion of Graves' ophthalmopathy in the Warnings and Precautions Section of prescribing information
- Evaluation of Graves' ophthalmopathy in alemtuzumab-treated patients in the postmarketing period through a post-marketing requirement to better characterize long-term sequelae

7.3.5.1.3. Autoimmune Diseases: Immune Cytopenias

Immune Thrombocytopenia (ITP)

The risk of ITP was identified in Study CAMMS223, when 3 cases of ITP were diagnosed, including a fatal index case. After these cases were diagnosed, alemtuzumab dosing was suspended and a safety monitoring program was implemented in alemtuzumab clinical studies. This program included subject and investigator education regarding the signs of ITP, monthly complete blood counts, and a monthly subject monitoring survey for ITP symptoms, offset by 2 weeks from the laboratory testing.

⁶² Bahn RS. N Engl J Med 2010; 362:726-738

⁶³ Wiersinga WM. Best Pract Res Clin Endocrinol Metab. 2012 Jun;26(3):359-70.

⁶⁴ Nineteen cases were identified by this reviewer in Pool C. The Genzyme analysis identified 16 cases by identifying adverse events with the Preferred Term 'Endocrine ophthalmopathy' through November 26, 2012 (4-month safety update). Additional cases identified by this reviewer by reading narratives and Medwatch forms.

The diagnosis of ITP relies on the exclusion of other causes of thrombocytopenia. An ISS analysis identified ITP cases through medical review using published criteria.⁶⁵⁻⁶⁶ These criteria were applied to subjects who met either the adverse event or platelet-based definitions for ITP (see table below).

Table 43. Definitions of Immune Thrombocytopenia Used in the ISS Analysis

Category	Definition
AE-based definition	<p>Reported AEs with PTs of:</p> <ul style="list-style-type: none"> • Autoimmune thrombocytopenia • Idiopathic thrombocytopenic purpura • Thrombocytopenic purpura
Platelet-based definition	<ul style="list-style-type: none"> • Platelet count $\leq 100,000/\mu\text{L}$ ($100 \times 10^9/\text{L}$) on ≥ 2 occasions over a period of at least 30 days with no platelet counts above the LLN during the 30 day period, or • Platelet count $\leq 50,000/\mu\text{L}$ ($50 \times 10^9/\text{L}$) on ≥ 2 occasions over any time period with no platelet counts above the LLN in the period between the 2 platelet counts $\leq 50,000/\mu\text{L}$

Source: ISS Table 6-23 on ISS p. 301

AEs = adverse events; PTs = preferred terms; LLN = lower limits of normal

Twenty six of 1485 (1.8%) of all alemtuzumab-treated subjects (Pool C) had confirmed ITP as of November 26, 2012 (Table 44).⁶⁷ Anti-platelet antibodies have been confirmed in cases of ITP.⁶⁸ Eighteen of 972 (1.9%) and 8 of 513 (1.6%) female and male subjects had confirmed ITP, respectively.

In addition to the ITP cases described in the 4-month safety update report, there was one post-study case (Subject 1085-5111) of ITP manifesting as autoimmune pancytopenia. The bone marrow biopsy reported as severe ITP suppressing bone marrow production of other cell lines.

There was one death (index case 113-1125) in a 39 year old CAMMS223 subject from the United States, who had petechiae and bruising for 2 weeks and right sided weakness for 3

⁶⁵ Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113(11):2386-93.

⁶⁶ Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussell JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115(2):168-86.

⁶⁷ 4-Month Safety Update, p. 101. Submitted to sBLA 103948 on March 19, 2013.

⁶⁸ In CAMMS223 final study report, 5 of 6 alemtuzumab-treated subjects with ITP were positive for anti-platelet antibodies (APA), confirming the autoimmune nature of the thrombocytopenia; one alemtuzumab-treated subject with ITP did not test positive for either serum or platelet-associated APA, however, this subject was not tested at the time of ITP onset. The presence of APA did not precede the onset of ITP, but appeared simultaneously with a drop in platelets (CAMMS223 Final CSR, Section 11.2.4.1.2).

days before having a fatal cerebral hemorrhage. This subject's ITP occurred 19 months after the first dose and 7 months after the last dose of alemtuzumab. Prior to the diagnosis of ITP, platelet counts performed during the study had been normal, with the exception of a count of $139 \times 10^9/L$ in November 2003. On [REDACTED] ^{(b) (6)}, approximately 6 weeks before admission, CBC had shown a normal platelet count of $174 \times 10^9/L$. On admission, the platelet count was $4 \times 10^9/L$, Hg 134 g/L and WBC $4.8 \times 10^9/L$ (normal ranges not available). PT and PTT were within normal limits. There was no evidence of microangiopathy in the peripheral smear. The subject died 1 day after admission. This subject's retained sera were tested for the presence of antiplatelet antibodies. A sample taken 3 months prior to alemtuzumab treatment was negative. A sample taken at month 18 (1.5 months prior to the event) was positive for antiplatelet glycoprotein IIb/IIIa. A blood sample obtained during the hospital admission when he presented with acute thrombocytopenia also tested positive for antiplatelet antibodies.

In Pool C, 17 of 1485 (1.1%) subjects had nadir platelet counts less than 20,000 platelets/mm³. Spontaneous, life-threatening or fatal bleeding is can occur with ITP, especially in subjects with a platelet count of less than 10,000 - 20,000 platelets/mm³.

Of the 26 subjects with confirmed ITP, 17 responded to first-line therapy with corticosteroids and/or intravenous immunoglobulin (IVIG). Four subjects responded to second-line therapies (e.g., rituximab, danazol). One subject required splenectomy, complicated by recurrent pancreatic pseudocyst, and had a prolonged hospitalization (3006-5807). Three subjects recovered without treatment for ITP. (One [Subject 111-1067] recovered after treatment for H. Pylori.)⁶⁹

In analyses of time from first and last dose of alemtuzumab to diagnosis of ITP, Subject 111-1067, who recovered after treatment for H. Pylori, was an outlier (ITP diagnosis 84 and 60 months from first and last dose of alemtuzumab, respectively). Excluding subject 111-1067, confirmed ITP was diagnosed from 4-51 months after the first alemtuzumab dose and 1-39 months after the last alemtuzumab dose. Confirmed cases of ITP occurred after 1-3 treatment cycles of alemtuzumab.

Based on European population-based studies,⁷⁰ the estimated incidence of ITP in adults is approximately 2 cases per 100,000 person-years. The incidence of ITP in alemtuzumab-treated subjects in Genzyme trials was 443 cases per 100,000 person-years.⁷¹

There were no cases of confirmed ITP in IFN β -1a subjects in controlled trials.

⁶⁹ Description of ITP therapies administered listed for 25 of 26 confirmed ITP cases. The fatal index case is not included in this description of ITP therapies administered.

⁷⁰ The epidemiology of immune thrombocytopenic purpura. Fogarty PF. Curr Opin Hematol. 2007 Sep;14(5):515-9.

⁷¹ As of April 20, 2013, the total number of person-years of follow-up in alemtuzumab-treated subjects (all doses) was 5874. Information on total number of person-years of follow-up in Genzyme trials was submitted to sBLA 103948 on May 14, 2013.

Table 44. Sponsor Table 5-16: Listing of Medically Confirmed Cases of Immune Thrombocytopenic Purpura, All Alemtuzumab-Treated Subjects (Pool C)

Study / Patient ID	Age in years at first onset of ITP (sex)	Number of Alemtuzumab Cycles at ITP onset (cumulative dose, mg)	Months From First Dose (Last Dose) to ITP Onset	Platelet Count Nadir ($10^9/L$)	Presenting Signs or Symptoms	ITP Therapy	Months From ITP onset to First Complete Response	In Complete Response at Last Follow-Up (Yes/No)
Alemtuzumab 12 mg/day								
CAMMS223 101-1074	49 (female)	3 (132)	25.2 (1.0)	1	Petechiae	Dexamethasone, hydrocortisone sodium succinate, platelets, prednisone, rituximab	2.0	Yes
CAMMS223 113-1021	34 (female)	3 (132)	40.1 (16.1)	41	Heavy menstrual cycles, bruises on legs	Dexamethasone, methylprednisolone sodium succinate	0.4	Yes
CAMMS323/ 03409 4006-3375	23 (female)	2 (96)	22.0 (9.7)	1	1+ occult blood and trace protein in urine	Hydrocortisone, immunoglobulin, platelets, prednisone	2.7	Yes
		2 (96)	24.3 (11.7)	2	Petechiae	Hydrocortisone, immunoglobulin, platelets, prednisolone	0.2	Yes
CAMMS323 4901-3632	22 (female)	2 (96)	19.6 (7.1)	1	Bleeding (mouth), petechiae, bloody effusions on elbow and thighs	Etamsilate, hydrocortisone, immunoglobulin, methylprednisolone, platelets, prednisolone, rituximab, tranexamic acid	1.0	Yes
CAMMS323 6010-3078	42 (female)	1 (60)	11.2 (11.0)	26	Decreased platelet count	Methylprednisolone, prednisolone, prednisone	0.4	Yes

Table 44. Sponsor Table 5-16: Listing of Medically Confirmed Cases of Immune Thrombocytopenic Purpura, All Alemtuzumab-Treated Subjects (Pool C)

Study / Patient ID	Age in years at first onset of ITP (sex)	Number of Alemtuzumab Cycles at ITP onset (cumulative dose, mg)	Months From First Dose (Last Dose) to ITP Onset	Platelet Count Nadir ($10^9/L$)	Presenting Signs or Symptoms	ITP Therapy	Months From ITP onset to First Complete Response	In Complete Response at Last Follow-Up (Yes/No)
		1 (60)	17 (17)	1	Heavy menstrual bleeding and a bruised hand	Methylprednisolone, prednisolone, prednisone	0.4	Yes
CAMMS324 1002-5092	35 (female)	1 (60)	3.7 (3.6)	1	Bruise and petechiae	Immunoglobulin, methylprednisolone sodium succinate, prednisone	0.2	Yes
CAMMS324 1049-5863	30 (female)	2 (96)	20.1 (7.9)	3	Bruises and petechiae	Immunoglobulin, methylprednisolone sodium succinate, prednisone	0.3	Yes
CAMMS324 3006-5807	44 (male)	2 (96)	20.5 (8.2)	9	Petechiae, ecchymosis	Danazol, hydrocortisone, methylprednisolone, prednisolone, prednisone	0.5	Yes
CAMMS324 7002-5798	43 (female)	2 (96)	15.2 (3.2)	10	Decreased platelet count	Methylprednisolone	0.5	Yes
CAMMS324 7102-5804	27 (female)	2 (84)	24.9 (13.1)	28	Decreased platelet count	Methylprednisolone, prednisone	0.7	Yes
CAMMS324 1043-5755	28 (female)	2 (96)	30.7 (18.4)	8	Decreased platelet count	Methylprednisolone sodium succinate, platelets, prednisone	0.5	Yes
CAMMS324 / 03409 1046-5366	34 (male)	2 (132)	39.4 (27.6)	6	Decreased platelet count, petechiae, bruising	Methylprednisolone sodium succinate, platelets, prednisone	0.4	Yes

Table 44. Sponsor Table 5-16: Listing of Medically Confirmed Cases of Immune Thrombocytopenic Purpura, All Alemtuzumab-Treated Subjects (Pool C)

Study / Patient ID	Age in years at first onset of ITP (sex)	Number of Alemtuzumab Cycles at ITP onset (cumulative dose, mg)	Months From First Dose (Last Dose) to ITP Onset	Platelet Count Nadir ($10^9/L$)	Presenting Signs or Symptoms	ITP Therapy	Months From ITP onset to First Complete Response	In Complete Response at Last Follow-Up (Yes/No)
CAMMS324 / 03409 1049-5940 (1081-5940)	34 (male)	2 (96)	38.3 (26.1)	51	Decreased platelet count	Prednisone	-	No
CAMMS323 / 03409 4901-5843	33 (male)	2 (96)	36.6 (24.3)	48	Decreased platelet count, petechiae, bruises in corners of mouth, bruises on lower limbs and shoulders	Etamsilate, methylprednisolone, tranexamic acid	0.3	Yes
Alemtuzumab 24 mg/day								
CAMMS223/ 03409 111-1067	35 (female)	3 (264)	84.3 (60.0)	69	Decreased platelet count	None (spontaneous recovery)	2.7	Yes

Table 44. Sponsor Table 5-16: Listing of Medically Confirmed Cases of Immune Thrombocytopenic Purpura, All Alemtuzumab-Treated Subjects (Pool C)

Study / Patient ID	Age in years at first onset of ITP (sex)	Number of Alemtuzumab Cycles at ITP onset (cumulative dose, mg)	Months From First Dose (Last Dose) to ITP Onset	Platelet Count Nadir ($10^9/L$)	Presenting Signs or Symptoms	ITP Therapy	Months From ITP onset to First Complete Response	In Complete Response at Last Follow-Up (Yes/No)
CAMMS223 113-1102	37 (female)	3 (264)	36.2 (12.0)	4	Easy bruising, petechiae, hematoma, prolonged heavy menses, bleeding gums, epistaxis, headache, dizziness, palpitations, dyspnea on exertion, muscle cramping at rest, mild polyuria, and blurred vision.	Methylprednisolone, platelets	0.2	Yes
CAMMS223 113-1125	39 (male)	2 (192)	19.2 (7.2)	4	Diffuse petechiae and easy bruising of approximately 2 weeks duration and right-sided weakness; cerebral hemorrhage	Not applicable - Fatal (index case)	NA	NA
CAMMS223 123-1081	30 (male)	2 (192)	23.8 (11.5)	2	Ecchymosis, petechiae	Danazol, dexamethasone, immunoglobulin, methylprednisolone sodium succinate, platelets, prednisone, rituximab	0.5	Yes

Table 44. Sponsor Table 5-16: Listing of Medically Confirmed Cases of Immune Thrombocytopenic Purpura, All Alemtuzumab-Treated Subjects (Pool C)

Study / Patient ID	Age in years at first onset of ITP (sex)	Number of Alemtuzumab Cycles at ITP onset (cumulative dose, mg)	Months From First Dose (Last Dose) to ITP Onset	Platelet Count Nadir (10 ⁹ /L)	Presenting Signs or Symptoms	ITP Therapy	Months From ITP onset to First Complete Response	In Complete Response at Last Follow-Up (Yes/No)
CAMMS223 201-1114	33 (female)	2 (192)	21.0 (9.0)	3	Easy bruising, blood blister in mouth	Prednisolone	1.0	Yes
CAMMS324 1007-5199	40 (female)	2 (192)	24.5 (12.2)	6	Bruising on gum line, headache, red spots on body, blood in mouth, sores in mouth	Prednisone	0.5	Yes
CAMMS324 1043-5357	27 (female)	2 (192)	22.4 (10.3)	34	Decreased platelet count	None (spontaneous recovery)	0.5	Yes
CAMMS324 1152-5387	39 (male)	1 (120)	5.3 (5.2)	37	Decreased platelet count	Prednisone	1.0	Yes
CAMMS324 / 03409 4004-5520	42 (female)	2 (192)	37.0 (24.7)	6	Decreased platelet count	Prednisolone	0.2	Yes
Cases Reported in the Late-Breaking Interval								
Alemtuzumab 12 mg/day								
CAMMS324 / 03409 1091-5468 ^a	48 (male)	2 (96)	44.7 (32.4)	30	Decreased platelet count	Dexamethasone, rituximab	-	No

Table 44. Sponsor Table 5-16: Listing of Medically Confirmed Cases of Immune Thrombocytopenic Purpura, All Alemtuzumab-Treated Subjects (Pool C)

Study / Patient ID	Age in years at first onset of ITP (sex)	Number of Alemtuzumab Cycles at ITP onset (cumulative dose, mg)	Months From First Dose (Last Dose) to ITP Onset	Platelet Count Nadir ($10^9/L$)	Presenting Signs or Symptoms	ITP Therapy	Months From ITP onset to First Complete Response	In Complete Response at Last Follow-Up (Yes/No)
CAMMS324 / 03409 7102-5792 ^a	41 (female)	2 (72)	41.9 (29.7)	1	Decreased platelet count, rash, bleeding, sores on lips and mouth, petechiae and erythema on thighs hematomas on thighs	Platelets, corticosteroids	-	No
Alemtuzumab 24 mg/day								
CAMMS324 / 03409 1039-5075 ^a	37 (female)	3 (228)	50.6 (38.6)	58	Decreased platelet count	None	-	No

Note: Only medically confirmed cases in alemtuzumab-treated patients are included in this table. The 8 cases in IFNB-1a treated patients and the 4 cases in alemtuzumab-treated patients that were not consistent with ITP are described in ISS Section 6.5.3.2.2.1 and ISS Section 6.5.3.2.2.2, respectively.

Note: Complete response refers to first recovery of platelet count $\geq 100 \times 10^9/L$ after the onset of ITP.

ID = identification; ITP = immune thrombocytopenic purpura; IFNB-1a = interferon beta-1a

^a Case reported during the late-breaking interval; See Section 9.

Source: Table 5-16. 4-Month Safety Update, p. 103-108. Submitted to sBLA103948 on March 19, 2013.

Data as of November 26, 2012.

Reviewer comment: Severe thrombocytopenia recurred in some subjects after first treatment response. Thus, “First Complete Response” as defined by the Sponsor is not equivalent to permanent response to therapy.

Anti-platelet Antibodies and ITP

In CAMMS223, the presence of serum anti-platelet antibodies (APA) was assessed at baseline. Beginning mid-study, serum APA and platelet-bound APA were assessed quarterly to explore the relationship between APA and platelet levels. In the expanded hematology substudies incorporated into the Phase 3 studies, the presence of serum platelet-bound APA was assessed at baseline and quarterly. In CAMMS223, 216 patients were evaluated,⁷² and in the Phase 3 studies 275 patients participated in the expanded hematology substudies.⁷³ The expanded hematology substudies in the Phase 3 studies were discontinued via amendments to the protocols,⁷⁴ which resulted in a limited dataset.

In CAMMS223, 5 of 6 alemtuzumab-treated patients with ITP were positive for APA, confirming the autoimmune nature of the thrombocytopenia; 1 alemtuzumab-treated patient with ITP did not test positive for either serum or platelet-associated APA, however, this patient was not tested at the time of ITP onset. The presence of APA did not precede the onset of ITP, but appeared simultaneously with a drop in platelets.⁷⁵

A substantial proportion of patients without ITP in the Phase 3 hematology substudies tested positive for APA at one or more post-baseline timepoints (34/44 patients tested [77.3%] in the IFN β -1a group and 62/97 patients tested [63.9%] in the alemtuzumab 12 mg/day group in CAMMS323;⁷⁶ and 6/17 patients tested [35.3%] in the IFN β -1a group and 32/94 patients tested [34.0%] in the pooled alemtuzumab dose group in CAMMS324.⁷⁷

*Reviewer comment: APA positivity is likely unsuitable for screening or diagnosis of ITP. In CAMMS223 the presence of APA did not precede the onset of ITP, but appeared simultaneously with a drop in platelets. In phase 3 hematology substudies, a substantial proportion of patients without ITP tested positive for APA. Sensitivity and specificity of APA assays for ITP have been reported to be limited.*⁷⁸

Autoimmune Hemolytic Anemia (AIHA)

In controlled trials (Pool E), 1 of 1188 alemtuzumab-treated subjects had AIHA, compared to 0 of 496 IFN β -1a subjects. There were 2 cases of AIHA in alemtuzumab-treated subjects in the extension trial. Table 45 describes cases of AIHA in alemtuzumab-treated subjects in Genzyme trials. The incidence of AIHA in alemtuzumab-treated

⁷² CAMMS223 clinical study report (CSR). Table 14.3.4.7.1.1.

⁷³ CAMMS323 CSR, Table 14.3.4.1.2.5.1; and CAMMS324 CSR, Table 14.3.4.1.2.5.1

⁷⁴ CAMMS323 CSR, Appendix 16.1.1 and CAMMS324 CSR, Appendix 16.1.1

⁷⁵ CAMMS223 CSR, Section 11.2.4.1.2.

⁷⁶ CAMMS323 CSR, Table 14.3.4.1.2.5.2.

⁷⁷ CAMMS324 CSR, Table 14.3.4.1.2.5.2.

⁷⁸ McMillan R. Antiplatelet antibodies in chronic immune thrombocytopenia and their role in platelet destruction and defective platelet production. Hematol Oncol Clin North Am. 2009;23(6):1163-75

subjects in Genzyme studies was 51 cases per 100,000 person-years.⁷⁹ Autoimmune hemolytic anemia (AIHA) is a rare disease with an estimated incidence of 0.8 cases per 100,000 person-years in a U.S. population-based study.⁸⁰

Table 45. Cases of Autoimmune Hemolytic Anemia. All Alemtuzumab-treated Subjects (Pool C).

Study Subject ID	Age Sex	Months First Alem to AIHA Onset	Nadir Hgb (g/dL)	Comments
CAMMS03409 4007-3635	43 F	27	6.7	Hospitalized for anemia, palpitations, and hyperthyroidism. Treated with folate and prednisolone. Coombs test was positive for direct antiglobulin. AIHA duration was 4 months.
CAMMS324 3006-5807	43 M	21	8.6	Presented with dark urine and icterus. Coombs test was positive for direct antiglobulin. Treated with calcium pantothenate / cyanocobalamin / folic acid / iron / nicotinamide / pyridoxine hydrochloride / riboflavin / thiamine nitrate (Combiron B12). AIHA duration was 2 months. Also had autoimmune thrombocytopenia.
CAMMS03409 1082-5935	52 F	39	2.9	On (b) (6) presented to the Emergency Department with hemoglobin of 2.9 g/dL. Received aggressive hydration and six units of blood; started on decadron. No antibody testing results were reported. Subject's hemoglobin improved to 9.3 g/dL on 24 Nov 2012 then went down to 6.7 g/dL on 28 Nov 2012. Received units of blood and on 29 Nov 2012 her hemoglobin was 8.6 g/dL.

Source: Narratives and manufacturer safety reports

Alemtuzumab = alemtuzumab

Hgb = hemoglobin

There was a fatal case of AIHA in a published case series of 7 patients treated for chronic inflammatory demyelinating polyneuropathy (CIDP).⁸¹ Eighteen months post-alemtuzumab, the patient presented to the hospital with a hemoglobin of 2 g/dL. He initially responded to transfusion and fluid support, but he had continuing hemolysis and required splenectomy; 24 hours post-operatively, the subject's hemoglobin dropped, and he had a cardiac arrest.

Autoimmune Pancytopenia

In controlled trials, 2 of 1188 (0.2%) alemtuzumab-treated subjects had autoimmune pancytopenia, compared to 0 of 496 IFN β -1a subjects. One subject with autoimmune

⁷⁹ As of April 20, 2013, the total number of person-years of follow-up in alemtuzumab-treated subjects was 5874.3. Information submitted to sBLA 103948 on May 14, 2013.

⁸⁰ Lechner K. Blood September 16, 2010 vol. 116 no. 11 1831-1838

⁸¹ Marsh E, et al. J Neurol (2010) 257:913–919. In this study, alemtuzumab was administered IV at doses varying from 12 to 30 mg/day, with total doses for a single course varying between 60 and 180 mg. The dose received by the subject who developed AIHA was not specified.

pancytopenia died from sepsis. There was one additional case in a CAMMS324 subject. Table 46 lists the cases of autoimmune pancytopenia in alemtuzumab-treated subjects in Genzyme trials. Because there are multiple types of autoimmune pancytopenia, this reviewer was not able to identify an overall population rate for autoimmune pancytopenia.

Table 46. Autoimmune Pancytopenia Cases. All Alemtuzumab-Treated Subjects (Pool C)

Study/ Subject ID	Age Sex Country	Months from First (last) Alem to Onset	Nadir Laboratory Measurements	Comments
CAMMS323 7105-3488	46 M Serbia	30 (18)	Hgb 6.5 g/dL Platelets $9 \times 10^9/L$ WBC $0.9 \times 10^9/L$ ANC $79 /\mu L$	Fatal case. Fatigue, hematomas, purpura, and nonspecified neurologic deficits at presentation. Laboratory results included platelets $17 \times 10^9/L$, hematocrit 34%, and ANC $79 /\mu L$. Treated with IVIG, filgrastim, and corticosteroids. Platelets increased to $189 \times 10^9/L$. Discharged, but readmitted 8 days later and died from sepsis.
CAMMS324 1085-5111 (post-study AE)	30 F USA	42 (30)	Hgb 2.7 g/dL Platelets 0 WBC $1.7 \times 10^9/L$	Presented with 3 weeks of fatigue and chest pain with exertion. Hemoglobin 2.7 g/dL, platelets $57 \times 10^9/L$, WBC $1.7 \times 10^9/L$. Bone marrow biopsy reported as severe ITP suppressing bone marrow production of other cell lines. Treated with transfusions, IVIG, corticosteroids, filgrastim, and rituximab monthly. Blood counts WNL Jul-Sep 2012.
CAMMS324 3006-5807	43 M Brazil	21 (8)	Hgb 8.6 g/dL Platelets $14 \times 10^9/L$ WBC $2.4 \times 10^9/L$	Presented with dark urine and icterus. Treated with calcium pantothenate / cyanocobalamin / folic acid / iron / nicotinamide / pyridoxine hydrochloride / riboflavin / thiamine nitrate (Combiron B12). AIHA duration was 2 months. Also had autoimmune thrombocytopenia.

Alem = alemtuzumab
 WBC = White blood cells
 ANC = Absolute Neutrophil Count

Immune Cytopenias: Reviewer Conclusions and Recommendations

Immune cytopenias seen after alemtuzumab treatment include ITP, AIHA, and autoimmune pancytopenia. Because of the risk for life-threatening or fatal bleeding and infection, rapid diagnosis of autoimmune cytopenias is imperative. Genzyme has recommended monitoring complete blood counts at monthly intervals for 48 months following treatment with alemtuzumab. The proposed Medication Guide has photographs of petechiae and ecchymoses to facilitate early identification of manifestations of ITP. If alemtuzumab is granted marketing approval, this reviewer thinks that attention to educating patients about ways to identify immune cytopenias will be essential.

It is unclear to what degree patients will adhere to monthly laboratory monitoring for 4 years. The proposed postmarketing monitoring plan provides less frequent surveillance compared to what was done in clinical trials. Subjects in Genzyme trials were scheduled to receive either a complete blood count laboratory measurement or a symptom monitoring survey every 2 weeks. If alemtuzumab is granted marketing approval, there is significant risk of increased rates of morbidity and mortality from ITP as compared to rates observed in clinical trials; this will need to be monitored closely in the postmarketing setting.

7.3.5.1.4. Autoimmune Coagulopathy: Acquired Hemophilia A (Factor VIII Inhibitor)

Acquired hemophilia A (AHA) is an autoimmune disease caused by an inhibitory antibody to coagulation factor VIII, a procoagulant component. Patients with AHA are at risk for life-threatening bleeding. Management consists of rapid diagnosis, controlling bleeding, and immunosuppression to eradicate the inhibiting antibody.⁸² The general incidence of AHA has been estimated to be 0.2–1.0 case per 1 million persons per year, but this figure may be an underestimate given the difficulty in making the diagnosis.⁸³

There are 3 reported cases of AHA in alemtuzumab-treated subjects: -- 1 in a CAMMS324 subject treated for MS and 2 cases in other indications.

Subject 1163-5684, a 32 year old male from the United States who received 2 cycles of alemtuzumab 12 mg/day in May 2009 and June 2010 for MS in CAMMS324, had a post-study event of AHA.⁸⁴ In (b) (6) (b) (6) months after his first dose of alemtuzumab and (b) (6) months after his last dose), he was hospitalized for cellulitis. During hospitalization, his hematocrit level dropped acutely to 28.8%, and he required multiple blood transfusions for subcutaneous bleeding. Extensive evaluation revealed AHA. He was treated with rituximab, cyclophosphamide, and prednisolone. The last provided hemoglobin was normal at 14.0 g/dL. The treating hematologist said that even if the subject has cleared his factor VIII inhibitor, he is likely to still have elevated PTT values. The event was not resolved as of the last provider update in Sept 2011, (b) (6) months after the event.

A search of the Genzyme postmarketing database identified 2 additional cases of AHA in subjects treated for indications other than MS.

The first case, manufacturer report 201013005GPV,⁸⁵ describes an event with a verbatim term of ‘ACQUIRED COAGULATION DISORDER PROBABLY ON THE BASIS OF ANTIBODIES AGAINST FACTOR VIII’ in a 68 year old male with relapsed Chronic Lymphocytic Leukemia. The subject received 6 cycles of fludarabine + alemtuzumab + cyclophosphamide in 2007 and three years later presented with multiple sites of

⁸² Collins PW. J Thromb Haemost. 2011 Jul;9 Suppl 1:226-35.

⁸³ Franchini M, et al. Am J Hematol. 2005 Sep;80(1):55-63.

⁸⁴ Manufacturer Report CAMP 1001696. Follow-up report # submitted to IND 010717 on Oct. 6, 2011.

⁸⁵ Medwatch form entered to sBLA 103948 on 5/14/2013 in Appendix 18.

subcutaneous bleeding and a psoas muscle hematoma with arterial bleeding. Hemoglobin was measured at 7.4 g/dL on (b) (6) and at 4.4 g/dL on (b) (6). The subject was transferred to another hospital, and the outcome of the event was not reported. *Reviewer comment: Autoimmune hemolytic anemia has been reported with fludarabine.⁸⁶ However, a role of alemtuzumab in this case cannot be ruled out.*

The second case, manufacturer GB-2006-008353,⁸⁷ describes events from a published report⁸⁸ of a 48 year old male who was treated for ANCA-associated vasculitis with cyclophosphamide, IVIG, corticosteroids, and Campath. Five years after onset of ANCA-associated vasculitis, the subject presented with oral hemorrhage and was noted with peritoneal irritation due to bleeding. A Factor VIII inhibitor antibody was identified. The subject was initially treated with recombinant FVIIa, tranexamic acid, prednisolone, and Rituximab. Treatment with rituximab was considered successful, as the autoantibody was eradicated and Factor VIII levels increased to normal range. Three months after rituximab treatment, the subject presented with duodenal ulceration and hemoglobin of 6.1 g/dL. He entered cardiac arrest and died. At the time of death, platelets, coagulation screen and Factor VIII levels were normal with no detectable inhibitor.

Reviewer comment: AHA is an autoimmune coagulopathy with an estimated mortality rate in the range of 7.9% to 22%.⁸⁹ If alemtuzumab is approved, cases of AHA should be described in Warnings and Precautions to facilitate rapid diagnosis of cases.

7.3.5.1.5. Autoimmune Kidney Diseases

Cases of autoimmune kidney disease, including anti-Glomerular Basement Membrane (anti-GBM) disease (also known as Goodpasture's disease) and membranous glomerulonephritis, have occurred after alemtuzumab treatment.

Anti-Glomerular Basement Membrane (anti-GBM) disease is a rare autoimmune disorder in which circulating antibodies are directed against an antigen present in the renal glomerular basement membrane (GBM) and alveolar basement membrane. The incidence of anti-GBM disease in the general population is approximately 0.5-1 case per million person-years.⁹⁰⁻⁹¹ The incidence of anti-GBM disease in subjects with MS has not been quantified. Clinical manifestations of anti-GBM disease may include a rapidly progressive glomerulonephritis with elevations in serum creatinine, hematuria, and/or proteinuria. Alveolar hemorrhage is a common component of anti-GBM disease, but it has not been observed in alemtuzumab clinical studies.

⁸⁶ Myint H, et al. Fludarabine-related autoimmune haemolytic anaemia in patients with chronic lymphocytic leukaemia. *British journal of haematology* 91.2 (1995): 341-344.

⁸⁷ Medwatch form entered to sBLA 103948 on 5/14/2013 in Appendix 18.

⁸⁸ Clatworthy MR, Jayne DR. *Am J Kidney Dis.* 2006 Apr;47(4):680-2.

⁸⁹ Franchini M, et al. *Am J Hematol.* 2005 Sep;80(1):55-63.

⁹⁰ Salama AD, Levy JB, Lightstone L, Pusey CD. Goodpasture's disease. *Lancet* 2001; 358: 917-20.

⁹¹ Turner AN, Rees AJ. Anti-glomerular basement membrane disease. In: Davison AM, Cameron JS, Grunfeld J-P, Kerr DNS, Ritz E, Winears CG, eds. *Oxford Textbook of Nephrology*. Oxford: Oxford University Press, 1998; 645-66.

Membranous glomerulonephritis is an autoimmune disorder in which circulating antibodies are directed against glomerular podocyte antigens; clinical manifestations include proteinuria with possible reduction in kidney function. In the general population, membranous glomerulonephritis can be idiopathic or secondary with causes including systemic lupus erythematosus, Hepatitis B and C, drugs (gold salts, D-penicillamine, and mercury compounds), and cancers. The clinical course of membranous glomerulonephritis is variable, and renal prognosis depends on the degree of continuing proteinuria.⁹²

In controlled trials (Pool E), 2 of 1188 (0.2%) had an adverse event of nephropathy or immune disorder,⁹³ compared to 0 of 496 IFN β -1a subjects had an adverse event of nephropathy or immune renal disorder in controlled trials. The cases included 1 case of membranous glomerulonephritis (Subject 1008-6030) and 1 case of tubulointerstitial nephritis (Subject 6013-5686). (See table below for additional details on these cases.)

In all alemtuzumab follow-up (Pool C), 6 of 1485 (0.4%) subjects had an adverse event of nephropathy or immune kidney disorder, which included:

- Anti-Glomerular Basement Membrane Disease (Anti-GBM Disease) (Subject 122-1319)
- Membranous Glomerulonephritis with positive Anti-GBM antibodies (2 Subjects: 6004-3087 and 7001-1041)
- Membranous glomerulonephritis (Subject 1008-6030)
- Tubulointerstitial nephritis (Subject 6013-5686)
- Nephropathy (unspecified) (Subject 6004-5588)

Table 47 provides descriptions of cases of nephropathy or immune kidney disorder in all alemtuzumab-treated subjects; events occurred in 5 of 972 (0.5%) female subjects and 1 of 513 (0.2%) male subjects.

In all alemtuzumab follow-up, the incidence of anti-GBM disease (calculated using 1 case in Subject 122-1319) was 170 per million person-years,⁹⁴ compared to the general population incidence of approximately 0.5-1 case per million person-years.⁹⁵⁻⁹⁶

⁹² Cattran DC. Idiopathic membranous glomerulonephritis. *Kidney Int*, Vol. 59 (2001), pp. 1983–1994.

⁹³ Nephropathies and immune renal disorders are defined as events identified from the MedDRA HLGT of Nephropathies within the SOC of renal and urinary disorders, and by the Preferred Terms of Goodpasture's syndrome, nephritis autoimmune, and pulmonary renal syndrome within the HLGT of Autoimmune disorders and the SOC of immune system disorders, as well as Preferred Terms of anti-GBM antibody and anti-GBM antibody positive.

⁹⁴ As of April 20, 2013, the total number of person-years of follow-up in alemtuzumab-treated subjects was 5874.3. Information submitted to sBLA 103948 on May 14, 2013.

⁹⁵ Salama AD, Levy JB, Lightstone L, Pusey CD. Goodpasture's disease. *Lancet* 2001; 358: 917–20.

⁹⁶ Turner AN, Rees AJ. Anti-glomerular basement membrane disease. In: Davison AM, Cameron JS, Grunfeld J-P, Kerr DNS, Ritz E, Winears CG, eds. *Oxford Textbook of Nephrology*. Oxford: Oxford University Press, 1998; 645–66.

The two cases of Membranous Glomerulonephritis with positive Anti-GBM antibodies (6004-3087 and 7001-1041) had clinical and biopsy findings characteristic of membranous glomerulonephritis with an additional finding of positive anti-GBM antibodies.

Table 47. Nephropathies and Immune Renal Disorders. All Alemtuzumab Subjects. (Pool C)

Subject Study	Age Sex Country	Alemtuzumab Dose # Cycles (Total Dose)	Months after first (last) Alem	Preferred Term (Verbatim Term)	Description/Comment
1008-6030 CAMMS 324	27 F USA	Alem 12 mg/day 2 Cycles (96 mg)	17 (5)	Glomerulonephritis membranous	Developed 3+ proteinuria, microhematuria, hypoalbuminemia and peripheral edema. Serum creatinine remained normal and Anti-GBM antibody measurements were normal. Nephrologist suspicious of nephrotic range proteinuria. Treated with Lasix and lisinopril. Kidney biopsy report on March 21, 2011 revealed stage 1-2 Membranous Glomerulopathy. Electron microscopy with widespread effacement of foot processes. Other than alemtuzumab, no potential causes of secondary membranous glomerulonephritis were reported.
122-1319 CAMMS 03409	35 F USA	Alem 12 mg/day	52 (40)	Goodpasture's syndrome	Hospitalized for Anti-GBM Disease (also called Goodpasture's Disease), hematuria, nephrotic syndrome. Nadir GFR was 20 cc/minute (creatinine 2.8 mg/dL). Treated with prednisone, plasmapheresis, and cyclophosphamide, which was held due to neutropenia. At last report Goodpasture's was in remission and creatinine in March 2010 was 1.1 mg/dL.
6004-3087 CAMMS 03409	25 F Russia	Alem 12 mg/day 3 Cycles (132 mg)	29 (4)	Glomerulonephritis (Anti-GBM Glomerulonephritis)	November 9, 2010 evaluated for proteinuria and hematuria, which was attributed to chronic cystitis. Nov 18, 2010 her creatinine was normal, but she had hematuria, proteinuria, and elevated anti-GBM. On 23 Dec 2010 urine protein was 5.7 g/day. Renal biopsy showed membranous nephropathy with secondary increased anti-GBM antibodies. Other than alemtuzumab, no potential causes of secondary membranous glomerulonephritis were reported. Treated with plasmapheresis, corticosteroids, and cyclophosphamide. Urine protein output peak was 14 g/24 hours in February 2011. Most recent value from June 2011 listed as "1+g/day". Her serum creatinine level remained normal, except for one value of 0.7 mg/dL listed as above the normal range.
7001-1041* CAMMS 03409	58 F Croatia	IFNβ-1a in CAMMS223 2 Cycles Alemtuzumab in CAMMS03409	26 (1)	Nephrotic Syndrome	Hospitalized for leg edema and diagnosed with nephrotic syndrome. Membranous glomerulonephritis with diffuse loss of podocyte pedicels on kidney biopsy. Other than alemtuzumab, no potential causes of secondary membranous glomerulonephritis were reported. Positive anti-GBM antibody test on 5/3/2012. Treatment with cyclophosphamide planned. Serum creatinine ranged from 0.7-1.6 mg/dL. Most recent serum creatinine provided, dated July 7, 2012 was 1.2 mg/dL. (Manufacturer report CAMP 1002197 follow-up #4 on 12 Dec 2012)

Subject Study	Age Sex Country	Alemtuzumab Dose # Cycles (Total Dose)	Months after first (last) Alem	Preferred Term (Verbatim Term)	Description/Comment
6013-5686 CAMMS 324	38 F Russia	Alem 12 mg/day 2 Cycles (96 mg)	22 (10)	Tubulointerstitial nephritis	Tubulointerstitial nephritis diagnosed March 2010. Subject had taken amoxicillin in November 2009. The subject was treated with canephron (herbal preparation). During the adverse event, the subject's serum creatinine level did not increase to more than the subject's baseline value of 1.0 mg/dL. <i>Reviewer comment: Limited details are available on this case. Interstitial nephritis is an immune-mediated condition that has been associated with anti-renal tubular antibodies.⁹⁷. This case may be related to alemtuzumab exposure.</i>
6004-5588 (304-1222 in CAMMS223) CAMMS 03409	27 M Russia	Alem 12 mg/day 2 Cycles (96 mg) In CAMMS324	25 (13)	Nephropathy	Neither clinical details nor laboratory results were provided for this adverse event, which was reported to be resolved after 160 days duration.

- Nephropathies and immune renal disorders are defined as events identified from the MedDRA HLGT of Nephropathies within the SOC of renal and urinary disorders, and by the Preferred Terms of Goodpasture's syndrome, nephritis autoimmune, and pulmonary renal syndrome within the HLGT of Autoimmune disorders and the SOC of immune system disorders, as well as Preferred Terms of anti-GBM antibody and anti-GBM antibody positive.

* Reported after the ISS cut-off date of December 31, 2011

- ISS Analysis includes cases reported as of December 31, 2011. The table includes all cases from the ISS analysis and cases submitted to IND 010717 until July 30, 2013. The table may not include all cases, as there is no specific requirement for the sponsor to submit cases of nephropathies and immune renal disorders which do not meet the requirements for a 15-Day Report.

-Alem = Alemtuzumab

⁹⁷ Border WA, et al. Antitubular basement-membrane antibodies in methicillin-associated interstitial nephritis. N Engl J Med. 1974 Aug 22;291(8):381-4.

Two published cases⁹⁸⁻⁹⁹ describe Anti-Glomerular Basement Membrane (Anti-GBM) Disease leading to End Stage Renal Disease (ESRD) after alemtuzumab treatment.

Subject 1 was a 40 year old female with relapsing-remitting multiple sclerosis who received a total dose of 100 mg of alemtuzumab. Nine months after treatment, she was diagnosed with acute renal failure secondary to anti-GBM disease. She developed a high titer of anti-GBM antibodies, which were not detectable in serum taken before alemtuzumab treatment and not detectable one month before her illness. Her renal biopsy showed crescentic glomerulonephritis (95% crescents) and linear deposition of IgG.

*Reviewer comment: With inflammatory glomerulonephritis, cellular glomerular crescents are a histologic marker of severe glomerular injury. In general, the severity of the renal failure correlates with the percentage of glomeruli that exhibit crescents.*¹⁰⁰

Despite treatment with steroids, plasma exchange, and cyclophosphamide, she became dialysis dependent and underwent kidney transplantation.

Subject 2 was a 43 year old white man with a refractory antineutrophil cytoplasmic antibody (ANCA) associated vasculitis, who was treated with a total dose of 788 mg of alemtuzumab. Ten months later, he was found to have acute renal failure with elevated titers of anti-GBM antibodies. Renal biopsy showed crescentic glomerulonephritis and strong linear IgG staining. Despite appropriate treatment (not specified in the published report), the subject became dialysis-dependent and eventually underwent kidney transplantation.

Two postmarketing cases of subjects treated with alemtuzumab for MS, who subsequently developed anti-GBM disease requiring kidney transplantation or chronic hemodialysis, have been submitted to Medwatch.

Medwatch Case 7134771

A 34 year old white female subject (Medwatch number 7134771; Manufacturer number US-BAYER-200933452NA) with relapsing-remitting MS (RRMS) was treated in the United Kingdom with IV alemtuzumab 20mg daily for 5 days in March 2002 and for 3 days in March 2003. She was diagnosed with anti-GBM disease in the U.S. in 2005. In January 2005 she had muscle/joint pain and physical fatigue for a couple of weeks and was unsure whether the symptoms were MS related. In February 2005 she noted decreased appetite and weight gain. In March 2005 she noted brown urine and then gross hematuria. She also developed flank pain, nausea, vomiting and low grade fever. She was hospitalized with acute renal failure and a serum creatinine of 11 mg/dL. Kidney biopsy was consistent with anti-GBM disease with severe crescentic and necrotizing glomerulonephritis. Pt was treated with corticosteroids, followed by plasmapheresis for 5

⁹⁸ Clatworthy MR, Wallin EF, Jayne DR. Anti-glomerular basement membrane disease after alemtuzumab. N Engl J Med. 2008 Aug 14;359(7):768-9. *This paper describes Subjects 1 and 2.*

⁹⁹ Coles AJ, et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. J Neurol. 2006 Jan;253(1):98-108. *This paper describes Subject 1, also described in the Clatworthy paper.*

¹⁰⁰ Jennette JC. Rapidly progressive crescentic glomerulonephritis. Kidney Int 2003; 63:1164.

months. She declined cyclophosphamide treatment due to safety concerns, and was treated instead with Cellcept (mycophenolate mofetil). She required dialysis and eventually underwent kidney transplantation.

Medwatch Case 8799413

A 24 year old female from the U.S. (Medwatch 8799413; Manufacturer report number US-GENZYME-CAMP-1002377) was reported to have anti-GBM disease leading to hemodialysis dependence. The subject received alemtuzumab off-label: Sept. 2007: 12 mg/day for 5 days, Sept. 2008: 24 mg/day for 3 days, and on unknown dates in 2010: 12 mg/day for 3 days (cumulative dose 168 mg). Upon review of the subject's urinalysis results, she had hematuria consistently since March 2012. (The Medwatch report first mentions hematuria in June 2012.) Anti-GBM antibodies were elevated on 6/29/2012. She was hospitalized 7/26/2012 for a kidney biopsy and plasmapheresis. Serum creatinine was 0.7 mg/dL on 7/28/2013. Kidney biopsy 7/26/2012 showed anti-GBM disease with 15% crescentic glomeruli.¹⁰¹ The subject initially refused cyclophosphamide but later received 5 cycles of cyclophosphamide from September 2012 to January 2013.

Kidney biopsy 1/22/2013¹⁰² which, according to the pathologist, showed anti-GBM disease with chronic injury strikingly more prominent compared to the biopsy from 7/26/2012 and at least 50% of glomeruli globally sclerotic with fibrous crescents. There was smoldering disease which may not truly be consistent with ESRD yet. She started maintenance hemodialysis in late summer 2012 and has continued hemodialysis treatment at last report in January 2013.

Autoimmune Kidney Diseases: Reviewer Discussion and Recommendations

Published cases and postmarketing cases of anti-GBM disease describe the development of end-stage renal disease despite treatment. Published Case Subject 1,¹⁰³⁻¹⁰⁴ did not have detectable anti-GBM antibodies 1 month prior to the start of acute renal failure and progressed to end stage renal disease despite appropriate treatment. This provides evidence that monthly monitoring and prompt treatment will likely not prevent all cases of end stage renal disease with anti-GBM disease, because of the aggressive nature of the disease.

Anti-GBM disease is typically treated with corticosteroids, plasmapheresis, and cyclophosphamide (brand name Cytoxan). Adverse effects of cyclophosphamide include carcinogenesis, immunosuppression, cytopenias, and potentially irreversible sterility in

¹⁰¹ Genzyme submission to sBLA 103948 dated February 25, 2013, p. 11-12.

¹⁰² Genzyme submission to sBLA 103948 dated February 25, 2013, p. 13-14.

¹⁰³ Clatworthy MR, Wallin EF, Jayne DR. Anti-glomerular basement membrane disease after alemtuzumab. *N Engl J Med.* 2008 Aug 14;359(7):768-9. *This paper describes Subjects 1 and 2.*

¹⁰⁴ Coles AJ, et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. *J Neurol.* 2006 Jan;253(1):98-108. *This paper describes Subject 1, also described in the Clatworthy paper.*

both sexes.¹⁰⁵ Of note, both patients in the Medwatch cases of anti-GBM disease initially refused treatment with cyclophosphamide.

When compared to anti-GBM disease, membranous glomerulonephritis has a more variable clinical course. When it occurs, renal impairment progresses at a slower pace. However, it is a condition with high morbidity, as 20-40 % of subjects with idiopathic membranous glomerulonephritis develop chronic or end-stage renal failure.¹⁰⁶ In subjects with nephrotic syndrome, potential complications include edema, hyperlipidemia, and increased thromboembolic risk.

Because clinical symptoms are nonspecific, the diagnosis of autoimmune kidney disease is largely based on laboratory testing. In the proposed prescribing information submitted by Genzyme, laboratory monitoring recommendations include:

- Serum creatinine levels prior to initiation of treatment and at monthly intervals thereafter for 48 months after the last infusion
- Urinalysis with urine cell counts every 3 months until 48 months after the last infusion.

As previously discussed, additional cases of end-stage renal disease from anti-GBM disease with alemtuzumab will likely occur despite these monitoring recommendations. However, this reviewer agrees with monthly monitoring of serum creatinine level, because adequate rates of subject adherence would be unlikely with more frequent monitoring.

In autoimmune kidney diseases, abnormalities in urinalysis often precede changes in serum creatinine. In Phase 3 studies, urinalysis was performed monthly. The recommended relative decrease in urinalysis frequency to every 3 months may result in longer delays in diagnosis, compared to clinical trials. If alemtuzumab is approved for marketing in the U.S. for treatment of MS, this reviewer recommends monthly urinalyses as a necessary part of prompt diagnosis of autoimmune kidney diseases.

It is unclear to what degree subjects will adhere to monthly laboratory monitoring for 4 years

7.3.5.1.6. Autoimmune (Type 1) Diabetes Mellitus

In all alemtuzumab follow-up, 9 of 1485 (0.6%) subjects had an ongoing adverse event in the MedDRA High Level Group Term 'Diabetes mellitus (incl subtypes).' Two of 9 subjects (Subjects 6001-3188 and 4701-5622) were diagnosed with autoimmune diabetes mellitus in CAMMS03409 (see table 48). It is unclear whether any of the other 7 cases of

¹⁰⁵ Cytoxan prescribing information. Accessed on August 20, 2013 at: http://packageinserts.bms.com/pi/pi_cytoxan.pdf

¹⁰⁶ York P. Predicting chronic renal insufficiency in idiopathic membranous glomerulonephritis. *Kidney International*, Vol. 42 (1992), pp. 960—966.

diabetes mellitus had an autoimmune etiology, because of testing was not routinely performed.

Table 48. Cases of confirmed autoimmune diabetes mellitus. All alemtuzumab subjects.

Study Subject	Age	Sex	Country	BMI	Cumulative Dose (mg)	Time from First Dose (Days)	Time from Last Dose (Days)	Verbatim Term	Preferred Term	AE Start Date	Treated with Insulin	Insulin Start Date	Diabetes related antibodies
CAMMS323													
60013188	29	Male	Russia	16.9	96	1551	1185	Diabetes mellitus 1 type	Type 1 diabetes mellitus	11 October 2012	Yes	29 November 2012	Not performed
CAMMS324													
47015662	37	Female	Sweden	25	96	1345	965	Diabetes mellitus	Type 1 diabetes mellitus	04 February 2013	Yes	04 February 2013	Islet cell autoantibodies: 1:1000 (normal <1:10) Glutamic acid decarboxylase antibodies >2000 iu/ml (normal <10) ZnT8 autoantibodies >2000 iu/ml (normal <10)

Both cases listed occurred in CAMMS03409.

Source: Table 4 in Genzyme response entered to sBLA 103948 on May 17, 2013 (p. 9).

A case of Type 1 diabetes mellitus in a 67 year old male from Sweden was reported in manufacturer report SE-SHR-03-018938.¹⁰⁷ He was treated with alemtuzumab for CLL. He developed insulin-dependent autoimmune diabetes mellitus approximately 2 years after discontinuing treatment with alemtuzumab. No other details were provided on this case.

No overall increased risk of diabetes mellitus was detected in controlled trials. In controlled trials (Pool E), 3 of 1188 (0.3%) had an ongoing¹⁰⁸ adverse event in the MedDRA High Level Group Term ‘Diabetes mellitus (incl subtypes),’ compared to 1 of 496 (0.2%) IFN β -1a-treated subjects.

7.3.5.1.7. Acute Epitheliopathy of the Retina

A 34 year old male from the UK (CAMMS324 Subject 4001-6041) was hospitalized for scotomata with headache 6 months after his first treatment cycle of alemtuzumab 12 mg/day. He was diagnosed with acute multifocal placoid pigment epitheliopathy (AMPPE), which is an idiopathic self-limited inflammatory disease of the choroidal vasculature.¹⁰⁹ The treating ophthalmologist, as well as a second ophthalmologist considered this condition to be autoimmune in origin. He had changes in visual fields for 6 months, after which the disease was declared ‘inactive.’ He did not receive treatment specifically for AMPPE. Details of this case are located in Appendix 9.3.

AMPPE lesions usually resolve spontaneously, but systemic complications and vision loss may occur and respond to corticosteroid therapy. Reported neurological complications include aseptic meningitis, headache, transient hearing loss, optic neuritis, meningoencephalitis, and stroke.¹¹⁰

7.3.5.1.8. Autoimmune Skin Disease

A published report by Hirst, et al¹¹¹ describes a case of autoimmune skin disease in an MS subject 6 months after her second cycle of alemtuzumab (treatment dose not reported). She was diagnosed as Pityriasis lichenoides chronicus and treated with ultraviolet treatment unsuccessfully.

¹⁰⁷ Genzyme response entered to sBLA 103948 on May 17, 2013 (p. 48-49).

¹⁰⁸ One resolved case of steroid-induced diabetes and one case of gestational diabetes were not included in this analysis.

¹⁰⁹ Spencer BR. Acute multifocal posterior placoid pigment epitheliopathy (AMPPPE) mimicking migraine with aura. *Cephalalgia*, 2009, 29, 694–698.

¹¹⁰ Spencer BR. Acute multifocal posterior placoid pigment epitheliopathy (AMPPPE) mimicking migraine with aura. *Cephalalgia*, 2009, 29, 694–698.

¹¹¹ Hirst CL, et al. Campath 1-H treatment in subjects with aggressive relapsing remitting multiple sclerosis.

J Neurol (2008) 255:231–238.

Pityriasis lichenoides chronicus is an autoimmune parapsoriasis. Small-plaque parapsoriasis has a minimal risk of progression to overt mycosis fungoides. Large-plaque parapsoriasis is part of a continuum with patch-stage mycosis fungoides; it can progress to overt mycosis fungoides (a cutaneous T cell lymphoma) at a rate of 10% per decade.¹¹² (The article did not specify whether the alemtuzumab-treated subject had small- or large-plaque parapsoriasis).

7.3.5.1.9. Undifferentiated Connective Tissue Disorders

In controlled trials (Pool E), 2 of 1188 (0.2%) alemtuzumab-treated subjects had an adverse event with a Preferred Term 'Connective Tissue Disorder,' compared to 0 IFN β -1a subjects.

A 48 year old female from the UK (CAMMS323 Subject 4006-3362; treated with 2 cycles of alemtuzumab 12 mg/day in November 2008 and 2009) reported hip pain (more prominent on the right) since May 2009, long-term pain in the balls of her feet, and widespread arthralgia after each alemtuzumab course which was worse in her hands and took up to 3 months to resolve. Anti-nuclear antibodies (ANA) were positive at 1:640 titer. The event was initially reported as lupus, and investigator changed term to undifferentiated connective tissue disorder.¹¹³ She did not receive treatment for this adverse event.

A 38 year old female from the United States (CAMMS324 Subject 1027-5067; treated with 2 cycles of alemtuzumab 12 mg/day in July 2008 and July 2009) reported symmetric small joint arthritis in the hands, elbows, hips, and feet associated with morning joint stiffness starting in August 2008. She had an anti-SSA (also known as anti-Ro) antibody test that had an elevated result (119 units/mL). Other antibody tests were negative, including ANA, P-ANCA, C-ANCA, Anti-SSB (also known as anti-La). Lip biopsy negative for Sjogren's Syndrome. She has been treated with oxycet, oxycodone, hydroxychloroquine, celecoxib, and cortisone injections.

Reviewer comment: Subjects 4006-3362 and 1027-5067 experienced widespread arthralgias with elevated antibody testing after alemtuzumab treatment. These adverse events were described as undifferentiated connective tissue disorder adverse events, because they did not meet the definition for any standard rheumatologic syndrome.

7.3.5.1.10 Autoimmune Diseases: Conclusion

The wide range of autoimmune diseases seen after alemtuzumab treatment indicates the broad nature of the pathophysiologic process of altered immune reconstitution with alemtuzumab. Because of this broad process, it is likely that

¹¹² Goldsmith L (2012) Fitzpatrick's Dermatology in General Medicine.

¹¹³ Sponsor response entered to sBLA103948 on May 14, 2013.; p. 1640 of Appendix 2.

additional autoimmune diseases may be documented after alemtuzumab treatment.

An understanding of risk factors for autoimmune disease with alemtuzumab is important to risk mitigation, and it is a potential area of additional research.

Female subjects experienced an increased incidence of thyroid, ITP, and nephropathy events.

Cosburn¹¹⁴ and colleagues reported analyses of prospective data from a multicenter cohort of 248 patients with MS treated with alemtuzumab. In these analyses, age and sex were not associated with increased risk of autoimmune disease. Patients with a positive family history of autoimmune disease had a relative risk point estimate for developing autoimmune disease of 3.2, compared to patients without a family history of autoimmune disease.¹¹⁵ Smoking histories were obtained from 196 patients, which included 49 of the 55 patients who developed autoimmune disease. The overall rate of ever smoking in this sample was 38.3%; 19.3% of patients were active smokers at the time of treatment. When compared with never-smokers, ever-smokers had an increased risk of autoimmune disease ($P < 0.001$; OR 3.05, 95% CI 1.50 – 6.19).¹¹⁶

In analyses of Genzyme studies of alemtuzumab in MS, younger age quartiles had higher frequencies of adverse events in the Endocrine disorders SOC, all but 1 of which were thyroid-related adverse events (Table 49). An opposite pattern was seen in INFB-1a subjects – endocrine disorders were more frequent in older age quartiles. In the SOC of ‘Endocrine Disorders’ the incidence of AEs for females in the alemtuzumab 12 mg/day group was 18.7% compared to 7.2% for males; increased endocrine AEs in females is consistent with the epidemiology of thyroid disease. Family history of autoimmune disease and history of smoking were not systematically collected in Genzyme studies of alemtuzumab in MS.

¹¹⁴ Cosburn M, et al. Autoimmune disease after alemtuzumab treatment for multiple sclerosis in a multicenter cohort

¹¹⁵ Crude relative risk point estimate was calculated from numbers provided in the Cosburn publication. Family history of autoimmune disease was obtained for 231 patients, which included all patients who developed autoimmune disease post-treatment. In 26 of 231 (11.26%), a family history of autoimmune disease was identified, and of these 16 (61.54%) developed autoimmune disease after alemtuzumab treatment. Thirty nine of 205 (19.0%) patients with a family history negative for autoimmune disease developed autoimmune disease after alemtuzumab treatment. The reported odds ratio [OR] was 7.31, 95% confidence interval [CI] 3.02–17.68).

¹¹⁶ There was insufficient information provided to calculate the relative risk. Because this is an analysis of a common outcome in this cohort study, the relative risk point estimate would be lower than the odds ratio point estimate (Zhang J, et al. JAMA. 1998;280:1690-1691).

Table 49. Incidence of treatment-emergent adverse events by age. Endocrine disorders SOC. Controlled trials (Pool E).

System Organ Class Preferred Term	SC IFNB-1a (N= 496)				Alemtuzumab 12 mg/day (N= 919)			
	<25 th percentile:	25 th -<50 th percentile:	50 th -<75 th percentile:	≥75 th percentile:	<25 th percentile:	25 th -<50 th percentile:	50 th -<75 th percentile:	≥75 th percentile:
	< 27.0 years	≥ 27.0-< 33.0 years	≥ 33.0-< 40.0 years	≥ 40.0 years	< 27.0 years	≥ 27.0-< 33.0 years	≥ 33.0-< 40.0 years	≥ 40.0 years
	(N=117)	(N=107)	(N=126)	(N=146)	(N=200)	(N=252)	(N=220)	(N=247)
n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Endocrine disorders	2 (1.7)	3 (2.8)	3 (2.4)	5 (3.4)	36 (18.0)	40 (15.9)	33 (15.0)	26 (10.5)
Hypothyroidism	1 (0.9)	1 (0.9)	2 (1.6)	4 (2.7)	10 (5.0)	13 (5.2)	9 (4.1)	14 (5.7)
Goitre	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.7)	3 (1.5)	3 (1.2)	3 (1.4)	4 (1.6)
Basedow's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (3.5)	12 (4.8)	7 (3.2)	3 (1.2)
Hyperthyroidism	1 (0.9)	2 (1.9)	1 (0.8)	0 (0.0)	14 (7.0)	9 (3.6)	12 (5.5)	3 (1.2)
Autoimmune thyroiditis	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	6 (3.0)	3 (1.2)	5 (2.3)	2 (0.8)
Thyroid mass	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Cushingoid	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Primary hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Thyroiditis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	2 (0.8)	2 (0.9)	0 (0.0)
Thyroiditis subacute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Thyrotoxic crisis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

Source: Table 13.3.2.11.1 ISS Appendix 14-4-5, p. 1214.

Reviewer comment: If alemtuzumab is approved, this reviewer recommends describing significant differences in risk for autoimmune disease between patient subgroups in prescribing information.

7.3.5.2. Malignancies

In controlled studies (Pool E), 9 of 1188 (0.8%) alemtuzumab-treated subjects reported malignant neoplasms, compared to 2 of 496 (0.4%) subjects in the IFNB-1a treatment groups (see table below).

Table 50. Incidence of Treatment-Emergent Malignancies by MedDRA Preferred Term. Controlled Trials (Pool E)

Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day (N=919) n (%)	Alemtuzumab 24 mg/day (N=269) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Any Event	2 (0.4)	4 (0.4)	5 (1.9)	9 (0.8)
Thyroid cancer	0 (0.0)	3 (0.3)	0 (0.0)	3 (0.3)
Basal cell carcinoma	1 (0.2)	1 (0.1)	1 (0.4)	2 (0.2)
Acute myeloid leukaemia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Cervix carcinoma	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Colon cancer	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Vulval cancer stage 0	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)

Source: Sponsor Table 13.3.9.1 ISS Appendix 14.5.5 p. 4451

Malignancies are identified through medical review of AEs with MedDRA SOC 'Neoplasms benign, malignant, and unspecified (including cysts and polyps)' for which the HLGt does not include the word 'benign'.

- This table includes Subject 4904-3557. Based on pathology results, the adverse event of 'Thyroid cancer' has been removed for this subject.

In all alemtuzumab-treated subjects (Pool C), there were 22 adverse events of malignancy at the time of the 4-month Safety Update Report (through November 26, 2012; see table below).¹¹⁷

Table 51. Annualized Rate (Per 100 Person-Years) of Treatment-Emergent Malignancies by MedDRA Preferred Term by Cycle (Through November 26, 2013; Pool C)

Preferred Term	Overall Events (rate)	Cycle 1 Events (rate)	Cycle 2 Events (rate)	Cycle 3 Events (rate)
Patients at risk	1486	1486	1424	346
Total Person-years	5401	1587	3138	594
Any Event	22 (0.407)	5 (0.315)	14 (0.446)	3 (0.505)
Thyroid cancer	6 (0.111)	1 (0.063)	4 (0.127)	1 (0.168)
Basal cell carcinoma	6 (0.111)	1 (0.063)	3 (0.096)	2 (0.337)
Breast cancer	5 (0.093)	1 (0.063)	4 (0.127)	0 (0.000)
Malignant melanoma in situ	2 (0.037)	1 (0.063)	1 (0.032)	0 (0.000)
Cervix carcinoma	1 (0.019)	0 (0.000)	1 (0.032)	0 (0.000)
Colon cancer	1 (0.019)	1 (0.063)	0 (0.000)	0 (0.000)
Vulval cancer stage 0	1 (0.019)	0 (0.000)	1 (0.032)	0 (0.000)

Source: Table 3.3.9.1.3 4-Month Safety Update Report p. 1701

- Rates are per 100 person-years and are based on the total number of person-years/100 in the corresponding treatment group and column.

-A cycle starts with the 1st infusion of the cycle and ends with the start of the subsequent cycle. If there is no subsequent cycle, the cycle continues until the end of follow-up.

Note: Malignancies are identified through medical review of AEs with MedDRA SOC

'Neoplasms benign, malignant, and unspecified (including cysts and polyps)' for which the HLGT does not include the word 'benign' and does not include the Preferred Terms 'Thyroid neoplasm', 'Lung neoplasm', 'Pituitary tumour', 'Neoplasm skin', 'Neoplasm', 'Meningioma', 'Neurilemmoma'.

- This table includes Subject 4904-3557. Based on pathology results, the adverse event of 'Thyroid cancer' has been removed for this subject.

There were 4 alemtuzumab-treated subjects with cases of malignancy that were reported after the 4-Month Safety Update Report cut-off date of November 26, 2012.¹¹⁸

- 1 subject had 1 event of Malignant melanoma (Subject 1008-1153, CAMP-1002791)
- 1 subject had 3 events of Basal cell carcinoma (Subject 1037-5283, CAMP-1002859)
- 1 subject had 1 event of Papillary thyroid cancer (Subject 7101-3411, CAMP-1002813)
- 1 subject had 1 event of non-small cell lung cancer (Subject 1086-3620, CAMP-1003083)

¹¹⁷ Submitted to sBLA103948 on 3/19/2013.

¹¹⁸ Cases submitted through August 22, 2013.

In addition, according to the 4-Month Safety Update report, information received regarding Subject 4904-3557 caused the diagnosis to be changed from ‘Thyroid cancer’ to ‘Goitre,’ because no carcinoma was found in the post-thyroidectomy pathology.

In total, 22 of 1485 (1.5%) alemtuzumab-treated subjects (Pool C) had a treatment-emergent malignancy. In exploratory analyses of adverse events by demographic subgroup, subjects from the U.S. and female subjects had markedly higher incidences and incidence rates of treatment-emergent malignancy (Table 52). All but 1 subject with a treatment-emergent malignancy was female.

Table 52. Incidence and incidence rate of treatment-emergent malignancy by sex and location. All alemtuzumab subjects (Pool C)

	Incidence n/N (%)	Incidence rate (cases per 100,000 person-years)
All subjects	22/1485 (1.5%)	374.5 ^a
Female subjects (worldwide)	21/972 (2.2%)	544.2 ^b
Male subjects (worldwide)	1/513 (0.2%)	49.6 ^c
U.S. subjects	15/555 (2.7%)	659.9 ^d
Non-U.S. subjects	7/930 (0.8%)	194.4 ^e
U.S. female subjects	15/397 (3.8%)	894.5 ^f

Incidence rates as of April 20, 2013. Information on the total number of person-years of follow-up in alemtuzumab-treated subjects submitted to sBLA 103948 on May 14, 2013.

^a 5874 person-years of follow-up for all alemtuzumab-treated subjects

^b 3859 person-years of follow-up for all female alemtuzumab-treated subjects

^c 2015 person-years of follow-up for all male alemtuzumab-treated subjects

^d 2273 person-years of follow-up for U.S. alemtuzumab-treated subjects

^e 3601 person-years of follow-up for non-U.S. alemtuzumab-treated subjects

^f 1677 person-years of follow-up for female U.S. alemtuzumab-treated subjects

There was one case of atypical melanocytic tumor of the right ear (Subject 1031-3042; CAMP-1001169) that was not judged to be a malignancy by the Sponsor. In the opinion of this reviewer, this case should be considered a malignancy.¹¹⁹ In the opinion of a Mayo clinic physician, based on pathology, this case should be treated like a malignant melanoma.

There was a case of insulinoma (1060-3437, CAMP-1002890). The subject presented with a blood glucose of 41 mg/dL, and a 2.0 cm vascular lesion in the pancreatic body on CT scan. The subject was told she needed surgery, but she wanted a second opinion and was discharged from the hospital.¹²⁰

¹¹⁹ Subject 1031-3042 was included in the Table 52 analyses.

¹²⁰ Subject 1060-3437 was not included in the Table 52 analyses.

Reviewer comment: The insulinoma is likely to be non-malignant (10% of insulinomas are malignant).¹²¹ However, whether the insulinoma is benign or malignant has not been confirmed.¹²²

Discussion of malignancies by site

Thyroid cancer

There were 6 (0.4%) cases of thyroid cancer in 1485 alemtuzumab-treated subjects (Pool C). Five cases were reported as of November 26, 2012 and are listed in the table below. Of note, subject 1027-3419 had a whole body scan that was concerning for metastatic activity in the lower neck. (A January 2011 scan revealed 3 areas near the sternal notch with abnormal activity.)¹²³

¹²¹ Tucker ON. The management of insulinoma. British Journal of Surgery 2006; 93: 264–275

¹²² Last follow-up report (follow-up #1) was entered to IND 010717 on May 14, 2013. No update of events after the subject's hospital discharge was provided.

¹²³ Subject narrative on p. 880 of ISS Appendix 14-3.

Table 53. Thyroid Cancer Cases in Alemtuzumab-Treated Subjects: All Available Follow-Up through November 26, 2012

Study / Patient ID (sex, age at diagnosis of malignancy)	Prior Medical History / Risk Factors	Number of Cycles (or weeks) at Time of Diagnosis (Cumulative Dose)	MedDRA Preferred Term (Severity Grade, seriousness, relation to study drug)	Time from First Dose to Diagnosis of Malignancy	Days from Last Dose to Diagnosis of Malignancy	Treatment / Outcome (at end of original study)	Follow-Up in CAMMS03409 ^a
Treatment: Alemtuzumab 12 mg/day							
CAMMS323 / 1001-3095 (female, 50)	Hypothyroidism, thyroid neoplasm / None	1 Cycle (60 mg)	Thyroid cancer (Grade 3, serious, not related)	325 days (11 months)	321 days (11 months)	Thyroid lobectomy /recovered	31.8 months
CAMMS323 / 1027-3419 (female, 24)	None / None	2 Cycles (96 mg)	Thyroid cancer (Grade 3, serious, related)	688 days (23 months)	315 days (10 months)	Hemi-thyroidectomy /not recovered	24.8 months
CAMMS324 / 1041-5232 (female, 33)	Submandibular node / None	2 Cycles (96 mg)	Thyroid cancer (Grade 3, serious, not related)	697 days (23 months)	328 days (11 months)	Thyroidectomy /not recovered	21.8 months
CAMMS324 / CAMMS03409 1037-5653 (female, 35)	Respiratory tract infection, sinusitis, granuloma annulare, tonsillectomy	2 Cycles (96 mg)	Thyroid cancer (Grade 1, serious, not related)	1,002 days (33 months)	629 days (21 months)	Not recovered/resolved	44.4 months
Treatment: Alemtuzumab 24 mg/day							
CAMMS32/ 124-1080 (female, 34)	None / None	3 Cycles (264 mg)	Thyroid cancer (Grade 3, serious, related)	2021 days (70 months)	1247 (41 months)	Thyroidectomy /Recovered	37.8 months

Source: Table 5-20 in the 4-Month Safety Update report (p. 132-140). Submitted to sBLA103948 on 3/19/2013.

Note: According to the 4-Month Safety Update report, updated information received regarding Subject 4904-3557 caused the diagnosis to be changed from 'Thyroid cancer' to 'Goitre,' because no carcinoma was found in the post-thyroidectomy pathology.

In addition to the 5 thyroid cancer cases listed in Table 53, there was 1 additional event of papillary thyroid cancer (Subject 7101-3411, CAMP-1002813). The subject was a 30 year old male from Serbia who was diagnosed with follicular variant papillary microcarcinoma of the thyroid, Stage 1, T1, N0. All of the 6 cases of thyroid cancer in alemtuzumab-treated subjects were cases of papillary thyroid cancer.

The SEER reference rate for thyroid cancer (for all races) was 18.2 per 100,000 person-years for U.S. females.¹²⁴ The incidence rate in all female alemtuzumab

¹²⁴ SEER Stat Fact Sheets: Thyroid. Accessed on 8/23/2013 at <http://seer.cancer.gov/statfacts/html/thyro.html>

subjects was 129.6 cases per 100,000 person-years.¹²⁵ Four¹²⁶ of five cases of thyroid cancer in female subjects occurred in subjects from the U.S.. The incidence of thyroid cancer in U.S. females was 1.0% in alemtuzumab studies (4 cases in 397 U.S. Pool C female subjects).¹²⁷ The incidence rate in U.S. female alemtuzumab-treated subjects was 238.5 cases per 100,000 person-years.¹²⁸

The SEER reference rate for thyroid cancer (for all races) was and 6.1 per 100,000 person-years for U.S. males.¹²⁹ The incidence rate in all male alemtuzumab subjects was 49.6 cases per 100,000 person-years.¹³⁰

The Division of Neurology Products requested a consultation from Qin Ryan, M.D., Ph.D. in the Division of Hematology Products regarding malignancy-related issues with alemtuzumab. If the product is approved, Dr. Ryan said that mitigation efforts for the risk of thyroid cancer should focus on informing patients and prescribers of an increased risk of thyroid cancer. Clinicians should be advised to carefully screen subject for preexisting thyroid disease¹³¹ and follow all MS patients under alemtuzumab treatment for thyroid cancer surveillance. How often, and exactly how to monitor, is not defined.

Reviewer comment: The increased risk of thyroid cancer with alemtuzumab is concerning and threatens the approvability of alemtuzumab for treatment of MS. If alemtuzumab is approved for MS, Dr. Ryan has recommended thyroid cancer surveillance, but the method and frequency has not been defined. Because of the increased risk of thyroid cancer, as well as other cancers, this reviewer recommends evaluating the rate of malignancies with alemtuzumab in the postmarketing period through a postmarketing requirement.

¹²⁵ 5 cases in 3859 person-years for all female alemtuzumab-treated subjects as of April 20, 2013. Information on the total number of person-years of follow-up in alemtuzumab-treated subjects submitted to sBLA 103948 on May 14, 2013.

¹²⁶ U.S. alemtuzumab subjects who developed cancer were: 1001-3095, 1027-3419, 1041-5232, and 124-1080 (all female)

¹²⁷ Cancer statistics (Siegel et al., 2013, CA Cancer 63:11-30) reported that risk for thyroid cancer is 3 times higher in female than male in US population. The SEER data suggested that, in alemtuzumab treated population, the risk for thyroid cancer is 2.6 times higher for female than male worldwide. SEER data also indicated that, among alemtuzumab treated female subjects, the risk of thyroid cancer is 1.8 times higher in US than worldwide.

¹²⁸ 4 cases in 1677 person-years from U.S. female alemtuzumab-treated subjects as of April 20, 2013. Information on the total number of person-years of follow-up in alemtuzumab-treated subjects submitted to sBLA 103948 on May 14, 2013.

¹²⁹ SEER Stat Fact Sheets: Thyroid. Accessed on 8/23/2013 at <http://seer.cancer.gov/statfacts/html/thyro.html>

¹³⁰ 1 case (Subject 7101-3411 from Serbia) in 2015 person-years for all male alemtuzumab-treated subjects as of April 20, 2013. Information on the total number of person-years of follow-up in alemtuzumab-treated subjects submitted to sBLA 103948 on May 14, 2013.

¹³¹ The number of alemtuzumab-treated subjects who developed treatment-emergent thyroid cancer and had pre-existing thyroid disease is being confirmed. This information is pending at the time of this review.

Melanoma

Three of 1485 (0.2%) of all alemtuzumab subjects (Pool C) developed melanoma. All cases occurred in extension trial CAMMS03409). In addition there was 1 case of atypical melanocytic tumor in CAMMS03409; based on pathology, a Mayo clinic physician said the atypical melanocytic tumor case should be treated like a malignant melanoma (see Table 54).

Table 54. Cases of melanoma or atypical melanocytic tumor with malignant pathologic features. All alemtuzumab subjects (Pool C)

Case Number	SUBJID	Age Sex Country	Cumulative Dose (mg)	Months from first alem to onset	Verbatim Term	Preferred Term
1	1007-5204	46 F USA	96	12	Melanoma In-situ right upper thigh	Malignant melanoma in situ
2	1031-3042	39 F USA	60	6	Atypical melanocytic tumor of the right ear	Neoplasm skin
3	1106-6026	46 F Canada	60	26	Melanoma in situ	Melanoma in situ
4	1008-1153	33 F USA	132	118	Melanoma left foot	Malignant melanoma

In a population-based study in Denmark, the incidence of melanoma in MS subjects from 1968 to 1997 was 18.8/100,000 subject-years.¹³² The overall, age-adjusted incidence rate for the general population in the US was 21.0 per 100,000 per year (27.2 per 100,000 for men and 16.7 per 100,000 for women) from 2005 to 2009 in 18 SEER geographic areas. Age-Specific SEER incidence rates in the following age groups 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, and 50-54 were 1.55, 4.02, 6.99, 9.67, 13.03, 17.84, 23.12, and 29.0 per 100,000 person-years, respectively (Howlader, SEER Cancer Statistics Review, 2012). For all alemtuzumab-treated subjects in Genzyme trials, median and interquartile range age were 33 and 28 to 41, respectively.

Worldwide incidence rate for melanoma in Genzyme MS trials as of April 20, 2013: 3 cases in 5874 person-years = 51.0 cases per 100,000 person-years; this rate is approximately 3 times reference rates. In female alemtuzumab subjects (Pool C), the worldwide incidence rate was 77.7 cases per 100,000 person-years.¹³³

USA incidence rate for melanoma in Genzyme MS trials as of April 20, 2013: 2 cases in 2273 person-years = 88.0 cases per 100,000 person-years; this rate is approximately 5 times reference rates.

¹³² Nielsen NM, et al. Int J Cancer: 118, 979-984 (2006)

¹³³ 3 cases in 3859 person-years for all female alemtuzumab-treated subjects as of April 20, 2013. Information on the total number of person-years of follow-up in alemtuzumab-treated subjects submitted to sBLA 103948 on May 14, 2013.

In addition to the cases reported in Genzyme trials of alemtuzumab for MS, there is a published case of melanoma in a 34 year old woman from the UK. The melanoma was diagnosed 6 months after a 24 mg/day course of alemtuzumab for MS.¹³⁴

In her consultation, Dr. Qin Ryan acknowledged that the rate of melanoma was substantially increased in alemtuzumab-treated subjects and recommended that “under a scenario of substantial clinical benefit, subjects without history of melanoma should be considered for therapy after careful screening and removal of any premalignant and malignant skin lesions by appropriate clinical specialties.” This reviewer agrees with Dr. Qin’s recommendations. If alemtuzumab is approved, this reviewer recommends that alemtuzumab-treated MS subjects undergo baseline and periodic skin examination.

Lymphoproliferative disorders and lymphoma

There were 3 cases of lymphoma or lymphoproliferative disorders (LPD) in alemtuzumab-treated MS subjects (Table 55):

- Burkitt’s lymphoma (CAMMS223 post-study)
- MALT lymphoma (Medwatch case)
- Castleman’s Disease (published case)

67 cases¹³⁵ of Epstein-Barr virus (EBV)-associated LPD were identified in the Campath post-marketing database:

- 36 hematologic stem cell transplant cases
- 6 solid organ transplant cases
- 24 oncology indication cases (leukemia and lymphoma)
- 1 refractory polymyositis case

EBV-associated lymphoproliferative disorder occurred in subjects with a history of receiving multiple immunosuppressive agents or in subjects who received alemtuzumab concurrently with other immunosuppressant agents. However, alemtuzumab is usually administered in subjects with other prior and/or concurrent immunosuppressant agents, so this does not necessarily indicate that EBV-associated LPD may not occur without the administration of other immunosuppressant agents.

EBV-associated lymphoproliferative disorder is listed in Postmarketing Experience Section 6.3 of the Campath prescribing information.

¹³⁴ Pace AA, Zajicek JP. Eur J Neur (2009) 16: e70-e71.

¹³⁵ 57 cases were reported as of 07 May 2011 in the Campath Post-Marketing Summary (p. 21); submitted to sBLA 103948 on 27 November 2012. Ten additional cases of EBV-associated lymphoproliferative disorder in non-transplant treatment indications were reported in a response to an FDA information request; submitted to sBLA 103948 on 17 May 2013.

Table 55. Cases of lymphoma or lymphoproliferative disorder in subjects treated with alemtuzumab for multiple sclerosis

Diagnosis Report Source	Age Sex Country	EBV Test Results	Time from alemtuzumab first (last) dose to diagnosis Cumulative alemtuzumab dose	Description/Comment
Burkitt's Lymphoma CAMMS223 201-1012 ¹³⁶	39 F United Kingdom	EBV Testing Negative	5.3 years (3.3 years) 264 mg	Subject was in the 24 mg alemtuzumab dose group in CAMMS223. She was diagnosed with Burkitt's lymphoma 5.3 years after her first alemtuzumab dose. The subject died from sepsis during the course of aggressive chemotherapy.
Mucosa- Associated Lymphoid Tissue (MALT) Lymphoma Medwatch case 7876232 ¹³⁷	41 F USA	Not evaluated for EBV	6.6 years (5.5 years) 192 mg	The subject participated in an Investigator Sponsored, Open-Label, Single-arm Study of High-Dose Campath in Subjects with Active Relapsing-Remitting Multiple Sclerosis Who Have Failed License Beta-Interferon Therapies (iCAM091). She had been treated with Avonex in 2002 and 2003 for MS. She was treated with alemtuzumab 24 mg daily x 5 doses in April 2004 and alemtuzumab 24 mg daily x 3 doses in May 2005. In (b) (6) The subject presented an acute abdomen. She had a large tumor in the body of the stomach with a perforation and enlarged perigastric lymph nodes basins. After an emergency gastrectomy, pathology revealed a gastric lymphoma of MALT type. Staging at diagnosis was reported as III-A. Immunoperoxidase stain was negative for Helicobacter organisms. She received radiation therapy Feb. to March 2011. A PET/CT scan on 08 June 2012 showed interval increase in size and activity of multiple abnormal internal mammary lymph nodes and new small hypermetabolic anterior mediastinal lymph nodes and several extrapleural lymph node deposits in the lower right hemithorax and right abdomen. She underwent 6 cycles of CVP (cyclophosphamide, vincristine, prednisone)/rituximab and is in clinical and

¹³⁶ Description on p. 41-42 of CAMMS ISS; submitted to sBLA 103948 on Nov. 27, 2012.

¹³⁷ Information on this case can be found in: 1) Medwatch case report 7876232; 2) Genzyme response to FDA information request submitted to sBLA 103948 13 May 2013 (p. , Appendix 10); and 2) Genzyme follow-up report submitted to sBLA 103948 24 May 2013 (p.2-4)

Diagnosis Report Source	Age Sex Country	EBV Test Results	Time from alemtuzumab first (last) dose to diagnosis Cumulative alemtuzumab dose	Description/Comment
				radiologic remission, according to a May 2013 report.
Castleman's Disease CAMMS223 201-1233 ¹³⁸	28 F United Kingdom	EBV testing was not performed	2.7 years (1.7 years) 192 mg	The subject participated in a trial of SM3, an antibody that differs from alemtuzumab by a single point mutation and is designed not to bind to the target antigen of alemtuzumab, CD52. ¹³⁹ Investigators evaluated whether treatment with SM3 prior to alemtuzumab administration can induce tolerance to alemtuzumab and reduce immunogenicity. The subject received a 500 mg bolus of SM3 followed by alemtuzumab 24 mg daily for 5 days in Sep 2005, and alemtuzumab 24 mg daily for 3 days in Sep 2006. On (b) (6) the subject was admitted to the hospital with abdominal pain. A computed tomography (CT) scan of the abdomen showed bilateral adrenal hypertrophy. She was diagnosed with systemic inflammatory syndrome and multicentric Castleman's disease in June 2008. Lymph node biopsy was consistent with Castleman's disease with features of both hyaline vascular and plasma cell variants. She received 6 cycles of R-CP (rituximab, cyclophosphamide, Prednisolone) from September 2008 to January 2009. She is in remission per May 2013 report.

¹³⁸ Information on the case of Castleman's Disease can be found in: 1) Medwatch case report 6701876; 2) Genzyme response to FDA information request submitted to sBLA 103948 213 May 2013 (p.61-67, Appendix 11); and Somerfield, et al. *J Immunol* 2010; 185:763-768.

¹³⁹ Somerfield, et al. *J Immunol* 2010; 185:763-768.

Reviewer comment: If alemtuzumab is approved for treatment of MS, I recommend describing cases of lymphoproliferative disorder and lymphoma with alemtuzumab in the prescribing information. I also recommend collecting information on the occurrence of these disorders in the postmarketing setting.

Breast cancer

There were 5 cases of breast cancer in 3859¹⁴⁰ person-years of follow-up in alemtuzumab trials (Pool C), which is an incidence rate of 129.6 cases per 100,000 person-years. See Table 56 below for listing of breast cancer cases.

The incidence of breast cancer was higher in subjects who received the alemtuzumab 24 mg/day dose (221 cases per 100,000 person-years)¹⁴¹, compared to subjects who received alemtuzumab 12 mg/day in controlled trials (44 cases per 100,000 person-years).¹⁴² There were no demographic differences between the alemtuzumab dose groups that contribute to this difference in breast cancer incidence.

Reference incidence rates for breast cancer are listed in Table 57. The median, interquartile range, and range for age in all alemtuzumab-treated subjects were 33, 28-41, and 18-56 years, respectively.

Reviewer comment: The incidence rate of breast cancer is increased compared to reference rates in the 24 mg/day dose group and is comparable to reference rates in the 12 mg/day dose group. Given the small number of cases, the confidence intervals for these point estimates are wide. If alemtuzumab is approved, this reviewer recommends mentioning information on the incidence of breast cancer in the prescribing information. Because there are multiple malignancy-related issues of interest, this reviewer also recommends evaluation of postmarketing cases of malignancy in a postmarketing requirement study.

¹⁴⁰ As of April 20, 2013, the total number of person-years of follow-up in female alemtuzumab-treated subjects (all doses) was 3859. Information on total number of person-years of follow-up in Genzyme trials was submitted to sBLA 103948 on May 14, 2013.

¹⁴¹ In subjects who received alemtuzumab 24 mg/day in controlled trials, there were 3 cases of breast cancer in 1354 person-years of follow-up through April 20, 2013.

¹⁴² In subjects who received alemtuzumab 12 mg/day in controlled trials, there were 2 cases of breast cancer in 4519 person-years of follow-up through April 20, 2013.

Table 56. Breast Cancer Cases in Alemtuzumab-Treated Subjects: All Available Follow-Up Through 20 April 2013

Study / Patient ID (sex, age at diagnosis of malignancy)	Prior Medical History / Risk Factors	Number of Cycles (or weeks) at Time of Diagnosis (Cumulative Dose)	MedDRA Preferred Term (Severity Grade, seriousness, relation to study drug)	Time from First Dose to Diagnosis of Malignancy	Days from Last Dose to Diagnosis of Malignancy	Treatment / Outcome (at end of original study)	Follow-Up in CAMMS03409 ^a
Treatment: Alemtuzumab 12 mg/day							
CAMMS323 / CAMMS03409 7001-3210 (female, 49)	None / None	2 Cycles (96 mg)	Breast cancer (Grade 3, serious, not related)	726 days (~24 months)	344 days (11 months)	Not recovered	52.8 months
CAMMS323 / CAMMS03409 4006-3362 (female, 50)	Mitral valve prolapse, fatigue, forearm fracture, joint dislocation, osteoarthritis, endodontic procedure, Raynaud's phenomenon / None	2 Cycles (96 mg)	Breast cancer (Grade 4, serious, related)	1,346 days (44 months)	973 days (32 months)	Not recovered/resolved	49.2 months
Treatment: Alemtuzumab 24 mg/day							
CAMMS223 / 204-1131 (female, 44)	None / family history of breast cancer	2 Cycles (192 mg)	Breast cancer (Grade 3, serious, not related)	943 days (31 months)	527 days (17 months)	Surgery and chemotherapy / recovered	24.8 months
CAMMS323/ CAMMS03409 1034-5515 (female, 29)	None / None	2 cycles (192 mg)	Breast cancer (Grade 2, serious, related)	816 days (27 months)	434 days (14 months)	Dose not changed/not recovered	20.8 months
CAMMS03409/ 1020-5651 (female, 38)	Arteriovenous malformation, cyst (sacral spine cyst), back pain, scoliosis, headache, and ingrowing nail/ None	1 cycle (60 mg)	Breast cancer (Grade 4, serious, related)	235 days (8 months)	229 days (8 months)	Mastectomy and breast reconstruction/ not resolved	11.3 months

Source: Table 5-20 in the 4-Month Safety Update report (p. 132-140). Submitted to sBLA103948 on 3/19/2013.

Table 57. Reference Incidence Rates of Breast Cancer in Women by Age and Region in 2008

	Age groups (years)			
	15-39	40-44	45-49	50-54
WHO Europe region	14.6	87.8	135.3	171.9
European Union	18.7	108.9	166.3	215.0
WHO Americas region	12.7	80.4	122.0	148.5
Sweden	17.7	104.6	167.4	218.7
Denmark	21	119.4	171.8	261.7
United States	18.1	114.7	163.2	187.8
World	10.9	63.3	89.1	108.7

Source: Genzyme response entered to sBLA103948 on 5/14/2013

GLOBOCAN 2008, International Agency for Research on Cancer; incidence rates: age-standardized rates per 100,000; <http://globocan.iarc.fr/>.

HPV-Related Malignancies (Cervical and Vulvar Cancer) and Cervical Dysplasia

Human papillomavirus (HPV) infection is the main etiological factor for cervical dysplasia, cervical cancer, and vulvar cancer. Decreases in CD4+ lymphocyte counts have been associated with increased risk of HPV-related disease. Alemtuzumab causes prolonged decreases in CD4+ lymphocyte counts.

In controlled trials (Pool E), 2 of 783 (0.3%) female alemtuzumab-treated subjects were diagnosed with HPV-related cancer, compared to 0 of 323 IFN β -1a-treated subjects. One case of vulvar cancer and one case of cervical cancer have been reported in alemtuzumab-treated subjects.

- Vulvar cancer: In December 2010, 20 months after starting alemtuzumab, CAMMS324 Subject 1025-5450 (32 F USA; alemtuzumab 24 mg/day; 2 alemtuzumab cycles at AE diagnosis) was diagnosed with cervical dysplasia (cervical intraepithelial neoplasia II), and vulvar cancer stage 0, and multifocal dysplasia of the lower genital tract. She underwent several procedures for diagnosis and treatment, including wide local excision of the labia majora for vulvar disease. The event of vulvar cancer was reported as resolved in April 2011, but the event of vulvar dysplasia was still ongoing.
- Cervical cancer: In January 2006, 22 months after starting alemtuzumab, CAMMS223 Subject 302-1224 (28 F Russia; alemtuzumab 24 mg/day; 2 alemtuzumab cycles at AE diagnosis) was diagnosed with HPV-associated squamous cell cervical cancer. She underwent diagnostic curettage of cervix, uterine cavity, and circular electroscission of cervix was performed. The histopathology results showed squamous cell nonkeratinous intraepithelial cervical carcinoma with ingrowth into glands. The event of cervical carcinoma was reported as resolved on the day of the procedure.

The incidence rate of cervical cancer in female alemtuzumab subjects (Pool C) is 25.9 cases per 100,000 person-years of follow-up.¹⁴³ The reported incidence of cervical cancer varies worldwide by region. The SEER incidence rate for females of all races in 2006-2010 was 7.9 per 100,000. Incidence rates of cervical cancer worldwide are listed in the table below.

Table 58. Incidence Rates of Cervical Cancer in Women By age and region in 2008*

	Age groups (years)			
	15-39	40-44	45-49	50-54
WHO Europe region	7.8	20.9	25.1	26.3
European Union	7.7	18.4	21.9	22.5
WHO Americas region	10.0	29.2	35.6	33.7
United States	5.7	13.8	11.8	10.5
World	8.0	32.1	36.8	41.9

* GLOBOCAN 2008, IARC; incidence rates: age-standardized rates per 100,000;
<http://globocan.iarc.fr/>.

Source: Sponsor Table 17. Genzyme response submitted to sBLA 103948 on May 14, 2013

The incidence rate of vulvar cancer in female alemtuzumab subjects (Pool C) is 25.9 cases per 100,000 person-years of follow-up.¹⁴⁴ Published data on the incidence rates of vulvar cancer in women are available and are summarized below. Since vulvar cancer is an infrequent cancer in women, age-adjusted incidence rates are not available in the GLOBOCAN database.

Table 59. Incidence Rates of Vulvar Cancer in Women^a

	Incidence rate (age-adjusted per 100,000)
Denmark (2004-2007) ^b	3.6
Spain (2008) ^c	1.6-4.0
Germany (2000-2004) ^d	4.3-4.8

^a Age-Adjusted SEER Incidence Rates per 100,000; <http://seer.cancer.gov/faststats/>

^b Olsen J, Jorgensen TR, Kofoed K, Larsen HK. Incidence and cost of anal, penile, vaginal and vulvar cancer in Denmark. BMC public health. 2012;12:1082

^c Rana C, Mann K, Wadhwa A, Pathak P. Incidence rate and burden of illness associated with human papillomavirus related genital cancers in Spanish women. Value in Health 2011;14(7): A442

^d Dittmer C, Katalinic A, Mundhenke C, Thill M, Fischer D. Epidemiology of vulvar and vaginal cancer in Germany. Arch Gynecol Obstet. 2011; 284(1):169-74

Source: Sponsor Table 19. Genzyme response submitted to sBLA 103948 on May 14, 2013

Reviewer comment: Incidence rates of cervical cancer and vulvar cancer are each based on a single case; thus, point estimates are unstable and are subject to change.

¹⁴³ As of April 20, 2013, the total number of person-years of follow-up for all female alemtuzumab-treated subjects (all doses) was 3858. Submitted to sBLA 103948 on May 14, 2013.

¹⁴⁴ As of April 20, 2013, the total number of person-years of follow-up for all female alemtuzumab-treated subjects (all doses) was 3858. Submitted to sBLA 103948 on May 14, 2013.

Because cervical dysplasia is a precursor to cervical cancer, cervical dysplasia adverse events are discussed in this section. No adverse event of dysplasia at other sites of HPV-related cancers (vulva, vagina, anus, or oropharynx) was reported.

In controlled trials (Pool E), 14 of 783 (1.8%) of female alemtuzumab-treated subjects had cervical dysplasia, compared to 5 of 323 (1.5%) of female IFN β -1a-treated subjects. Four alemtuzumab-treated subjects had moderate (CIN II) or higher grade cervical dysplasia, compared to 0 IFN β -1a-treated subjects in controlled trials. In all female alemtuzumab-treated subjects (Pool C), 19 of 972 (2.0%) had an adverse event of cervical dysplasia.

Reviewer comment: If alemtuzumab is approved for treatment of MS, this reviewer recommends a description HPV-related cancer and cervical dysplasia in Warnings and Precautions with a recommendation that female subjects undergo yearly HPV cervical testing and a yearly gynecologic exam.

7.3.5.3. Infusion Reactions

Infusion of alemtuzumab¹⁴⁵ is associated with a cytokine release syndrome. Postmarketing cases of serious and fatal infusion-associated reactions (IARs) have been reported with use of alemtuzumab for B-CLL. Fatal infusion reactions included cardiac arrest and anaphylactic shock.

Based on the experience in B-CLL subjects, subjects in the MS clinical program received pretreatment with IV steroids (1 g methylprednisolone) on the first 3 days of any alemtuzumab treatment course.¹⁴⁶ Additional pretreatment medication, including antihistamine and/or antipyretic treatment, could be administered at the investigator's discretion.¹⁴⁷

In sponsor analyses, IARs were defined as adverse events which occurred between the start of any alemtuzumab infusion and the stop of infusion plus 24 hours.

The most common IARs in alemtuzumab-treated subjects (Pool C) included fever, nausea, headache, rash, flushing, hypotension, and tachycardia (see table below).

¹⁴⁵ Sponsor-proposed prescribing information recommends administering a 12 mg dose as an intravenous infusion over a period of approximately 4 hours.

¹⁴⁶ Patients treated with alemtuzumab also received methylprednisolone (1 gram IV infused over approximately 1 hour) immediately prior to alemtuzumab infusion on the first 3 days of each treatment cycle as prophylaxis for infusion-associated reactions.

Methylprednisolone was also administered to the IFNB-1a-treated patients on the same annual schedule to reduce the possibility of impacting study outcomes by differential use of this steroid across the treatment arms. (ISE p. 29)

¹⁴⁷ ISS p.33.

Table 60. Sponsor Table 6-12: Infusion-Associated Reactions Reported in $\geq 5\%$ of Subjects in Any Treatment Group. All Alemtuzumab-Treated Subjects (Pool C)

	Alemtuzumab 12 mg/day (N=1216)	Alemtuzumab Pooled (N=1485)
System Organ Class Preferred Term	n (%)	n (%)
Any Event	1095 (90.0)	1360 (91.6)
Cardiac disorders	149 (12.3)	186 (12.5)
Tachycardia	80 (6.6)	100 (6.7)
Eye disorders	42 (3.5)	58 (3.9)
Vision blurred ^a	23 (1.9)	37 (2.5)
Gastrointestinal disorders	344 (28.3)	468 (31.5)
Nausea	195 (16.0)	267 (18.0)
Dyspepsia	72 (5.9)	98 (6.6)
Vomiting	63 (5.2)	91 (6.1)
General disorders and administration site conditions	617 (50.7)	794 (53.5)
Pyrexia	318 (26.2)	392 (26.4)
Chills	122 (10.0)	163 (11.0)
Fatigue	96 (7.9)	142 (9.6)
Chest discomfort	77 (6.3)	118 (7.9)
Pain	66 (5.4)	88 (5.9)
Musculoskeletal and connective tissue disorders	201 (16.5)	257 (17.3)
Myalgia ^a	49 (4.0)	73 (4.9)
Back pain ^a	45 (3.7)	63 (4.2)
Nervous system disorders	580 (47.7)	762 (51.3)
Headache	507 (41.7)	674 (45.4)
Dysgeusia	75 (6.2)	100 (6.7)
Dizziness	63 (5.2)	89 (6.0)
Psychiatric disorders	170 (14.0)	222 (14.9)
Insomnia	136 (11.2)	171 (11.5)
Respiratory, thoracic and mediastinal disorders	204 (16.8)	280 (18.9)
Dyspnoea	81 (6.7)	113 (7.6)
Skin and subcutaneous tissue disorders	826 (67.9)	1072 (72.2)
Rash	516 (42.4)	682 (45.9)
Urticaria	168 (13.8)	242 (16.3)

	Alemtuzumab 12 mg/day (N=1216)	Alemtuzumab Pooled (N=1485)
System Organ Class Preferred Term	n (%)	n (%)
Pruritus	144 (11.8)	199 (13.4)
Rash generalized	81 (6.7)	101 (6.8)
Erythema ^a	50 (4.1)	68 (4.6)
Vascular disorders	192 (15.8)	233 (15.7)
Flushing	117 (9.6)	143 (9.6)

Note: MedDRA version 13.1 was used for coding.

Note: Percentages are based on the number of treated patients in the corresponding treatment group.

Note: A patient is counted only once within each SOC/PT.

Note: SOC's are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

Note: IARs refer to AEs that occur between the start and stop of any Alemtuzumab infusion + 24 hours.

^a These events occurred at an incidence of $\geq 5\%$ in the alemtuzumab 24 mg/day group only.

SOC = system organ class; PT = preferred term

Source: Table 3.3.4.7

An investigator-sponsored pilot study in MS showed that the first dose of alemtuzumab was associated with a transient recurrence of previous neurologic symptoms.¹⁴⁸ With first dosing of alemtuzumab Coles et al describe the general occurrence of “a systemic response accompanied by a transient and often severe, but invariably reversible, reactivation of previous neurological relapses that lasted for a few hours.” Adverse events in the Nervous System Disorders SOC were commonly reported within 24 hours of infusion (762 total adverse events in 1486 alemtuzumab-treated subjects). However, no information was provided on whether any of these adverse events represented a recurrence of previous neurologic symptoms.

The overall incidence of infusion reactions was higher in Cycle 1 compared with subsequent cycles (85.2% of subjects in alemtuzumab 12 mg/day group in Cycle 1 compared with 69.3%, 68.0%, and 68.2% for Cycles 2, 3, and 4, respectively). Results were similar for the alemtuzumab pooled dose group.

IARs were also analyzed by time of occurrence with respect to the start of the infusion (during the infusion; and 0 to 1, 1 to 2, 2 to 6, 6 to 12, and 12 to 24 hours post infusion; and not classified). Subjects may have had IARs at multiple time points with respect to

¹⁴⁸ Coles AJ, Wing MG, Molyneux P, Paolillo A, Davie CM, Hale G, et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol.* 1999;46(3):296-304.

the infusion. For subjects in the alemtuzumab 12 mg/day group, the IARs most frequently occurred during the infusion (61.3% of the subjects), with headache (28.9%), rash (14.3%), pyrexia (13.7%), chills (6.5%) and nausea (6.5%) being the most common events during this time.

Post-infusion, events occurred in each of the specified time periods of analysis, but no period had an incidence of IARs as high as that of the period of actual product infusion. Serious IARs occurred in 0.3% of subjects from 0-1 hours post infusion, in 0.2% from 1-2 hours post-infusion, in 0.2% from 2-6 hours post-infusion and in 0.6% from 12-24 hours post-infusion. No SAEs were reported in the period 6-12 hours post-infusion. Approximately 24% of serious IARs did not have a specific time interval reported with the 24 hour window. Results were similar for subjects in the alemtuzumab pooled dose group.

Infusion Reactions: Serious Adverse Events

In the ISS analysis, 37 of 1485 (2.5%) of all alemtuzumab-treated subjects (Pool C) had a serious infusion reaction. Serious infusion-related AEs included:¹⁴⁹

- Chest pain (5)
- Sinus bradycardia (heart rate in 30's-40's) (4)
- Headache (4)
- Atrial fibrillation (3)
- Hypotension (3)
- Anaphylactic shock (2)¹⁵⁰
- Hypertension (2)
- Sinus tachycardia (2)
- Increased liver transaminases (2)
- Rash (2)
- Brain stem syndrome (1)
- Angioedema (1)
- Pneumonitis (1)
- Pyrexia (1)
- Edema (1)
- Cellulitis (1)

Additional details on serious adverse events associated with alemtuzumab infusion are included in Table 61.

¹⁴⁹ Serious adverse events during which an incorrect dose of alemtuzumab was administered (Subjects 3006-3281 and 3006-3282) are not included in this list.

¹⁵⁰ Preferred term for one of the events was 'Anaphylactoid reaction.' The World Allergy Organization (Johansson. J Allergy Clin Immunol. 2004 May;113(5):832-6) suggested in its nomenclature that the term 'anaphylactoid' be eliminated. The nomenclature proposes that anaphylaxis refer to a "severe, life-threatening, generalized or systemic hypersensitivity reaction" and that anaphylaxis can be divided into 'allergic anaphylaxis' and 'non-allergic anaphylaxis.'

Table 61. Alemtuzumab-treated subjects with infusion reaction serious adverse events. All alemtuzumab subjects. (Pool C)

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
Dose prior to Infusion Reaction: Alemtuzumab 12 mg/day						
6103-3091 CAMMS323	31 M Ukraine	Cycle 1 Day 1 During infusion	N	Anaphylactic shock	N	Two hours after the start of infusion the subject developed anaphylactic shock. Blood pressure was 60/40 mmHg, pulse was 60 bpm. Had cyanosis, rigor, tremor and involuntary urination. Infusion was stopped, and the subject was treated with 4mg of dexamethasone and 2 ml of cordiamin (nikethamide) administered intramuscularly. After 15 minutes and after 45 minutes, the subject's blood pressure was 65/40 mmHg and 90/60 mm Hg, respectively. After one hour and 15 minutes the subject's blood pressure was 104/62 mm Hg, his pulse was 88 bpm and the event anaphylactic shock recovered without sequelae. According to the narrative: "The subject received his Month 12 dose from Day 365 (18 May 2009) to Day 367 (20 May 2009) with no infusion-associated reactions." <i>Reviewer note: This subject experienced acutely life-threatening anaphylactic shock. The Sponsor says the subject received a subsequent cycle of alemtuzumab 1 year after the first dose without infusion reaction. (After the anaphylactic shock, the remainder of the first cycle was cancelled.) During the second cycle, no additional premedication for infusion is listed and infusion times were extended to 5-6 hours. Whether the subject was hospitalized for infusion was not mentioned.</i>

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
1040-5309 CAMMS03409	25 F USA	Cycle 3 Day 1 During infusion	N	Anaphylactoid reaction	Y	Received alemtuzumab 24 mg/day in CAMMS324. Subject had a life-threatening episode of anaphylaxis ¹⁵¹ with redness and swelling of eyes, lips, hands and face, as well as itching and swelling in mouth and throat with cough. No vital signs for this adverse event were provided. Infusion was stopped, and she was treated with epinephrine, Benadryl, and oxygen via nasal canula, Event resolved within 50 minutes. Because of this event, treatment with alemtuzumab was permanently stopped.
122-1319 CAMMS223	32 F USA	Cycle 2 Day 3 Within 24 h of infusion	N	Hypertension	N	Hypertensive emergency with BP 206/126. Prior to this infusion reaction, BP was documented to be 110-130/64-82. The subject also had a headache with photophobia, chest tightness, and fullness in her throat. After 3 days BP was controlled and she was discharged from the hospital.
404-1334 CAMMS223	22 M Poland	Cycle 3 Day 1 Within 24 h of infusion	Y	Hypotension	N	Hypotension 90/60, vomiting, chills, headache. Treatment included dexamethasone, calcium, paracetamol, and IM clemastine (antihistamine) . Not discussed in narrative. Only discussed in Medwatch camp 1000342. Subject was routinely hospitalized prior to admission.
3006-3281 CAMMS323	21 M Brazil	Cycle 1 Day 1 1-2 h post-infusion	N	Incorrect dose administered Arterial hypotension	N	Incorrect dose administered -- 60 mg infused over 4 hours. Subject was hypotensive with a blood pressure of 83/43 and acidosis. Baseline BP 110/80. Also had decreased strength in lower extremities and blurred vision. Discharged from hospital after 4 days.
3006-3282	24 F	Cycle 1	N	Incorrect dose	N	Incorrect dose administered -- 48 mg infused over 3 hours.

¹⁵¹ Current terminology per the World Allergy Organization is anaphylaxis. The term ‘anaphylactoid’ has been eliminated in the revised terminology. (Johansson. J Allergy Clin Immunol. 2004 May;113(5):832-6)

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
CAMMS323	Brazil	Day 1 During infusion		administered Sinus Tachycardia		Sinus tachycardia with HR 200-220, which resolved the same day.
3208-3552 CAMMS323	19 F Argentina	Cycle 1 Day 4 During infusion	N	Sinus bradycardia	N	Received infusions on Days 1-4. On Day 4, after 4 mg of study drug, pt had sinus bradycardia. EKG had negative T waves. Lowest HR was 42 bpm. Had a normal HR on Day 5 and returned to baseline (HR 75-80) on Day 6.
4005-3056 CAMMS323	40 F UK	Cycle 2 Day 1 During infusion	Y	Brain stem syndrome	N	Subject was routinely hospitalized prior to infusion. Infusion started at 13:00. At 17:00 she became nauseated, vomited, and had a grade 3 brain stem syndrome. The subject was weak, mildly dysarthric, was unable to stand., and had diplopia. Upon examination, the subject had grade 4/5 power throughout, brisk reflexes with bilateral upgoing plantars, truncal ataxia, and ataxia in her limbs with right greater than left. Vital signs revealed temperature at 37.8 C and pulse at 120 beats per minute. She was treated with cyclizine and dexamethasone. The symptoms resolved at around 22:00. She was rechallenged the same day and “received further infusion of study drug without any problems”, according to the narrative. <i>Reviewer comment: Genzyme’s explanation for the brainstem syndrome adverse event is that it may have been similar to a transient recurrence of previous MS symptoms that sometimes occurs during alemtuzumab infusion.</i> ¹⁵²
4006-3074	27 F	Cycle 1	N	Hypotension	N	Had hypotension with a nadir BP of 84/51

¹⁵² Genzyme submission to sBLA 103948 on March 11, 2013, p. 7.

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
CAMMS323	UK	Day 5 During infusion				(baseline 139/91). Subject had dizziness, blurred vision, deafness, parasthesia, and was presyncopal upon standing. BP improved to 100's-120's/70 within 2 hours of stopping infusion.
1009-3170 CAMMS323	37 M USA	Cycle 2 Day 1 During infusion	N	Tachycardia Headache Nausea Pyrexia Myalgia	N	Transferred to ER for nausea, fever (102.4 F), sinus tachycardia (140's; baseline HR 60's), myalgia, headache. Lactic acid at 4.10 mmol/L (normal 0.67 - 2.47 mmol/L) (Appendix 14-3 p. 796).
104-1127 CAMMS223	44F USA	Cycle 3 Day 3 Two hours post- infusion	N	Atrial Fibrillation	N	Two hours after receiving the 3rd daily dose of cycle 3 of CAMMS223, developed atrial fibrillation with rapid ventricular response (HR not specified). H/O atrial fibrillation of 3 days duration 10 years prior to this event.
134-1234 CAMMS223	29 F USA	Cycle 2 Day 1 During infusion	N	Infusion Reaction	Y	During infusion, subject had shivering, tachycardia (HR not provided), chest pain, dyspnea, and was in acute distress. BP remained normal. Treated with diphenhydramine and 3 mg sc epinephrine. Symptoms resolved 15 min after discontinuation of IV infusion. This adverse event resulted in study discontinuation and treatment discontinuation.
1002-3004 CAMMS323	24 F USA	Cycle 1 Day 3 <1 hour post-infusion	N	Atrial fibrillation	N	Atrial fibrillation rate 119. diagnosed 30 minutes after infusion. Treated with metoprolol tartrate, flecainide and enoxaparin sodium. Atrial fibrillation resolved after 1 day.
4006-3675 CAMMS323	35 F UK	Cycle 1 Day 4	N	Chest discomfort Urticaria Angioedema	N	Hospitalized due to the event of angioedema. Treated with intravenous hydrocortisone, piriton, sodium chloride, and volplex along with 15 liters of oxygen via non-rebreather

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
		During infusion		Throat tightness		mask. Sent to the emergency room for further management where she received 40 mg prednisolone, hospitalized. Urticaria ad chest discomfort resolved after 4 days, and she was discharged from the hospital. The throat tightness and dyspnea resolved 6 months after infusion.
4634-3725 CAMMS323	39 M Germany	Cycle 1 Day 2 12-24 hours post-infusion	N	Atrial fibrillation	N	Atrial fibrillation with rate up to 160 bpm. Subject treated with metoprolol. Atrial fibrillation lasted 7 hours.
4634-3738 CAMMS323	28 F Germany	Cycle 1 Day 1 <1 hour post-infusion	N	Migraine	N	Migraine headache requiring hospitalization. Subject had a history of migraine headaches prior to alemtuzumab treatment. The migraine resolved on the same day after several hours.
4701-3701 CAMMS323	21 F Sweden	Cycle 1 Day 2 3 hours post-infusion	N	Pleuritis Bradycardia	N	Shortness of breath started 3 hours after the Cycle 1 Day 2 infusion. He received a third infusion and had hemoptysis and plauritis. Chest x-ray showed 6 mm fluid in the pleura. Pleuritis resolved after 3 days. He had bradycardia (heart rate 48 bpm) on the day of the third infusion, which resolved the same day. No beta-blockers or calcium-channel blockers were listed in the subject's concomitant medications.
1007-5029 CAMMS324	30 M USA	Cycle 1 Day 5 <1 h post-infusion	N	Chest tightness Cough	N	Hives were noted bilaterally on the subject's arms, upper torso and face during infusion. Decadron and Benadryl were given and the subject completed infusion. Following infusion, the subject experienced chest tightness and dry cough that were grade 3 in intensity and required medical intervention. The subject was diaphoretic and pale.

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
						Epinephrine was administered subcutaneously and oxygen applied via a non-rebreather mask. The subject was given epinephrine and saline intravenously. The subject was transported to the emergency room, observed, and discharged the same day.
1082-6025 CAMMS324	50 M USA	Cycle 1 Day 4 12-24 h post-infusion	N	Chest pain	N	Evaluated in ER for evaluation of chest pain. EKGs, cardiac enzymes, and vital signs within normal limits. Released on the same day.
1090-5393 CAMMS324	33 F USA	Cycle 2 Day 3 Within 24 h of infusion	N	Status Migranosus	N	H/O Migraines. Hospitalized for 2 days with status migrainosus. Event duration was 10 days.
1097-6073 CAMMS324	32 F USA	Cycle 2 Day 3 During infusion	N	Infusion related reaction	Y	Subject had severe flushing of face, intermittent chest tightness, throat swelling, irregular heart rate and dizziness and required hospitalization. This adverse event caused the subject to discontinue treatment.
2002-5276 CAMMS324	31 M Australia	Cycle 2 Day 3 12-24 h post-infusion	N	Haemoptysis	N	Hospitalized for hemoptysis and intermittent shortness of breath, associated with some pleuritic chest pain. Discharged after 1 day. Had residual ground glass densities on chest x-ray 2 months later.
2015-5832 CAMMS03409	35 F Australia	Cycle 3 Day 3	N	Headache Post lumbar puncture	N	Subject developed a severe headache on the last day of the third alemtuzumab cycle (9/7/2011). Her headache was evaluated in the emergency department with a CT scan and

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
		2-6 hours post-infusion		syndrome		lumbar puncture and she was sent home (9/8/2011). Hospitalized (b) (6) for management of headache post-infusion and headache after lumbar puncture (LP). the principal diagnosis for the admission was listed as post-LP headache. (Medwatch form p. 476 ISS Appendix 14-3-2-4)
4008-5733 CAMMS324	30 F UK	Cycle 2 Day 3 Within 24 h of infusion	Y	Nausea Vomiting	N	Had nausea, vomiting, diplopia, and reduced urine output post-infusion. Also had tachycardia (HR 102), hypotension (no measurement provided), increased respiratory rate (32 breaths/minute), reduced oxygen saturation levels and pyrexia (38.9 C). She was treated with oxygen, choline salicylate, salbutamol, chlorpheniramine, glucose, ondansetron, sodium chloride, metoclopramide, co-trimoxazole, piperacillin / tazobactam, domperidone, zopiclone, levomepromazine, prochlorperazine, nitrofurantoin, and baclofen. She was hospitalized for 1 month. Nausea and vomiting continued for about 1 month after hospital discharge.
4202-5057	37 F Netherlands	Cycle 1 Day 5 Within 24 h of infusion	Y	Pyrexia	N	Subject was hospitalized prior to dosing. Fever related to the infusion prolonged the planned hospitalization by 1 day. The subject's fever was treated with doxycycline, which was discontinued due to an allergic reaction.
4608-5660	20 M Germany	Cycle 1 Day 2 2-6 hours post-infusion	N	Urticaria	N	Subject developed generalized urticaria that required hospitalization. He was treated with intravenous methylprednisolone 500 mg on (b) (6) and the generalized urticaria improved. On the morning of (b) (6) the subject was treated with desloratadine, ranitidine, methylprednisolone, and Fenistil. The urticaria completely

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
						resolved, and day 3 of study drug was infused without interruption or delay.
4610-5691 CAMMS324	47 M Germany	Cycle 1 Day 5 1-2 h post-infusion	Y	Pyrexia	N	Fever (38.6 C) starting on (b) (6) prolonged the subject's routine hospitalization for alemtuzumab dosing. Fever was reported as resolved on (b) (6) and he was discharged on (b) (6). Details on why the hospitalization continued after the fever resolved were not provided.
5301-5996 CAMMS324	32 F Denmark	Cycle 1 Day 4 Within 24 h of infusion	N	Urticaria	N	Urticaria post-infusion treated with methylprednisolone and tavegyl. Hospitalized for 2 days.
5302-5300 CAMMS324	51 M Denmark	Cycle 2 Day 2 12-24 h post-infusion	N	Hypothyroidism Oedema peripheral	N	Hospitalized for 5 days for hypothyroidism and edema requiring diuretic treatment.
5501-5528 CAMMS324	52 M Israel	Cycle 2 Day 2 12-24 h post-infusion	N	Non-cardiac chest pain Dyspnoea	Y	Hospitalized for evaluation of chest pain. No ischemic dynamics reported on ECG. No elevation in cardiac enzymes was reported. The subject was discharged on an unspecified date.
1031-3042 CAMMS03409	37 F USA	Cycle 1 Day 5 Within 24 h of infusion	N	Oral herpes cellulitis	N	Subject received IFNβ-1a in CAMMS323. After the 5 th dose in the first cycle of alemtuzumab, she developed oral herpes and cellulitis of the left face. She developed an abscess on her left jaw and was hospitalized for possible incision and drainage. (No details on any surgical treatment were provided.) <i>Reviewer comment: This AE is unlikely</i>

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
						<i>related to infusion.</i>
Dose prior to Infusion Reaction: Alemtuzumab 24 mg/day						
401-1257 CAMMS223	34 F Poland	Cycle 2 Day 3 Within 24 h of infusion	Y	Bradycardia Increased AST Increased ALT	N	Routinely hospitalized on (b) (6) for treatment with alemtuzumab. Asymptomatic bradycardia was observed (38-40/min) after the subject's dose of Campath on (b) (6). Atropine was given as corrective treatment for bradycardia. Atropine was stopped on 06 Jun 2005 prior to Holter monitoring on 08 Jun 2005. The Holter monitoring results revealed sinus rhythm (48-117/min). Three episodes of bradycardia (39/min) lasting 4 seconds were observed. Bradycardia resolved on 08 Jun 2005. In addition to the three episodes of bradycardia, Holter monitoring revealed 59 extrasystolic, supraventricular- single events during a 24 hour and 23 minute period. In addition, the subject had increased levels of ALT 420 IU/L (normal range 0-31 IU/L), AST 209 IU/L (normal range 0-31 IU/L), and GGTP 70 IU/L (normal range 9-50 IU/L). Liver function tests normalized after 4 weeks.
1009-5030 CAMMS324	38 F USA	Cycle 1 Day 4 6-12 h post-infusion	N	Migraine Hypertension	N	Admitted with severe headache and hypertension with blood pressure 180/98.
2015-5586 CAMMS324	36 F Australia	Cycle 1 Day 2 Within 24 h of infusion	N	Acute gastritis Hepatotoxicity	Y	Subject had acute gastritis and liver toxicity. Near the end of infusion for Day 2 treatment, the subject complained of tightness in her chest. The tightness resolved following administration of oxygen for a short time and the subject was sent home. Later that evening the subject experienced extreme pain beginning in the back and migrating toward

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
						the abdomen. Subject was hospitalized for 3 days. Vital signs upon admission included temperature 37.3C, heart rate 58 bpm, blood pressure 160/85 mmHg, and P02 saturation 99%. Labs included ALT 880 U/L, AST 470 U/L, GGT 60 U/L, and C-reactive protein 84.0 mg/L. Transaminases normalized after 2 weeks. Treatment was discontinued because of this adverse event. <i>Reviewer comment: The hepatotoxicity is likely related to cytokine release syndrome with infusion. Hepatotoxicity with cytokine release syndrome has been described with rituximab treatment (Winkler U, et al. Blood. 1999 Oct 1;94(7):2217-24.)</i>
4007-5521 CAMMS324	40 F UK	Cycle 2 Day 1 During infusion	N	Sinus tachycardia	Y	Subject developed tachycardia of 140 bpm during infusion. According to the discharge summary for the event of tachycardia, the diagnosis was tachycardia with questionable atrial flutter. Medwatch report CAMP 1000646. The adverse event lead to study treatment discontinuation after tachycardia occurred again during a rechallenge of alemtuzumab.
4609-5124 CAMMS324	43 F Germany	Cycle 1 Day 3 Within 24 h of infusion	Y	Rash	N	The subject was hospitalized on (b) (6) to receive Cycle 1 of study treatment. On (b) (6), the subject experienced a skin rash with itching and bruising. She was kept in the hospital overnight for safety monitoring purposes.
2013-5322 CAMMS324	48 F Australia	Cycle 1 Day 2 Within 24 h of infusion	N	Pneumonia Bradycardia	N	Subject hospitalized for pneumonia with dyspnea, coughing and expectoration of blood stained sputum. Also had sinus bradycardia with heart rate 38-44 (not categorized as an SAE). Baseline HR 67. Duration of bradycardia was not specified. Heart rate was documented at baseline 1 month

Subject Study	Age Sex Country	Cycle and Day of most recent alemtuzumab Time of AE in relation to last infusion	Evidence of Routine admission before dosing	Preferred Term (Verbatim Term)	W/D	Description/Comment
						after the start of the bradycardia. No beta-blockers or calcium-channel blockers were listed in the subject's concomitant medications.

Source: Narratives ISS Appendix 13-3.

If the precise start time for the infusion reaction was not available, an infusion is described as occurring within 24 hours of infusion.

h = hours C = Celsius sc = subcutaneous

Infusion Reactions: Vital Signs

Cytokine release syndrome was known to result in serious and fatal infusion reactions in B-CLL subjects when Phase 2-3 studies in MS subjects were designed. However, vital signs were not systematically measured during and after infusion in Phase 2-3 trials. (The study protocols did not instruct sites to collect this information.) Table 62 summarizes adverse events indicating abnormal vital signs and the vital sign measurements provided by Genzyme.¹⁵³

Table 62. Abnormal vital sign adverse events within 24 hours of infusion. Alemtuzumab-treated subjects.

Vital sign adverse events within 24 hours of infusion		Provided vital sign measurements														
<div>Blood Pressure</div> <table><tr><th>Adverse Event Preferred Term</th><th>Number of Events</th></tr><tr><td>Hypertension</td><td>40</td></tr><tr><td>Hypotension</td><td>40</td></tr><tr><td>Blood pressure increased</td><td>15</td></tr><tr><td>Orthostatic hypotension</td><td>3</td></tr><tr><td>Blood pressure decreased</td><td>2</td></tr><tr><td>Hypertensive crisis</td><td>1</td></tr></table>		Adverse Event Preferred Term	Number of Events	Hypertension	40	Hypotension	40	Blood pressure increased	15	Orthostatic hypotension	3	Blood pressure decreased	2	Hypertensive crisis	1	Zero blood pressure measurements related to abnormal adverse events were submitted.
Adverse Event Preferred Term	Number of Events															
Hypertension	40															
Hypotension	40															
Blood pressure increased	15															
Orthostatic hypotension	3															
Blood pressure decreased	2															
Hypertensive crisis	1															
<div>Temperature</div> <table><tr><th>Adverse Event Preferred Term</th><th>Number of Events</th></tr><tr><td>Pyrexia</td><td>555</td></tr><tr><td>Hyperthermia</td><td>66</td></tr><tr><td>Hyperpyrexia</td><td>1</td></tr><tr><td>Hypothermia</td><td>1</td></tr></table>		Adverse Event Preferred Term	Number of Events	Pyrexia	555	Hyperthermia	66	Hyperpyrexia	1	Hypothermia	1	Three temperature measurements were provided for events with the Preferred term 'Pyrexia'. However, none of the measurements met the standard definition for pyrexia and ranged from 97.0-97.5 C.				
Adverse Event Preferred Term	Number of Events															
Pyrexia	555															
Hyperthermia	66															
Hyperpyrexia	1															
Hypothermia	1															
<div>Heart Rate</div> <table><tr><th>Adverse Event Preferred Term</th><th>Number of Events</th></tr><tr><td>Tachycardia</td><td>224</td></tr><tr><td>Bradycardia</td><td>60</td></tr><tr><td>Tachycardia paroxysmal</td><td>2</td></tr></table>		Adverse Event Preferred Term	Number of Events	Tachycardia	224	Bradycardia	60	Tachycardia paroxysmal	2	Five heart rate measurements for tachycardia adverse events were provided. Heart rate measurements ranged from 89-109. Two of 5 heart rate measurements were <100 bpm and did not meet the usual definition for tachycardia.						
Adverse Event Preferred Term	Number of Events															
Tachycardia	224															
Bradycardia	60															
Tachycardia paroxysmal	2															

¹⁵³ Sponsor response submitted to sBLA 103948 on May 14, 2013

Anaphylaxis

There has been no universally accepted definition of anaphylaxis.¹⁵⁴ The Sponsor performed analyses of anaphylaxis, including: 1) a search of events derived from Category A of the MedDRA Anaphylaxis SMQ; 2) a search using a modification of the MedDRA SMQ for anaphylaxis based on the Second National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network symposium definition of anaphylaxis (Sampson, 2006, J Allergy Clin Immunol); and 3) medical review of events identified using the Sampson SMQ criteria.

The incidence of SMQ identified events in all active-controlled studies over 3 years of follow up (Pool E) is summarized in Sponsor Table 6-16. Events that met the Sampson SMQ criteria were identified in 78 (8.5%) subjects in the alemtuzumab 12 mg/day group, compared with 2 (0.4%) IFNB-1a-treated subjects.

The Genzyme medical review identified 1 potential anaphylactic reaction in the controlled trials (alemtuzumab 12 mg/day group; Subject 6103-3091). and 1 anaphylactic reaction in the extension study (Subject 1040-5309) (see Table 61 for brief narratives).

¹⁵⁴ Sampson, H.A., et al. "Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium." *Annals of emergency medicine* 47.4 (2006): 373-380.

Table 63. Sponsor Table 6-16: Incidence of Potential Anaphylactic Reactions Overall and by Cycle in Controlled Studies (Pool E)

	SC IFNB-1a (N= 496) n (%)	Alemtuzumab 12 mg/day (N= 919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Overall			
Patients Treated	496	919	1188
Sampson Method	0 (0.0)	1 (0.1)	1 (0.1)
Standard MedDRA Query Category A	2 (0.4)	78 (8.5)	123 (10.4)
Cycle 1			
Patients Treated		919	1188
Sampson Method		1 (0.1)	1 (0.1)
Standard MedDRA Query Category A		68 (7.4)	98 (8.2)
Cycle 2			
Patients Treated		891	1151
Sampson Method		0 (0.0)	0 (0.0)
Standard MedDRA Query Category A		14 (1.6)	34 (3.0)
Cycle 3			
Patients Treated		24	46
Sampson Method		0 (0.0)	0 (0.0)
Standard MedDRA Query Category A		0 (0.0)	2 (4.3)

Note: Percentages are based on the number of treated patients in the corresponding treatment group and cycle.

Note: For alemtuzumab-treated patients, AEs identified as a potential anaphylactic reactions had to occur from the start of an infusion to 24 hours after the end of the infusion in each alemtuzumab treatment cycle. For IFNB-1a-treated patients, all AEs during the applicable follow-up period are used.

SC = subcutaneous; IFNB-1a = interferon beta-1a; MedDRA = Medical Dictionary for Regulatory Activities; AE = adverse event; IFNB-1a = interferon beta-1a

Source: Table 13.3.4.9.1

Reviewer comment: Vital signs during and after infusion were generally not collected or reported, so this reviewer and the sponsor are lacking objective criteria needed to assess the severity of the majority of anaphylaxis events identified by the MedDRA Anaphylaxis SMQ.

Angioedema

The incidence of events identified by the MedDRA Angioedema SMQ in all active-controlled studies was 171 (18.6%) subjects in the alemtuzumab 12 mg/day group and 84 (31.2%) subjects in the alemtuzumab 24 mg/day group. For the alemtuzumab 12 mg/day group, the incidence of events in the Angioedema SMQ was highest in Cycle 1 (153 subjects, 16.6%) and decreased in Cycle 2 (53 subjects, 5.9%). The most common event was urticaria (a frequent IAR), reported for 135 (14.7%) subjects. Other events occurring

in ≥ 2 subjects were peripheral edema (16; 1.7%), wheezing (13; 1.4%), throat tightness (5; 0.5%), swelling face (4; 0.4%), and events occurring in 2 (0.2%) subjects each: face edema, choking sensation, and pharyngeal edema.

Serious events within the Angioedema SMQ were reported for 2 subjects; 1 occurred during an infusion in a treatment-naïve subject, and 1 occurred outside the defined 24-hour window after infusion in a subject who had previously been treated prior to treatment with alemtuzumab.

- Subject 4006-3675 (CAMMS323; 35 year old female) was reported to have Grade 4 angioedema on Cycle 1, Day 4, which was part of a constellation of IARs during Cycle 1, including dyspnea on Day 3 and lower grade headache, dizziness, peripheral edema, chest discomfort, pyrexia, throat tightness, urticaria, and hypertension. Alemtuzumab infusion was interrupted; the subject received oxygen and was treated with IV hydrocortisone, chlorphenamine, sodium chloride, succinylated gelatin solution, and prednisolone. The angioedema resolved the next day. No further study drug was administered in Cycle 1. The subject completed Cycle 2, during which she experienced non-serious IARs of headache and rash.
- Subject 1055-5753 (CAMMS324; 47 year old female) was reported to have Grade 3 angioedema 5 days after the third infusion for Cycle 2. An IAR of headache (Grade 1) preceded the event of angioedema. The subject was hospitalized and treated with prednisone and was dispensed an epinephrine pen. The event occurred outside of the defined 24-hour window following an alemtuzumab infusion for IAR analysis, so it is not included in the analysis.

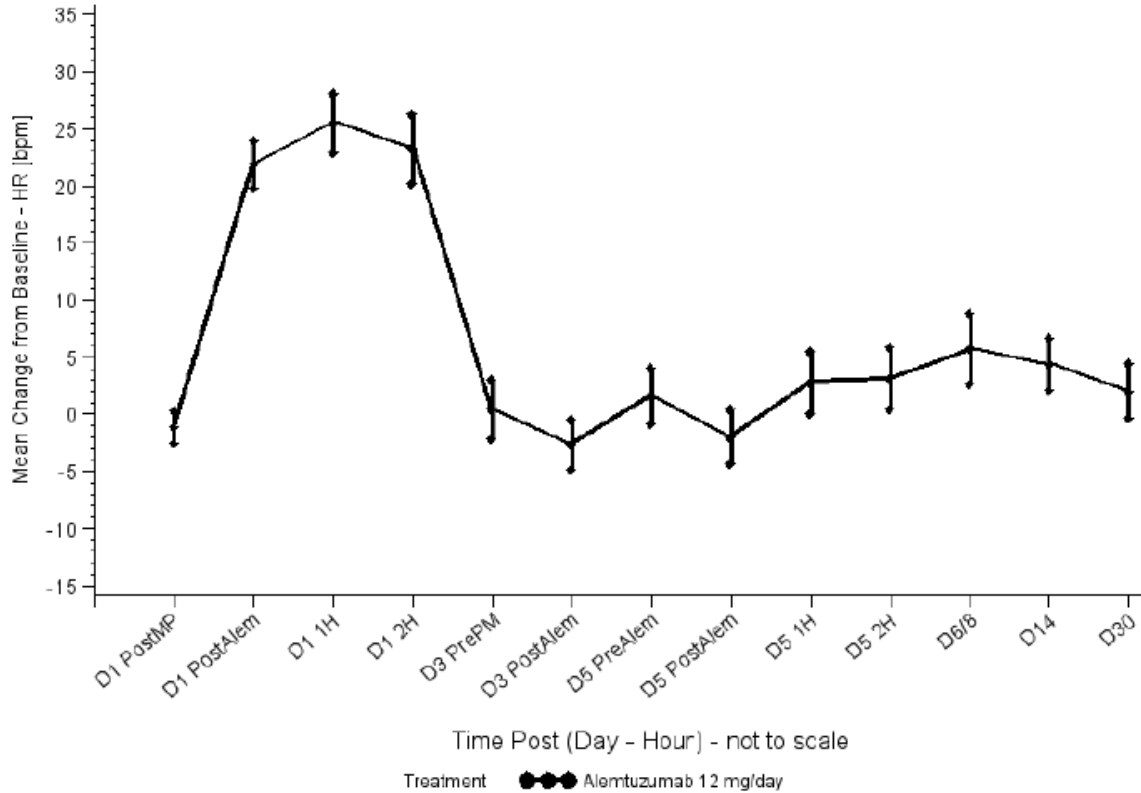
Reviewer comment: The case of angioedema occurring 5 days after infusion highlights the importance of subject education in mitigating the risks of infusion reactions.

QT Substudy: ECG changes during and after infusion

As part of extension study CAMMS03409, a substudy was conducted to examine potential effects of alemtuzumab on the electrocardiographic QT interval. This substudy was conducted in subjects with MS per agreement with FDA to fulfill the requirements of a postmarketing commitment for alemtuzumab as used in the B-CLL indication. The QT substudy included 53 subjects who received IFNB-1a or glatiramer acetate in a Phase2-3 study and received alemtuzumab for the first time in CAMMS03409.

Limited information on heart rate during and post-infusion was available from ECGs performed in the QT substudy. The mean change from baseline was in the range of 22 to 26 bpm during the two hour period following the initial infusion of alemtuzumab on Day 1. No heart rate measurements were performed during infusion in the QT substudy. The increase in heart rate was not observed at subsequent doses with higher exposure of alemtuzumab.

Figure 3. QT Substudy: Mean Change (\pm 90% CI) from Baseline in Heart Rate (HR)



Source: Figure 6-3 QT Substudy report (p. 36). Submitted to sBLA 103948 on February 27, 2013

When asked, Genzyme commented that one factor that may contribute to the increase in heart rate seen mainly with the first infusion of alemtuzumab is target cell number.¹⁵⁵ Infusion reactions may result from either lysis or activation of cells triggered by alemtuzumab binding. A higher number of target cells may be expected to lead to a higher incidence or severity of infusion reactions. Coles reported that substantial depletion of CD52-positive cells occurs within an hour of receiving 5–10 mg of alemtuzumab infusion.¹⁵⁶ The lower number of target cells on subsequent infusion days could contribute to the observed lower incidence and severity of infusion reactions with those subsequent infusions.

Reviewer comment: There is a large first dose effect seen in the mean change in heart rate after alemtuzumab infusion. Mean change in heart rate was substantially greater after the first infusion in the QT sub-study, as compared to after subsequent infusions. For infusion reactions overall, the difference in incidence between first dose and subsequent doses is relatively minor.

No large changes in QT were detected, but ST segment and T wave changes were seen in 23 and 30 percent of subjects, respectively. The significance of these ST segment and T

¹⁵⁵ Genzyme response submitted to sBLA 10394 8 on June 7, 2013.

¹⁵⁶ Coles AJ, et al. The window of therapeutic opportunity in multiple sclerosis. J Neurol (2006) 253 : 98–108.

wave changes is unclear. History of clinically significant heart disease was an exclusion criterion for the QT substudy.

Monitoring for Alemtuzumab Infusion: Setting and Duration

Infusion Setting: Routine Hospitalization before Alemtuzumab Infusion

Because alemtuzumab can cause acutely life-threatening infusion reactions, including anaphylaxis and cardiac dysrhythmias, the appropriate setting for alemtuzumab infusion is an important consideration.

In narratives for some subjects who had serious adverse events, routine hospitalization prior to infusion of alemtuzumab is described. The number of subjects who were routinely hospitalized prior to alemtuzumab infusion is not known. According to Genzyme:

“The protocol did not require that subjects be hospitalized for administration of alemtuzumab, and this information was not recorded on the study CRF since such information was not required per protocol. These data are not available. In some countries it may have been standard practice to hospitalize subjects prior to infusion; however in the U.S. infusions were routinely given on an outpatient basis.”¹⁵⁷

No vital signs during or after infusion were available for subjects routinely hospitalized for alemtuzumab infusion.

Knowledge of the type of facility in which a subject was infused is an important part of evaluating the infusion reaction data. This knowledge is also important in determining the appropriate setting for infusion of alemtuzumab if it is approved for treatment of MS. The rate of reported serious adverse events may be affected by routine hospitalization; events usually requiring hospitalization for monitoring or treatment may not be reported as serious adverse events, because the monitoring or treatment may be a usual part of the routinely hospitalized subject’s care. Adverse event outcomes in a population of hospitalized subjects may be different from a similar population that is not hospitalized.

Investigators hospitalized subjects, even though this was not part of the Genzyme clinical trial protocols. Also, a published article co-authored by Alasdair Coles, a Cambridge scientist who has been integral in the development of alemtuzumab, describes hospitalization as a necessity: “The treatment regimen of alemtuzumab necessitates hospital attendance for an intravenous infusion for a few consecutive days on 2 consecutive years, with drug-free intervals in between.”¹⁵⁸

¹⁵⁷ Response to FDA information request entered to sBLA 103948 on May 14, 2013, p. 108.

¹⁵⁸ Williams T, Coles A, Azzopardi L. The Outlook for Alemtuzumab in Multiple Sclerosis. BioDrugs. 2013 Apr 5.

Genzyme does not propose routine hospitalization prior to alemtuzumab infusion. According to the sponsor-proposed prescribing information, “Observation for infusion reactions is recommended during and for 2 hours after each LEMTRADA infusion.”

Duration of Monitoring after Alemtuzumab Infusion

According to the sponsor-proposed prescribing information, “Observation for infusion reactions is recommended during and for 2 hours after each LEMTRADA infusion.” Serious adverse events that occurred more than 2 hours after the end of alemtuzumab infusion included bradycardia and atrial fibrillation; these adverse events may not be recognized or treated promptly outside of a monitored setting. The optimal duration of routine observation post-infusion is unclear. In 24% of serious infusion-related adverse events, event timing relative to infusion was not recorded.

Infusion Reactions: Reviewer Conclusion and Recommendations

In the Genzyme studies, vital signs were not routinely measured during infusion or post-infusion. Thus, information that is essential for evaluating and mitigating risks of alemtuzumab during and after infusion is unavailable.

This reviewer recommends that alemtuzumab be infused in a setting capable of treating acutely life-threatening medical emergencies, including anaphylaxis and cardiac dysrhythmias. These capabilities include the ability to administer emergency cardiac medications, on-site professionals trained in Advanced Cardiovascular Life Support and management of anaphylaxis, and on-site cardiac monitoring. Periodic measurement of vital signs during and after infusion is recommended by this reviewer.

There is insufficient information to determine the optimal duration of observation post-infusion. Because If alemtuzumab is approved for marketing in the U. S., patients should be provided with detailed instructions on identifying and seeking care for infusion-related reactions. This reviewer also recommends a post-marketing study in which vital signs and adverse events during and after infusion are evaluated.

Because of the potential for infusion reactions, which can include anaphylaxis and cardiac dysrhythmias, alemtuzumab should be used with caution in patients with a history of cardiac disease. Additional information has been requested regarding instructions to investigators regarding infusion of alemtuzumab after a previous infusion reaction.

7.3.5.4. Infections

The incidence of infection AEs¹⁵⁹ in controlled trials (Pool E) for the alemtuzumab 12 mg/day group was 71.8%, compared with 54.2% in the IFNB-1a group. The most frequently reported infections ($\geq 5\%$ of subjects) for both the alemtuzumab 12 mg/day and

¹⁵⁹ Infections AEs refers to AEs coded to MedDRA SOC ‘Infections and infestations’

IFNB-1a groups were nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis, and influenza. Additionally, for the alemtuzumab 12 mg/day group, oral herpes (8.8%) bronchitis (7.1%) and rhinitis (4.6%) were on the list of frequent events (see table below).

Table 64. Incidence of Infections Reported in $\geq 5\%$ of Subjects in Any Treatment Group in All Active Controlled Studies (3-Year Follow Up, Pool E)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled (N=1188)
Preferred Term	n (%)	n (%)	n (%)
Any Event	269 (54.2)	660 (71.8)	866 (72.9)
Nasopharyngitis	84 (16.9)	216 (23.5)	289 (24.3)
Urinary tract infection	42 (8.5)	164 (17.8)	215 (18.1)
Upper respiratory tract infection	58 (11.7)	145 (15.8)	203 (17.1)
Sinusitis	36 (7.3)	101 (11.0)	133 (11.2)
Oral herpes	7 (1.4)	81 (8.8)	98 (8.2)
Influenza	27 (5.4)	78 (8.5)	97 (8.2)
Bronchitis	16 (3.2)	65 (7.1)	92 (7.7)
Rhinitis	11 (2.2)	42 (4.6)	52 (4.4)
Herpes zoster	4 (0.8)	39 (4.2)	57 (4.8)
Pharyngitis	7 (1.4)	36 (3.9)	53 (4.5)

- Source: Sponsor ISS Table 6-30; ISS p. 362

-Percentages are based on the number of treated subjects in the corresponding treatment group.

- A subject is counted only once within each PT.

Source: Sponsor ISS Table 6-30; ISS p. 362

In all active-controlled studies during the first 3 years of follow up, the incidence of any upper respiratory tract infection was 51.1% in the alemtuzumab 12 mg/day group compared with 37.9% in the IFNB-1a group. The overall incidence of any lower respiratory tract infection was 9.7% in the alemtuzumab 12 mg/day group compared with 4.2% in the IFNB-1a group.

Serious infections were reported for 27 (2.9%) subjects in the alemtuzumab 12 mg/day group and 6 (1.2%) subjects in the IFNB-1a group over 3 years of follow up.

In the ISS analysis, serious infections were reported for 46 (3.8%) subjects in the alemtuzumab 12 mg/day group and 66 (4.4%) subjects in the alemtuzumab pooled dose group. The incidence rates of serious infection were similar in Years 1 to 5 (Table 65).

Table 65. Serious Adverse Events. Infections and infestations SOC. All alemtuzumab-treated subjects. Integrated Summary of Safety analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	66 (4.4)	28 (1.9)	14 (1.1)	16 (1.4)	7 (1.3)	2 (1.2)	0 (0.0)	0 (0.0)	2 (1.7)
Herpes zoster	9 (0.6)	3 (0.2)	2 (0.2)	3 (0.3)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	7 (0.5)	1 (0.1)	4 (0.3)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Appendicitis	5 (0.3)	3 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	6 (0.4)	5 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis	4 (0.3)	1 (0.1)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subcutaneous abscess	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Tooth infection	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Appendicitis perforated	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cervicitis	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disseminated tuberculosis	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Febrile infection	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis viral	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infective myositis	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Labyrinthitis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningitis herpes	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oesophageal candidiasis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oral herpes	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pasteurella infection	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia legionella	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Postoperative wound infection	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Pyelonephritis	2 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Uterine infection	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Varicella	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Viral infection	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchitis	2 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis of male external genital organ	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diverticulitis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Furuncle	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Herpes ophthalmic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningitis listeria	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningitis viral	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary tuberculosis	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tracheobronchitis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

-Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.

- Years defined by calendar time.

Infection-related deaths

There were two alemtuzumab-treated subject deaths involving infection. CAMMS324 Subject 4008-5485 died of aspiration pneumonia. (*Reviewer comment: This adverse event of aspiration pneumonia occurred in the setting of advanced MS and is unlikely to be related to treatment.*) Originally treated with alemtuzumab 12 mg/day in CAMMS323, Subject 7105-3488 died in CAMMS03409 of sepsis a year and a half after the second annual cycle of alemtuzumab 12 mg/day. The subject was hospitalized for autoimmune pancytopenia, febrile neutropenia, and sepsis. A bone marrow biopsy revealed non-specific morphological findings corresponding to immune mediated bone marrow impairment. He died from sepsis 2 days after his hospitalization.

Herpetic infections

While active controlled studies CAMMS323 and CAMMS324 were ongoing, alemtuzumab-treated subjects began receiving prophylactic treatment with aciclovir, based on data monitoring committee (DMC) recommendation. Aciclovir 200 mg twice daily was administered beginning on the first day of any alemtuzumab treatment cycle and continuing for 28 days following the last infusion day of any cycle. CAMMS223 subjects did not receive aciclovir prophylaxis.

In all active-controlled studies (Pool E), the overall incidence of herpes viral infection was higher in the alemtuzumab 12 mg/day group (15.7%) than the IFNB-1a group (3.0%) (see table below).

Table 66. Incidence of treatment-emergent herpes viral infections by MedDRA High Level Term and Preferred Term. Controlled trials (Pool E).

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
High Level Term Preferred Term	n (%)	n (%)	n (%)	n (%)
Patients with Events	15 (3.0)	144 (15.7)	42 (15.6)	186 (15.7)
Herpes viral infections	15 (3.0)	144 (15.7)	42 (15.6)	186 (15.7)
Oral herpes	7 (1.4)	81 (8.8)	17 (6.3)	98 (8.2)
Herpes zoster	4 (0.8)	39 (4.2)	18 (6.7)	57 (4.8)
Herpes simplex	2 (0.4)	17 (1.8)	3 (1.1)	20 (1.7)
Genital herpes	1 (0.2)	12 (1.3)	4 (1.5)	16 (1.3)
Varicella	0 (0.0)	5 (0.5)	2 (0.7)	7 (0.6)
Herpes virus infection	1 (0.2)	2 (0.2)	1 (0.4)	3 (0.3)
Herpes dermatitis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Herpes simplex ophthalmic	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Herpes zoster multi-dermatomal	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Meningitis herpes	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Pneumonia herpes viral	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)

- Percentages are based on the number of treated subjects in the corresponding treatment group.

- A subject is counted only once within each HLT/PT.

- Source: Table 13.3.5.12.12. A link to this table is located on ISS p. 375.

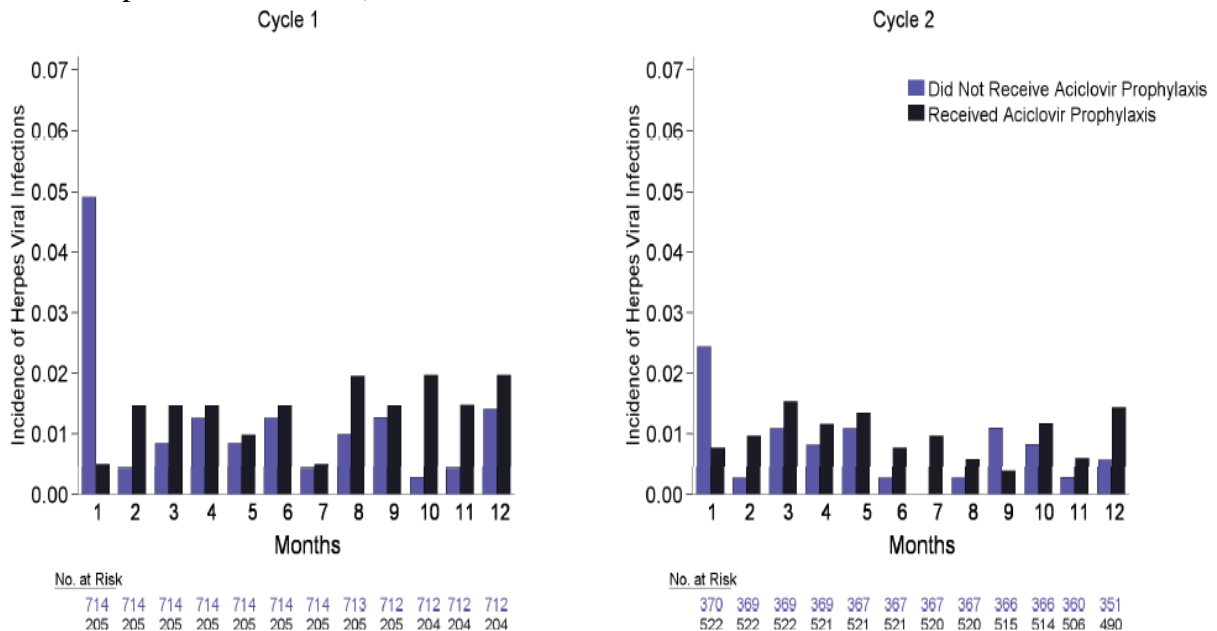
The incidence of herpes viral infections by month and prophylactic use of acyclovir during each cycle for all active-controlled studies (2-year follow up) is provided in Table 67 and in Figure 4 below. Acyclovir was administered during infusion and 28 days after infusion. During month 1, during which acyclovir prophylaxis was administered, there was a decreased rate of herpes virus infections in subjects who received prophylaxis with acyclovir, compared to subjects who received no acyclovir prophylaxis. However, there was an overall increased rate of herpes virus infections in subjects who received prophylaxis with acyclovir, compared to subjects who received no acyclovir prophylaxis.

Table 67. Incidence of treatment-emergent herpes viral infections by prophylactic use of acyclovir during each alemtuzumab treatment cycle. Alemtuzumab 12 mg/day group. Two year follow-up, controlled trials.

	Acyclovir Used	No Acyclovir
Cycle 1	43 events N=205 Incidence 21.0%	102 events N=714 Incidence 14.3%
Cycle 2	60 events N=522 Incidence 11.5%	33 events N=370 Incidence 8.9%

- Source: Table 1.3.5.12.11 in ISS Appendix 14-4-1. Link located on ISS p. 374.
- Percentages are based on the number of alemtuzumab subjects at risk in the corresponding time period.
- Acyclovir prophylaxis refers to acyclovir administration continuing for at least 29 days from the beginning of an alemtuzumab cycle.

Figure 4. Incidence of herpes viral infections by month and acyclovir prophylaxis during each cycle in the alemtuzumab 12 mg/day Group. All Active-Controlled Studies (2-Year Follow Up, Controlled trials)



- Incidence is based on the number of alemtuzumab subjects at risk in the corresponding time period.
- Acyclovir prophylaxis refers to acyclovir administration continuing for at least 29 days from the beginning of an alemtuzumab cycle.

- Subjects in the Phase 2 Study CAMMS223 did not receive acyclovir prophylaxis at all, and are therefore only counted in Figure 6-7 as “did not receive acyclovir prophylaxis”.
- No. = number
- Source: Figure 6-7. ISS p. 378.

Reviewer comment: The higher rate of herpetic infections in subjects who received acyclovir prophylaxis is concerning. This reviewer recommends the evaluation of different herpes prophylaxis regimens, including regimens with different durations of acyclovir treatment.

Human Papilloma Virus (HPV) Infections

HPV is the most frequent cause of cervical cancer which is the second most common cause of cancer in women worldwide (Ho, 1998, *N Engl J Med*). Immunosuppressed women have a several-fold higher rate of cervical cancer compared with the general population (Goedert, 1998, *Lancet*).

The Sponsor’s Analysis of HPV infections, including selected PTs within the HLTs of cervix disorders (NEC), papilloma viral infections, skin neoplasms benign, vaginal neoplasms benign, virus identification and serology, and vulvovaginal disorders NEC is shown in the table below.

Table 68. Incidence of Treatment-Emergent Papilloma Viral Infections by MedDRA High Level Term and Preferred Term. Controlled Trials.

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
High Level Term Preferred Term	n (%)	n (%)	n (%)	n (%)
Patients with Events	7 (1.4)	22 (2.4)	9 (3.3)	31 (2.6)
Cervix disorders NEC	5 (1.0)	10 (1.1)	5 (1.9)	15 (1.3)
Cervical dysplasia	5 (1.0)	10 (1.1)	5 (1.9)	15 (1.3)
Papilloma viral infections	0 (0.0)	5 (0.5)	0 (0.0)	5 (0.4)
Papilloma viral infection	0 (0.0)	3 (0.3)	0 (0.0)	3 (0.3)
Anogenital warts	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)
Skin neoplasms benign	2 (0.4)	8 (0.9)	2 (0.7)	10 (0.8)
Skin papilloma	2 (0.4)	8 (0.9)	2 (0.7)	10 (0.8)
Vaginal neoplasms benign	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Vulvovaginal human papilloma virus infection	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Virus identification and serology	0 (0.0)	5 (0.5)	3 (1.1)	8 (0.7)
Human papilloma virus test positive	0 (0.0)	5 (0.5)	3 (1.1)	8 (0.7)
Vulvovaginal disorders NEC	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Vulvar dysplasia	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)

Source: Table 13.3.5.12.2 in ISS Appendix 14-4-5.

In addition to the adverse events listed in Table 68, there were two cases of HPV-related malignancies in subjects who received alemtuzumab 24 mg/day :

- Subject 302-1224 (28 year old female from Russia): Cervical carcinoma grade 1
- Subject 1025-5450 (33 year old female from USA): Vulval cancer stage 0 and high grade cervical lesion (CIN II)

There were no cases of HPV-associated malignancy in subjects treated with IFNB-1a.

Reviewer comment: In its proposed prescribing information, Genzyme has recommended that HPV screening be performed annually in female subjects. This reviewer agrees with this recommendation.

Fungal Infections

The overall incidence of any fungal infection was higher in the alemtuzumab 12 mg/day group (12.1%) than in the IFNB-1a group (3.6%). The most commonly reported events (reported for $\geq 2\%$ of subjects) in the alemtuzumab 12 mg/day and IFNB-1a groups were vulvovaginal candidiasis and oral candidiasis.¹⁶⁰ A serious event of distal esophageal candidiasis was reported for Subject 1055-5753 in the 12 mg/day group. The event occurred following cycle 1 of alemtuzumab and responded to treatment with oral fluconazole (treatment duration 11 days) and oral nystatin (treatment duration 126 days).

Listeria meningitis

There was one serious adverse event of listeria meningitis in alemtuzumab-treated subjects (CAMMS223 Subject 201-1159, 36 year old female from the UK; Alemtuzumab 24 mg/day treatment group). No listeria infection was reported in subjects treated with IFN β -1a. The subject developed listeria meningitis after eating Brie cheese.

Reviewer comment: Given the potential for morbidity and mortality with listeria infections, this reviewer supports including information about listeriosis prevention¹⁶¹ in any future prescribing information for alemtuzumab for MS. Dietary advice has been discussed as a safety measure for alemtuzumab-treated subjects in published literature.¹⁶²

Tuberculosis (TB)

The overall incidence of any TB infection was 0.1% (1 subject) in the alemtuzumab 12 mg/day group (reported as disseminated TB) and 0.2% (1 subject) in the IFNB-1a group (recorded as renal TB). Three additional events were identified in the alemtuzumab 24 mg/day group (recorded as latent TB, pulmonary tuberculoma, and pulmonary TB), with an incidence of 0.3% (4 subjects) in the alemtuzumab pooled dose group (see table below).

¹⁶⁰ Table 13.3.5.12.1 ISS Appendix 14-4-5, p. 4192.

¹⁶¹ Centers for Disease Control (CDC)-Prevention-Listeriosis. Accessed on August 9, 2013 at: <http://www.cdc.gov/listeria/prevention.html>

¹⁶² Coles AJ. Semin Neurol 2013;33:66–73. P. 69.

Table 69. Sponsor Table 13.3.5.12.9 Incidence of Treatment-Emergent Tuberculosis by MedDRA High Level Term and Preferred Term. Controlled Trials (Pool E).

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
High Level Term Preferred Term	n (%)	n (%)	n (%)	n (%)
Patients with Events	1 (0.2)	1 (0.1)	3 (1.1)	4 (0.3)
Tuberculous infections	1 (0.2)	1 (0.1)	3 (1.1)	4 (0.3)
Disseminated tuberculosis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Latent tuberculosis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Pulmonary tuberculoma	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Pulmonary tuberculosis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Renal tuberculosis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Sponsor Table 13.3.5.12.9, p.4202 of ISS appendix 14-4-5. Link on ISS p. 385.

All 4 events of tuberculous infection in alemtuzumab-treated subjects occurred in the first 2 years of follow up.

There were 2 serious events of active TB. Both serious events occurred in endemic regions:¹⁶³

- Subject 6103-3193 (38 F Ukraine; alemtuzumab 12 mg/day) developed Grade 1 serious pulmonary TB after receiving Cycle 2 of alemtuzumab 12 mg/day. The subject was hospitalized, treated, and was discharged after 3 months in the hospital. The subject received no additional alemtuzumab treatment.
- Subject 6001-5557 (26 F Russia; alemtuzumab 24 mg/day) developed Grade 2 serious pulmonary TB. The subject was treated and the TB resolved. The subject received no alemtuzumab treatment.

There were 2 events of latent TB in the alemtuzumab 24 mg/day group:

- Subject 304-1200 (Russia) was reported to have a Grade 2 pulmonary tuberculoma of the left lung after receiving 2 cycles of alemtuzumab treatment before the event occurred. No active TB was diagnosed.
- Subject 1152-5387 (USA) was noted to have a reactive tuberculin skin test during the first day of Cycle 1, 2 days after the TB test was placed. This was reported as Grade 2 latent TB. No active TB was diagnosed.

Two U.S. subjects (Subject 1183-5961 and Subject 1072-5063) entered CAMMS324 with a history of TB, completed 2 full cycles of alemtuzumab treatment 12 mg/day and 24 mg/day respectively, and had no reactivation of the TB infection after alemtuzumab treatment. There were no events of extra pulmonary disseminated TB across treatment groups.¹⁶⁴

¹⁶³ World Health Organization (WHO) Tuberculosis country profiles. Accessed at <http://www.who.int/tb/country/data/profiles/en/> on August 9, 2013.

¹⁶⁴ ISS p. 386.

Reviewer comment: This reviewer recommends screening for tuberculosis prior to initiation of treatment, according to Centers for Disease Control (CDC) recommendations for high risk persons.¹⁶⁵ This reviewer does not recommend treatment with alemtuzumab for patients who test positive for tuberculosis (latent infection or active disease).

Viral hepatitis

Individuals who have been exposed to hepatitis B virus (HBV) are at risk for reactivation of infection when their immune response is suppressed (*Gupta, 1990, J Clin Gastroenterol*). No data are available on the association of alemtuzumab with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) reactivation, as subjects with evidence of active or chronic infections were excluded from the clinical trials.

Of all alemtuzumab-treated subjects (N=1485), there was one adverse event with the Verbatim Term 'Chronic infection of hepatitis B' in CAMMS03409 Subject 207-1239 (39 M Croatia; CAMMS223 treatment assignment alemtuzumab 24 mg/day) after one treatment cycle in CAMMS223 and one cycle in CAMMS03409.

Reviewer comment: In its proposed prescribing information, Genzyme has recommended: "Screening subjects at high risk of HBV and/or HCV infection before initiation of LEMTRADA should be considered and caution should be exercised in prescribing LEMTRADA to subjects identified as carriers of HBV and/or HCV as these subjects may be at risk of irreversible liver damage relative to a potential virus reactivation as a consequence of their pre-existing status." This reviewer thinks that use of alemtuzumab should be contraindicated in subjects identified as carriers of HBV and/or HCV, until there is some evidence related to the safety of treating these subjects with alemtuzumab, possibly through a Sponsor study.

Cytomegalovirus (CMV) Infections

One subject reported a CMV infection in the alemtuzumab 24 mg/day group (Subject 4301-5316). The event was a mononucleosis-like condition.¹⁶⁶

Serious and fatal events of CMV infection occurred in subjects who received alemtuzumab (proprietary name Campath) for B-cell chronic lymphocytic leukemia (B-CLL). The prescribing information for Campath advised that prescribers administer famciclovir 250 mg BID or equivalent as herpetic prophylaxis for a minimum of 2 months after completion of Campath or until the CD4+ count is ~ 200 cells/μL,

¹⁶⁵ CDC Guidelines for TB Testing and Diagnosis. Accessed on September 28, 2013 at: <http://www.cdc.gov/tb/topic/testing/default.htm>

¹⁶⁶ ISS p. 376.

whichever occurs later.¹⁶⁷ This prophylaxis for herpetic infections also acts as prophylaxis for CMV.

Reviewer comment: End-organ disease caused by CMV occurs among persons with advanced immunosuppression, typically those with CD4+ counts <50 cells/μL (Kaplan, 2009, MMWR). CMV infection was not observed as a frequent adverse event. (The population of B-CLL subjects is generally younger than the population of MS subjects. Also, the dose of alemtuzumab used for B-CLL is higher than the dose used for MS.) Continued monitoring of CMV cases with alemtuzumab treatment for MS will be necessary.

7.3.5.5 Pneumonitis

Cases of pneumonitis and potential pneumonitis have been reported with alemtuzumab use:

- 9 cases of potential drug-induced pneumonitis during and after controlled trials of alemtuzumab for MS
- 2 cases of hypersensitivity pneumonitis from a published post-study report of alemtuzumab in MS¹⁶⁸ with details obtained from an unpublished report.
- 1 published case of fatal pneumonitis after treatment with alemtuzumab for CLL¹⁶⁹
- 1 published case of diffuse alveolar hemorrhage after alemtuzumab for immunosuppression post-transplant¹⁷⁰

The Division of Neurology Products (DNP) requested a consultation from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). Excerpts from the consultation by Tracy Kruzick, M.D., M.P.H. are provided below.

Case Narratives

1) Genzyme Studies of Alemtuzumab in MS

- **Case 1: 1173-5718 CAMMS324 (pulmonary fibrosis and pneumonitis)**
A 50 year old white female with multiple sclerosis, asthma, bronchitis, COPD, and former 17 pack year smoker (quit 2 years prior to event), on multiple medications was treated for two cycles of alemtuzumab therapy with the first dose on June 1, 2009 and the last dose on June 14, 2010 (8 total days treated, 96 mg total exposure). Soon after

¹⁶⁷ Campath (alemtuzumab) for B-CLL U.S. Prescribing Information. Accessed on August 9, 2013 at: <http://www.campath.com/pdfs/2009-08-Campath%20US%20PI.pdf>

¹⁶⁸ Cossburn, et al. Autoimmune disease after alemtuzumab treatment for multiple sclerosis in a multicenter cohort. *Neurology* 2011;77:573–579

¹⁶⁹ Creelan, B and Ferber, A. A fatal case of almetuzumab-associated interstitial pneumonitis. *American Journal of Therapeutics* 15, 82-84 (2008).

¹⁷⁰ Sachdeva, A and Matuschak, G. Diffuse alveolar hemorrhage following alemtuzumab. *Chest*, 133: 6, June 2008.

the last dose (August 5, 2010), subject began to complain of yellowish productive cough, but radiographic data did not suggest inflammation. Pulmonary symptoms of cough/wheeze sporadically recurred until March 7, 2012, when a chest CT showed septal thickening and ground glass opacities (GGO) in the RUL, RLL, and LLL. Bronchoscopy on a subsequent hospitalization was unrevealing. On October 17, 2012, biopsy via VATS demonstrated a chronic fibrosing process with dense scarring, some foci consistent with honeycombing, as well as active fibroplastic proliferation. There was also some epithelial metaplasia and organizing pneumonia centrally in the biopsy. Pigmented macrophages (characteristic of smokers) were in many of these fibrotic foci. There were features that were consistent with usual interstitial pneumonia (UIP) and/or smoking related lung disease.

Reviewer's comment: Although the causative nature of smoking cannot be rule out definitively, usual interstitial pneumonitis on biopsy could be secondary to alemtuzumab. Although the biopsy report makes reference to idiopathic pulmonary fibrosis, it is important to note that IPF is a clinical diagnosis. UIP on histopathology can be caused by a number of drugs and disease processes. When no causative agent or underlying disease is found, the UIP is deemed "idiopathic", and a diagnosis of IPF is made. In this case, however, the diagnosis of IPF cannot be made in the face of alemtuzumab treatment. The fibrotic changes may be burned out inflammation from a previous inflammatory drug-induced pneumonitis.

- **Case 2: 3208-5867 CAMMS03409 (hospitalization for pleurisy pain syndrome related to pneumonitis)**

A 30 year old male in Paraguay with multiple sclerosis and no other reported past medical history, received alemtuzumab for 2 cycles (June 30, 2009 to July 4, 2009; June 29, 2010 to July 1, 2010). On (b) (6) the subject was hospitalized for "pleurisy pain syndrome secondary to pneumonitis" as reported by the investigator. A chest CT showed bilateral nodules and pleural effusion. A right upper lobe cavitory lesion (measuring 18 mm) was also noted. ANCA antibodies and microbiologic work-up, including induced sputum for tuberculosis, was negative.

Reviewer's comment: While infection (lung abscess) is also a possible diagnosis, one cannot definitely rule out the role of alemtuzumab in this case. Also, the bilateral nodules may represent drug-induced lung disease as well.

- **Case 3: Subject 3006-5807 CAMMS324 (pneumonitis)**

The subject is a 46 year old M with unknown treatment dates. Past medical history was significant for pancreatic pseudocyst, splenectomy, thrombocytopenic purpura, and neutropenia. The subject was diagnosed with pneumonitis. No radiographic or histopathologic evidence was obtained.

- **Case 4: 7103-3500 CAMMS323 (pneumonitis)**

The subject is a 36 year old M with MS, arterial hypotension, and 20 pack-year smoking history. The subject received his last dose of alemtuzumab on December 26, 2008 (11 total doses, 132 mg). On (b) (6) subject was diagnosed with pneumonitis and hospitalized. CT scan showed multiple nodular changes bilaterally. Bronchoscopy was performed with normal findings. The lung biopsy on September 4, 2009 revealed desquamative pneumonitis.

- **Case 5: 2015-5586 CAMMS324 (pneumonitis)**

The subject is a 36 year old F with MS, asthma, and multiple drug allergies. The subject received 3 doses of drug: (b) (6). Near the end of infusion on day 2, subject complained of chest discomfort that initially resolved with oxygen. Subject presented to the ER later that day with abdominal pain. Chest CT revealed right-sided pleural effusion with bilateral (predominantly right sided) ground glass opacities. She also experienced a rash on her arms, legs, and torso. She went on to receive drug again on May 3, 2010 during which she experienced similar symptoms. Alemtuzumab therapy was discontinued. No pulmonology consultation or biopsy was obtained.

Reviewer's comment: Given the subject's history of multiple drug allergies and skin rash following infusion, pneumonitis is a plausible diagnosis.

- **Case 6: 1046-5011 CAMMS324 (pneumonitis and grade 4 hepatitis)**

The subject is a 38M with MS, with a past medical history including seasonal allergies, who received the last dose of alemtuzumab on February 27, 2009. On January 19, 2010, subject experienced acute hepatitis and pneumonitis, as reported by the investigator. The subject received steroids and symptoms of hepatitis and pneumonitis reportedly resolved. On February 10, 2010, that subject experienced cough, sputum production, and chest tightness. Pulmonology was consulted; chest CT showed bronchiectatic changes with mucoid impaction. Subject was treated with corticosteroids with resolution.

Reviewer's comment: Considering the most common drug-induced lung diseases, this case may represent either pneumonitis or bronchiolitis obliterans.

- **Case 7: 2002-5276 CAMMS324 (hemoptysis associated with infusion)**

The subject is a 31 year old M with MS, treated with alemtuzumab for 2 cycles, last dose February 24, 2010. One day post-dose, subject awoke with rattling in his chest and chest pain, and coughed up an estimated 20 mL of blood. He was hospitalized after 3 episodes of hemoptysis with intermittent shortness of breath. A chest CT revealed patchy, ground glass bilateral fluffy opacities, predominantly in the lower lobes, and right middle lobe atelectasis.

Reviewer's comment: This may represent a case of diffuse alveolar hemorrhage, although without bronchoscopic diagnosis, it is difficult to know definitively.

- **Case 8: 1034-5515 CAMMS324 (pulmonary granuloma)**

The subject is a 32 year old F with MS who received alemtuzumab from March 30, 2009 to April 3, 2009 and then from April 14, 2010 to April 16, 2010. The subject has a family history of breast, uterine, and stomach cancer. The subject had a history of breast cancer on June 24, 2011, with surgical intervention. The subject also received chemotherapy starting on September 8, 2011. On September 2, 2011, the subject had a CT of the chest which showed an 8mm nodule in the medial basal segment of the right lower lobe. Per the oncologist, the lesion was too small for a definitive diagnosis.

Reviewer's comment: These imaging findings are unlikely to represent a drug-induced inflammatory process in the lung.

- **Case 9: 201-1290 CAMMS223 (allergic alveolitis)**

The subject is a 34 year old F with MS, hypothyroidism, who received alemtuzumab from April 19-23, 2004 and April 18-20, 2005. On November 7, 2008, she experienced progressively worsening dry cough and wheeze. The subject was diagnosed with extrinsic allergic alveolitis. Subject had kept parrots at home for 7 years.

Reviewer's comment: This may be hypersensitivity pneumonitis due to the parrots. However, alemtuzumab cannot be excluded with certainty.

2) *Post-study case reports*

- **Case 10: /Cossburn et al. *Neurology*, 2011/Cossburn et al. unpublished report (hypersensitivity pneumonitis following alemtuzumab for treatment of MS)**

Reviewer's comment: This appears to be hypersensitivity pneumonitis due to the parrots

- **Case 11: Cossburn et al. *Neurology*, 2011 and Cossburn et al. unpublished report (hypersensitivity pneumonitis following alemtuzumab for treatment of MS)**

3) *Published case reports from other treatment indications*

- **Case 12: Creelan et al., *American Journal of Therapeutics*, 2008 (fatal case of interstitial pneumonitis following alemtuzumab for CLL)³**

A 36 year old F with CLL initially treated with two chemotherapy regimens without success. One month prior to presentation she underwent alemtuzumab salvage therapy in preparation for potential stem cell transplantation. Specifically, she received 3, 10, and 30mg of alemtuzumab over sequential days, followed by 30 mg three times weekly for 3 weeks. Her medical history also included essential hypertension. She was a nonsmoker and did not have any occupational exposure to chemicals. She reported a history of an allergic rash to doxycycline. Pulmonary function testing revealed a 30% reduction in her adjusted diffusion capacity (DLCO), and 32% reduction in forced vital capacity (FVC) compared with her baseline from 1 year previously. Bronchoscopy with bronchoalveolar lavage (BAL) was negative for malignant cells and microbial organisms, and transbronchial biopsy revealed interstitial inflammation without evidence of infection. Despite broad-spectrum antibiotic coverage, her respiratory status continued to decline. Wedge biopsy via VATS revealed prominent non-specific interstitial pneumonitis (NSIP) and inflammation, consistent with chemotherapy-induced pneumonitis.

To treat her toxic lung injury, the subject began receiving intravenous methylprednisone, 80 mg/day, with minimal improvement in symptoms. A nasotracheal viral culture showed parainfluenza virus type 3, and although there was no evidence of parainfluenza

viral changes on biopsy, she was treated with intravenous immunoglobulin (IVIG, 400 mg/kg), without improvement. Her respiratory distress gradually worsened despite continued empiric antibiotic coverage, and she was intubated 2 months after admission. Shortly thereafter, a decision was made by the family to withdraw care, and her family declined requests for autopsy.

- **Case 13: Sachdeva et al., *Chest*, 2008 (diffuse alveolar hemorrhage after alemtuzumab for immunosuppression post-renal transplant)⁴**

The subject was a 26M, non-smoker, with Alport syndrome, on hemodialysis consequent to a previously rejected living donor renal allograft. His medical history was significant for the occurrence of DAH two years previously, which had been thought to be secondary to sirolimus therapy in the setting of chronic allograft nephropathy and uremia. Alemtuzumab was administered intraoperatively for immunosuppression when subject underwent repeat renal transplantation. On post-operative day 2, the subject experienced mild hemoptysis and dyspnea, along with new onset anemia and thrombocytopenia (PLT count: 54K).

Pulmonary consultation was sought after his symptoms failed to improve, and he continued to have worsening hemoptysis and a requirement for oxygen therapy. Arterial blood gas levels obtained with a 0.4 fraction of inspired oxygen showed a Pao₂ of 74 mm Hg, with a Pao₂/fraction of inspired oxygen ratio of 185. A physical examination of the chest revealed bilateral late, fine, inspiratory crackles in the mid-to-lower lung fields. The results of serial chest radiographs showed evolving bilaterally diffuse alveolar opacities, which were confirmed by a chest CT scan. BAL fluid, which demonstrated characteristic increasingly bloody return in the sequential aliquots, was obtained from the RML. He required intubation and mechanical ventilation for 5 days. The subject was eventually discharged on post-operative day 28.

Dr. Kruzick provided a response to these DNP Questions:

Which cases do you consider consistent with pneumonitis or possible pneumonitis? Are there cases which likely represent a disease process other than pneumonitis? (If additional information should be requested to assess these cases, please inform DNP.) Can you rule out the role of alemtuzumab in these cases?

DPARP response:

Of the 13 cases presented, all but one case may be consistent with pneumonitis or possible pneumonitis due to alemtuzumab, if the investigator's report is accepted at face value. Specifically, Case 8, reported as pulmonary granuloma, makes no mention of an inflammatory process in the lung, making pneumonitis improbable.

In most cases, it is difficult to exclude all other causes; many of the cases have confounding medications, exposures (parrots) and co-morbid conditions (including former tobacco use) making it difficult to definitively implicate alemtuzumab as a causative agent. Further difficulty in implicating alemtuzumab stems from the delayed reaction in a number of the cases. However, given the complex immunologic mechanism being postulated for lung toxicity, the timing issue is not as clear. As drug-induced pneumonitis is a diagnosis of exclusion, it is difficult to definitively rule out the causal role of alemtuzumab in any of these cases. It is important to note that although we are considering all the case reports as

“pneumonitis”, this is a general term, and each of the subjects may be experiencing different clinical syndromes of lung toxicity (see Table 70).

Table 70. DPARP Consult Table 1. Clinical Syndromes Associated with Drug-induced Lung Disease (DILD)

Clinical syndromes	Potential causes
Alveolar hypoventilation	Narcotics, aminoglycosides, corticosteroids
Acute bronchospasm	NSAIDs, β -blockers, mitomycin C
Bronchiolitis obliterans	Cyclophosphamide, methotrexate, CCNU, penicillamine
Noncardiogenic pulmonary edema	Narcotics, salicylates, tocolytics, hydrochlorothiazide, protamine
Hypersensitivity	β -Lactam antibiotics, sulfa-containing drugs, nitrofurantoin, methotrexate, bleomycin, phenytoin
Organizing pneumonia	Amiodarone, bleomycin, carbamazepine
Chronic alveolitis	Bleomycin, amiodarone, cyclophosphamide
Drug-induced systemic lupus erythematosus	Hydralazine, procainamide, quinidine, isoniazid, penicillamine
Alveolar hemorrhage	Oral anticoagulants, amiodarone, sirolimus, crack cocaine

Bhadra et. al. The Journal of Respiratory Diseases, January 2009.

Neurology reviewer comment: Eight of 1496 (0.5%) alemtuzumab-treated subjects from Genzyme studies in MS had potential drug-induced pneumonitis.

Because symptoms of pneumonitis are nonspecific, it is possible that not all cases have been identified. There were increased frequencies of symptoms associated with pneumonitis (cough and dyspnea) in Genzyme Controlled Trials of Alemtuzumab for MS (see tables below).

Table 71. Number of Subjects with Adverse Events of Dyspnea in Genzyme Controlled Trials of Alemtuzumab for MS

	Alemtuzumab Pooled Dose (N=1188)	IFN β -1a (N=496)
All Dyspnea AEs	134 (11.3%)	9 (1.8%)
Infusion-Associated Dyspnea AEs	99 (8.3%)	NA
Non-Infusion-Associated Dyspnea AEs	35(2.9%)	9 (1.8%)

Adverse Events of Dyspnea included Preferred Terms ‘Dyspnoea,’ ‘Dyspnoea exertional,’ and ‘Nocturnal dyspnoea.’

Each subject was counted once per table cell.

NA = Not applicable.

Table 72. Number of Subjects with Adverse Events coded to the Preferred Term ‘Cough’ in Genzyme Controlled Trials of Alemtuzumab for MS

	Alemtuzumab Pooled Dose (N=1188)	IFN β -1a (N=496)
All AEs	120 (10.1%)	20 (4.0%)
Infusion-Associated AEs	25 (2.1%)	NA

Non-Infusion-Associated AEs	95 (8.0%)	20 (4.0%)
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NA = Not applicable

Each subject was counted once per table cell.

Neurology reviewer comment: Hypersensitivity pneumonitis is described in multiple cases after alemtuzumab use; this condition can progress to fibrosis and end-stage lung disease.¹⁷¹ I agree with the assessments made by DPARP. I recommend discussing pneumonitis in the Warnings and Precautions section of prescribing information, as well as a Medication Guide, if alemtuzumab is approved.

7.3.5.6. Suicidal Behavior and Ideation

Adverse events of suicidal behavior and ideation were analyzed in controlled trials (Pool E) and all alemtuzumab studies (see table below).

¹⁷¹ Matar LD. Hypersensitivity pneumonitis. *American Journal of Roentgenology* 174, no. 4 (2000): 1061-1066.

Table 73. Suicidal Behavior or ideation events. All alemtuzumab subjects (Pool C)

Subject Study	Age Sex Country	Controlled Trial Treatment	SAE	Preferred Term (Verbatim Term)	Description/Comment	Thyroid Disorder during Suic AE
Alemtuzumab-treated subjects: Controlled trials						
1007-3479 CAMMS323	20 F USA	Alemtuzumab 12 mg/day	Y	Suicide attempt	PMH of anxiety and depression. Three months after first dose of alemtuzumab, she had suicidal thoughts, and 5 months after first dose she attempted suicide by cutting her wrists. At the time of the attempt, she was taking Cymbalta, which is labeled for suicidal behavior and ideation. No thyroid AE.	N
404-1321 CAMMS223	38 F Poland	Alemtuzumab 24 mg/day	Y	Suicide attempt	Two years and 3 months after first alemtuzumab, the patient was hospitalized due to a life-threatening grade 4 suicide attempt. The patient had no previous history of suicide attempts and had no other psychiatric history. The patient attempted suicide by injection of benzodiazepine and phenothiazine. No thyroid AE or lab abnormality at the time of suicide attempt. Developed hyperthyroidism 3 months later.	N
1037-5001 CAMMS324	23 F USA	Alemtuzumab 24 mg/day	Y	Suicide attempt	PMH of depression and previous suicide attempt in 2008. Three years and 9 months after first alemtuzumab and 2 years and 9 months after last alemtuzumab, she ingested 20 acetaminophen (500 mg) tablets. Was taking Effexor at the time of the event. No thyroid AE or lab abnormality at the time of suicide attempt.	N
1020-5895 CAMMS324	42 M USA	Alemtuzumab 12 mg/day	Y	Suicidal ideation	No previous psychiatric history. Eleven months after first dose of alemtuzumab, had intense suicidal thoughts while having personal problems and was hospitalized. No thyroid AE.	N
1007-3027 CAMMS323	41 F USA	Alemtuzumab 12 mg/day	N	Suicidal ideation	Past medical history included anxiety, depression, and suicidal ideation. She had suicidal thoughts 10 months after first cycle of alemtuzumab. No thyroid AE or thyroid lab abnormality in Genzyme ISS database.	N
1079-5212 CAMMS324	39 F USA	Alemtuzumab 24 mg/day	Y	Suicidal ideation	Past medical history included anxiety. Major depression with psychosis. No thyroid AE or lab abnormality at the time of suicidal ideation.	N
Alemtuzumab-treated subjects: Extension trial CAMMS03409						
1005-3016	28 M	IFNβ-1a	Y	Suicidal	No previous psychiatric history. Eight months after last	N

Subject Study	Age Sex Country	Controlled Trial Treatment	SAE	Preferred Term (Verbatim Term)	Description/Comment	Thyroid Disorder during Suic AE
CAMMS03409	USA			ideation	alemtuzumab, subject had suicidal ideation after arguing with his father. He was hospitalized, and treated with venlafaxine. TSH normal, FT3 and FT4 not measured at time of suicidal ideation.	
1182-5701 CAMMS03409	35 M USA	IFNβ-1a	Y	Suicidal ideation	History of depression prior to taking alemtuzumab. Six months after his first cycle of alemtuzumab, he had worsening depression and suicidal ideation. No thyroid AE or lab abnormality in CAMMS studies.	N
1101-3515 CAMMS03409	33 F Canada	IFNβ-1a	Y	Suicidal ideation Overdose	<i>Reviewer comment: This SAE assigned to Preferred Term 'Overdose' needs to be categorized as a suicide attempt.</i> Past medical history included postpartum depression and attention deficit/hyperactivity disorder. First cycle and second cycles of alemtuzumab were in January 2009 and January 2010, respectively. She had a hyperthyroid crisis with manic episode, agitation, and irritation in July 2010. She was hospitalized for worsening depression and suicidal ideation (b) (6). She left against medical advice (b) (6). On 9/26/2011 she had an overdose and took 50 quetiapine (25 mg) pills. She was treated with activated charcoal and counseling.	Y
1039-3028 CAMMS03409	24 F USA	Alemtuzumab 12 mg/day	N	Suicidal Ideation	She was taking escitalopram upon study entry, although no psychiatric history was documented. Event occurred 2 years and 5 months after the last dose of alemtuzumab. No details of the event were provided. Abnormal thyroid labs at time of AE.	Y
2009-5598* CAMMS03409	38 F Australia	Alemtuzumab 24 mg/day	Y	Suicide attempt	On (b) (6) the patient experienced hyperthyroidism associated with hypomanic episode. The discharge summary mentions the patient had attempted suicide the week prior to this hospital admission (she took an impulse overdose of her son's methylphenidate). No other details regarding the suicide attempt were reported. Follow up information was received on 20 Nov 2012. The Investigator indicated that the patient's suicide attempt was likely misreported by a junior physician and after speaking with the patient's Psychiatrist it was felt	Y

Subject Study	Age Sex Country	Controlled Trial Treatment	SAE	Preferred Term (Verbatim Term)	Description/Comment	Thyroid Disorder during Suic AE
					the patient had more likely overdosed to 'get high' while hypomanic. The patient was not hospitalized for the suicide attempt and did not receive any treatment. The event of suicide attempt has been deleted. <i>Reviewer comment: This adverse event of suicide attempt has been deleted from the adverse event database by the sponsor. Because the treating physician considered the event a suicide attempt, this reviewer thinks the case should be considered as a possible case of suicide attempt.</i> Information obtained from CAMP 1002402. Follow-up #3 entered to IND 010717 on 27 Nov 2012.	
IFN β -1a-treated subjects						
2011-3698 CAMMS323	20 M Australia	IFN β -1a	Y	Mood altered	<i>Reviewer comment: This event should be categorized as suicidal ideation.</i> Past history of depression. Nine months after starting IFN β -1a, he expressed suicidal thoughts. No thyroid AE or lab abnormality at the time of suicidal ideation. Diagnosed with bipolar disorder and treatment was discontinued.	N
1163-5312 CAMMS324	41 F USA	IFN β -1a	N	Suicidal ideation	History of depression. Seven months after starting IFN β -1a, an AE of suicidal ideation was reported.	N
1039-5098 CAMMS324	39 F USA	IFN β -1a	N	Suicidal Ideation	No psychiatric history documented. AE of suicidal ideation 15 months after starting IFN β -1a.	N

In controlled trials (Pool E) events included:

- Alemtuzumab
 - 3 of 1188 (0.3%) suicide attempts
 - 3 of 1188 (0.3%) suicidal ideation
 - 6 of 1188 (0.6%) total
- IFN β -1a
 - 3 of 496 (0.6%) suicidal ideation

There were 2 cases of suicide attempt and 3 cases of suicidal ideation in CAMMS03409. In all alemtuzumab studies (Pool C), 11 of 1496 (0.7%) experienced an event of suicidal attempt or ideation. Three of the 11 events were associated with thyroid abnormalities. Seven had a history of psychiatric illness prior to receiving alemtuzumab. (Of the 3 cases seen with IFN β -1a, 2 had a history of prior psychiatric illness.)

Reviewer comment: The first Warning in the Rebif (IFN β -1a) prescribing information is Depression and Suicide.¹⁷² Alemtuzumab had an equal incidence of suicide attempt or suicidal ideation as IFN β -1a, but the severity of events was worse with alemtuzumab (3 events were suicide attempts). This reviewer recommends description of suicidal behavior and ideation with alemtuzumab in the Warnings and Precautions section of prescribing information, if alemtuzumab is approved.

7.3.5.7. Hepatobiliary disorders

In controlled trials (Pool E), elevated levels of alanine transaminase (ALT), aspartate aminotransferase (AST), and specified concomitant increases in AST and/or ALT and total bilirubin were less frequent in alemtuzumab subjects, compared to IFN β -1a subjects (Sponsor Table 7-8). Increases in total bilirubin were more frequent in alemtuzumab subjects, compared to IFN β -1a subjects.

¹⁷² The text of the Depression and Suicide Warning from the Rebif prescribing information, accessed on September 15, 2013 at http://www.emdserono.com/cmge.mdserono_us/en/images/rebif_tcm115_19765.pdf

“Rebif® (interferon beta-1a) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased incidence in patients receiving interferon compounds, including Rebif®. In addition, there have been postmarketing reports of suicide in patients treated with Rebif®. Subjects should be advised to report immediately any symptoms of depression and/or suicidal ideation to the prescribing physician. If a patient develops depression, cessation of treatment with Rebif® should be considered.”

Table 74. Sponsor ISS Table 7-8: Liver Function Test Abnormalities in All Active-Controlled Studies (3-Year Follow Up; Pool E)

Test Category	SC IFNB-1a (N=496) Overall n (%)	Alemtuzumab 12 mg/day (N=919) Overall n (%)	Alemtuzumab Pooled (N=1188) Overall n (%)
ALT			
≥3 x ULN	57/492 (11.6)	16/919 (1.7)	25/1188 (2.1)
≥5 x ULN	27/492 (5.5)	7/919 (0.8)	10/1188 (0.8)
≥10 x ULN	9/492 (1.8)	1/919 (0.1)	1/1188 (0.1)
≥20 x ULN	2/492 (0.4)	1/919 (0.1)	1/1188 (0.1)
AST			
≥3 x ULN	33/492 (6.7)	7/919 (0.8)	10/1188 (0.8)
≥5 x ULN	16/492 (3.3)	2/919 (0.2)	3/1188 (0.3)
≥10 x ULN	4/492 (0.8)	0/919 (0.0)	0/1188 (0.0)
≥20 x ULN	1/492 (0.2)	0/919 (0.0)	0/1188 (0.0)
Total Bilirubin			
≥1.5 x ULN	10/492 (2.0)	33/919 (3.6)	41/1188 (3.5)
≥2 x ULN	4/492 (0.8)	14/919 (1.5)	16/1188 (1.3)
Concomitant Increases			
ALT and/or AST ≥3 x ULN and Total Bilirubin ≥1.5 x ULN	6/492 (1.2)	1/919 (0.1)	1/1188 (0.1)
ALT and/or AST ≥3 x ULN and Total Bilirubin ≥3 x ULN	3/492 (0.6)	1/919 (0.1)	1/1188 (0.1)
ALT and/or AST >3 x ULN and Total Bilirubin ≥2 x ULN and Alkaline Phosphatase <2 x ULN	3/492 (0.6)	1/919 (0.1)	1/1188 (0.1)

Note: Percentages are based on the number of treated patients at risk and with liver function data in the corresponding year and treatment group.

SC = subcutaneous; IFNB-1a = interferon beta-1a; ULN = upper limits of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase;

Source: ISS Table 7-8, p. 476.

Reviewer comment: The prescribing information for Rebif (IFNβ-1a) contains a Warning regarding hepatic injury.¹⁷³ Thus, less frequent hepatotoxicity compared to the IFNβ-1a group does not necessarily indicate a lack of hepatotoxic potential for alemtuzumab.

¹⁷³ The Rebif Warning regarding hepatic injury contains the following text:

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in patients taking Rebif®. Symptoms of liver dysfunction began from one to six months following the initiation of Rebif®. If jaundice or other symptoms of liver dysfunction appear, treatment with Rebif® should be discontinued immediately due to the potential for rapid progression to liver failure.

One¹⁷⁴ of 1485 subjects in Pool C had laboratory results that met criteria for Hy's law:¹⁷⁵

- **1021-5382:** The subject was a 26 year old white male from the USA. At the time of the event, he had received 2 cycles (96 mg) of alemtuzumab. The last dose of study drug prior to the laboratory abnormalities was February 17, 2010. He reported intermittent abdominal pain, nausea and vomiting and an episode of dark urine.¹⁷⁶ Ten days after these symptoms, on March 2, 2011, during the scheduled 24 month visit, the subject was noted with high (CTCAE Grade 3) levels of alanine aminotransferase (464 IU/L; reference range: 0-48 IU/L), aspartate aminotransferase (235 IU/L; reference range: 0-42 IU/L), bilirubin (92 µMOL/L; reference range: 0-22 µMOL/L), and alkaline phosphatase (142 IU/L; reference range 20-125 IU/L). The investigator judged this event as not related to the study drug and no action was taken with the study drug. The event was reported as resolved on 26 Apr 2011 and all the hepatic enzyme levels returned to normal (see table below). The subject continued in the study.

Table 75. Hepatic laboratory results for Subject 1021-5382

Date	ALT			AST			Bilirubin		
	Lab Value IU/L	CTC Grade	Reference Range IU/L	Lab Value IU/L	CTC Grade	Reference Range IU/L	Lab Value µMOL/L	CTC Grade	Reference Range µMOL/L
02 Mar 2011	464	3	0-48	235	3	0-42	92	3	0-22
04 Mar 2011	419	3	0-48	127	2	0-42	30	1	0-22
08 Mar 2011	302	3	0-48	103	1	0-42	16	0	0-22
29 Mar 2011	102	1	6-43	32	0	11-36	7	0	3-21
26 Apr 2011	26	0	6-43	16	0	11-36	9	0	3-21

ALT - Alanine Aminotransferase, AST - Aspartate Aminotransferase

Source: Subject Narrative p. 2073 ISS Appendix 14-3.

Asymptomatic elevation of hepatic transaminases (particularly SGPT) is common with interferon therapy (see ADVERSE REACTIONS). Rebif® should be initiated with caution in patients with active liver disease, alcohol abuse, increased serum SGPT (> 2.5 times ULN), or a history of significant liver disease. Also, the potential risk of Rebif® used in combination with known hepatotoxic products should be considered prior to Rebif® administration, or when adding new agents to the regimen of patients already on Rebif®. Reduction of Rebif® dose should be considered if SGPT rises above 5 times the upper limit of normal. The dose may be gradually re-escalated when enzyme levels have normalized. (See PRECAUTIONS: Laboratory Tests and Drug Interactions; and DOSAGE AND ADMINISTRATION)

¹⁷⁴ A second case (Subject 2003-5372) was flagged as meeting Hy's Law criteria (ISS Appendix 14-3 p. 73), but it did not meet the criterion of total bilirubin $\geq 2 \times$ ULN. This case is described in the section covering grade 4 transaminase elevations.

¹⁷⁵ A Hy's Law case is defined as a subject with any elevated aminotransferase of $>3 \times$ ULN, alkaline phosphatase $<2 \times$ ULN, and associated with an increase in bilirubin $\geq 2 \times$ ULN. FDA Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Accessed on 9/12/2013 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

¹⁷⁶ Genzyme response to FDA information request. Submitted to sBLA103948 on September 20, 2013 (p.8)

Table 76. Alkaline phosphatase laboratory results for Subject 1021-5382

Date	Alkaline Phosphatase (IU/L)	Reference range (IU/L)
2010-11-17	72	20-125
2011-03-02	142	20-125
2011-03-04	176	20-125
2011-03-08	123	20-125
2011-03-29	74	31-129
2011-04-26	73	31-129

Source: Dataset ADLBCH

Prior to the abnormal laboratory results in March 2011, all reported ALT, AST, and bilirubin measurements were normal, except for a single increase in ALT to 84 IU/L (2x ULN) on February 10, 2010.¹⁷⁷

Reviewer comment: At the time of the elevated hepatic laboratory results, no concomitant medications were listed in the subject profile. Prior to March 2, 2011, the most recent laboratory measurements submitted were dated November 17, 2010. Thus, it is unclear when the hepatic abnormalities started. Because his symptoms occurred 10 days before laboratory measurements, the peak laboratory values were likely not measured. Information regarding evaluation of the cause of the hepatic laboratory abnormalities was not provided in the ISS submission. A viral hepatitis panel was not performed to rule out an infectious etiology. The cause of the hepatic laboratory abnormalities is unclear.

Subjects 3105-5066 and 2003-5372 had treatment-emergent Grade 4 increases in ALT ($\geq 20 \times$ ULN):

- **3105-5066:** Subject was a 34 year old female from Mexico, who received 2 cycles of 12 mg/day of alemtuzumab in CAMMS324 in July 2008 and August 2009. Laboratory results are listed in the tables below.
A grade 2 non-serious drug-induced hepatitis adverse event was reported in association with the above mentioned liver function abnormalities, with a start date of Oct.12, 2009 and reported as resolved on July 1, 2010. The patient received treatment with ursodeoxycholic acid (ursodiol) from Nov. 3 2009 to March 20, 2010. However, abnormalities in liver enzymes have not been associated with ursodiol therapy.¹⁷⁸ Ursodiol may have been taken for gallstone dissolution, and gallstones may have caused the liver enzyme abnormalities.

¹⁷⁷ Subject profile p. 27. Submitted to sBLA 103948 on November 27, 2012. (Module 5.3.5.3)

¹⁷⁸ Ursodiol prescribing information. Accessed September 29, 2013 at:
<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a061bb07-a85d-4b08-877f-ce02156f0de7>

Table 77. Subject 3015-5066. ALT and AST Values (IU/L) at Select Time Points.

Lab Date	Alanine Aminotransferase (ALT)			Aspartate Aminotransferase (AST)		
	Lab Value (IU/L)	CTC Grade (IU/L)	Reference Range (IU/L)	Lab Value (IU/L)	CTC Grade (IU/L)	Reference Range (IU/L)
13 Jul 2009	9	0	0 – 48	15	0	0 – 42
26 Oct 2009	333	3	0 – 48	189	2	0 – 42
13 Jan 2010	16	0	0 – 48	19	0	0 – 42
30 Nov 2011	10	0	6 – 34	13	0	9 – 34
27 Dec 2011	732	4	6 – 34	452	3	9 – 34
22 Feb 2012	18	0	6 – 34	23	0	9 – 34
23 May 2012	18	0	6 – 34	19	0	9 – 34

Source: Sponsor IR Response submitted Sept. 20, 2013 (p. 182)

Table 78. Subject 3015-5066. Bilirubin Values (μMOL/L) at Select Time Points

Lab Date	Bilirubin	
	Lab Value (μMOL/L)	Reference Range (μMOL/L)
13 Jul 2009	8	0 – 22
26 Oct 2009	30	0 – 22
13 Jan 2010	16	0 – 22
30 Nov 2011	7	3 – 21
27 Dec 2011	22	3 – 21

Source: Sponsor IR Response submitted Sept. 20, 2013 (p. 182)

Reviewer comment: The cause of the hepatic laboratory abnormalities for Subjects 3105-5066 is not clear.

- **2003-5372:** The subject was a 36 year old female who received 2 cycles of alemtuzumab 12 mg/day in CAMMS324 in March 2009 and March 2010. She had a history of cholelithiasis. At the time of her transaminase elevations, she had an episode of gallstone pancreatitis and underwent cholecystectomy.

Reviewer comment: The hepatic enzyme abnormalities in Subject 2003-5372 were not related to alemtuzumab.

Serious Adverse Events

Five of 1188 (0.4%) alemtuzumab-treated subjects in controlled trials had SAEs coded to the Hepatobiliary disorders SOC, compared to 8 of 496 (1.6%) IFN β -1a subjects (Table 79). Of all alemtuzumab-treated subjects (Pool C), 7 of 1485 (0.5%) had an SAE in this SOC (Table 80).

Table 79. Serious Adverse Events. Hepatobiliary disorders SOC. Controlled trials (Pool E). Integrated Summary of Safety analysis.

System Organ Class Preferred Term	SC IFNB-1a (N=496) n (%)	Alemtuzumab 12 mg/day N=(919) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Hepatobiliary disorders	8 (1.6)	4 (0.4)	5 (0.4)
Cholecystitis	3 (0.6)	2 (0.2)	2 (0.2)
Cholecystitis acute	0 (0.0)	2 (0.2)	2 (0.2)
Biliary colic	1 (0.2)	0 (0.0)	0 (0.0)
Hepatic failure	1 (0.2)	0 (0.0)	0 (0.0)
Hepatitis acute	1 (0.2)	0 (0.0)	1 (0.1)
Hepatitis toxic	1 (0.2)	0 (0.0)	0 (0.0)
Liver disorder	1 (0.2)	0 (0.0)	0 (0.0)

Source: ISS Table 6-10

Table 80. Serious Adverse Events. Hepatobiliary disorders SOC. All alemtuzumab-treated subjects. Integrated Summary of Safety analysis.

	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of Subjects at Risk	1485	1485	1298	1147	521	168	142	118	120
Total	7 (0.5)	4 (0.3)	1 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Cholecystitis	3 (0.2)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis acute	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Biliary dyskinesia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Sphincter of Oddi dysfunction	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis acute	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Appendix 14-4-3 Table 3.3.3.2. Submitted to sBLA103948 on 27 November 2012. Cut-off date December 31, 2011.

Note: -Percentages are based on the number of treated subjects in the corresponding time period and treatment group.

- A subject is counted only once within each SOC/PT.

- Years defined by calendar time.

- Subject 1046-5011 had an SAE of grade 4 acute hepatitis.¹⁷⁹ She was a 36 year old white female from the USA (CAMMS324; 24 mg/day; cumulative dose 156 mg). The last dose of study drug prior to the event was 27 Feb 2009. On Day 687 (b) (6), the subject was hospitalized with acute hepatitis, acute pneumonitis, and acute bronchitis. She had symptoms of chills, nausea, and vomiting. No abdominal pain, jaundice, or dark urine were reported. Laboratory results from her hospitalization are summarized in the table below.

Table 81. Acute Hepatitis SAE. Subject 1046-5011. Laboratory results.

Date	AST	AST reference range	ALT	ALT reference range	Alkaline phosphatase	Alkaline phosphatase reference range	Total bilirubin	Total bilirubin reference range
(b) (6)	6	5-35	37	7-56	59	20-125	0.3	-
	5282	5-35	2967	7-56	565	20-125	1.5	-
	3100	5-35	2558	7-56	462	20-125	-	-
	12	5-35	11	7-56	-	20-125	-	-

Note: Units for laboratory tests and the reference range for total bilirubin were not provided.

Source: Medwatch report

Prior to this event, all ISS-reported hepatic enzyme measurements were normal, except for an isolated increased ALT of 76 IU/L on 8/26/2008. The subject had positive ANA along with thyroid microglobulin antibody. Acute viral hepatitis panel was non-reactive. The subject reported no alcohol intake prior to the event.

She was treated with steroids and improved. The subject was discharged from the hospital (b) (6). According to the subject's neurologist, a clear etiology for the acute hepatitis was not determined.

In controlled trials, SAEs of cholecystitis occurred with comparable incidence in the alemtuzumab and IFN- β -1a groups. However, 2 of 5 cholecystitis cases in alemtuzumab subjects (Subjects 1097-5494 and 1097-6073) were cases of acute acalculous cholecystitis:

- Subject 1097-5494 (CAMMS324 Alemtuzumab 12 mg/day) was a 28 year old female from the USA, who was diagnosed with acalculous cholecystitis on May 8, 2009 (7 weeks after the first alemtuzumab cycle). CD4 count on April 20, 2009 was <20 cells/ μ L. A hepatobiliary scan with cholecystokinin (CCK) revealed acalculous cholecystitis and poor contractility of the gallbladder (gallbladder ejection fraction was 2%; LLN was 35%). She underwent laparoscopic cholecystectomy and recovered. Intraoperative cholangiogram confirmed absence of duct stones. No bile or blood cultures were done.
- Subject 1097-6073 (CAMMS324 Alemtuzumab 12 mg/day) was a 31 year old female from the USA, who was diagnosed with acalculous cholecystitis on September 30, 2009 (7 weeks after the first alemtuzumab cycle). CD4 count on September 8, 2009 was 50 cells/ μ L. A nuclear medicine scan showed a non-

¹⁷⁹ A copy of the Medwatch report for this case (Manufacturer report # CAMP-1000630; ISS Appendix 14-3-2-3 p. 698-705) is located in Appendix

functioning gallbladder (0% ejection fraction). She underwent laparoscopic cholecystectomy and recovered. The pathology report showed no stones in the specimen. No bile or blood cultures were done.

Acalculous cystitis usually accounts for approximately 10 percent of all cases of acute cholecystitis and is associated with high morbidity and mortality rates.¹⁸⁰

Biliary stasis is hypothesized to be central to the pathogenesis of acute acalculous cholecystitis.¹⁸¹ Biliary stasis causes increased gallbladder intraluminal pressure, which decreases gallbladder perfusion pressure and facilitates invasion of pathogenic organisms¹⁸² into ischemic tissue.

Immune compromise also contributes to the pathogenesis of acute acalculous cholecystitis, which usually occurs in intensive care unit subjects with multisystem failure, burn victims, and subjects with end-stage HIV disease with low CD4 counts.¹⁸³ The SAEs of acalculous cholecystitis occurred in the setting of absolute CD4 counts of <50 cells/ μ L.

Another case of biliary dysfunction included an SAE of Biliary dyskinesia (104-1127): and Sphincter of Oddi dysfunction (1027-3096):

- Subject 104-1127 (Originally in CAMMS223 alemtuzumab 12 mg/day group; CAMMS03409 Subject 1002-1127) was a 46 year old female from the USA. Six years and 7 months after first alemtuzumab and 1 year 5 months after last alemtuzumab, she underwent a scheduled cholecystectomy due to inactive gallbladder. CD4 count 6 months prior to surgery was 249 cells/ μ L.
- Subject 1027-3096 (CAMMS03409; originally in CAMMS323 12 mg/day group) was a 40 year old female from the USA diagnosed with sphincter of Oddi dysfunction (stenosis), upper gastrointestinal hemorrhage, and anemia in October 2011 (3 years and 5 months after first alemtuzumab and 2 years 5 months after last alemtuzumab). The ERCP performed with placement of stent in common bile duct showed ampullary edema however no ulcers, blood, stones or other significant pathology was identified.

Reviewer comment: This SAE occurred 6 months after the subject underwent cholecystectomy for cholecystitis. Sphincter of Oddi dysfunction can occur after cholecystectomy. Thus, it is unclear whether this case is related to alemtuzumab.

¹⁸⁰ Ryu JK, Ryu KH, Kim KH. Clinical features of acute acalculous cholecystitis. J Clin Gastroenterol 2003; 36:166.

¹⁸¹ Barie PS. Acute Acalculous Cholecystitis. Current Gastroenterology Reports 2003, 5:302–309

¹⁸² Brun reports that in HIV subjects, “likely organisms implicated are cytomegalovirus, Cryptosporidium, microsporidia, Salmonella enteritis, Pneumocystis carinii, Campylobacter, Isospora belli, and Candida albicans. However, in as much as 53% of subjects no etiologic agent is identified after extensive microbiologic evaluation.” (Brun, et al. Practical gastroenterology 34, no. 9 (2010): 24-32.)

¹⁸³ Brun, Alexander, and C. S. Pitchumoni. Biliary diseases in HIV. Practical gastroenterology 34, no. 9 (2010): 24-32.

Hepatobiliary disorders: Reviewer conclusions recommendations

There were concerning cases of hepatic enzyme abnormalities in alemtuzumab-treated subjects, including a reported case meeting criteria for Hy's law, an SAE of acute hepatitis, and 1 case with ALT increases $>20 \times$ ULN, and a case of acute hepatitis. If alemtuzumab is approved, this reviewer recommends that these cases be described in the Warnings and Precautions section of prescribing information.

There were SAEs of biliary dysfunction (cases of acalculous cholecystitis, biliary dyskinesia, and sphincter of Oddi dysfunction) in alemtuzumab-treated subjects. In addition, elevations in bilirubin were more frequent in alemtuzumab subjects, compared to IFN β -1a subjects. If alemtuzumab is approved, this reviewer recommends that biliary dysfunction and acute acalculous cholecystitis be described in the Warnings and Precautions section of the prescribing information.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The incidence of AEs occurring in $\geq 5\%$ of subjects in any treatment group in all controlled trials (Pool E) is presented in Sponsor Table 6-5. The 3 most frequently affected MedDRA SOCs in the alemtuzumab 12 mg/day treatment group were 'Skin and subcutaneous tissue disorders' (77.9%), 'Nervous system disorders' (73.4%), and 'Infections and infestations' (71.6%). The most frequent events reported in the alemtuzumab 12 mg/day group in the 'Skin and subcutaneous tissue disorders' SOC were rash (48.4%), urticaria (17.1%) and pruritus (16.5%). The most frequent events reported in the alemtuzumab 12 mg/day group in the 'Nervous system disorders' SOC were headache (53.0%) and MS relapse (27.2%). The incidence of MS relapse was higher in the IFNB-1a group (43.5%). The most frequent events reported in the alemtuzumab 12 mg/day group in the 'Infections and infestations' SOC were nasopharyngitis (23.5%), UTI (17.8%), and upper RTI (15.8%).

Table 82. Sponsor Table 6-5: Incidence of Adverse Events Reported in $\geq 5\%$ of Subjects in Any Treatment Group in Controlled Trials (Pool E)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled^a (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)
Any Event	470 (94.8)	897 (97.6)	1163 (97.9)
Blood and lymphatic system disorders	71 (14.3)	135 (14.7)	178 (15.0)
Lymphopenia	13 (2.6)	51 (5.5)	65 (5.5)
Cardiac disorders	24 (4.8)	153 (16.6)	197 (16.6)
Tachycardia	10 (2.0)	75 (8.2)	97 (8.2)
Ear and labyrinth disorders	35 (7.1)	87 (9.5)	120 (10.1)
Vertigo	18 (3.6)	40 (4.4)	54 (4.5)
Endocrine disorders	13 (2.6)	135 (14.7)	176 (14.8)
Hypothyroidism	8 (1.6)	46 (5.0)	59 (5.0)
Hyperthyroidism	4 (0.8)	38 (4.1)	55 (4.6)
Eye disorders	75 (15.1)	157 (17.1)	215 (18.1)
Vision blurred	17 (3.4)	44 (4.8)	68 (5.7)
Gastrointestinal disorders	166 (33.5)	454 (49.4)	633 (53.3)
Nausea	51 (10.3)	200 (21.8)	293 (24.7)
Diarrhoea	29 (5.8)	108 (11.8)	158 (13.3)
Vomiting	21 (4.2)	97 (10.6)	141 (11.9)
Dyspepsia	25 (5.0)	80 (8.7)	112 (9.4)
Abdominal pain	18 (3.6)	49 (5.3)	70 (5.9)
Constipation	31 (6.3)	43 (4.7)	61 (5.1)
Abdominal pain upper	10 (2.0)	40 (4.4)	54 (4.5)
General disorders and administration site conditions	318 (64.1)	602 (65.5)	803 (67.6)
Pyrexia	47 (9.5)	278 (30.3)	371 (31.2)
Fatigue	78 (15.7)	192 (20.9)	269 (22.6)
Chills	20 (4.0)	90 (9.8)	132 (11.1)
Chest discomfort	10 (2.0)	70 (7.6)	114 (9.6)
Pain	18 (3.6)	70 (7.6)	98 (8.2)
Influenza like illness	136 (27.4)	65 (7.1)	91 (7.7)
Asthenia	19 (3.8)	54 (5.9)	74 (6.2)
Oedema peripheral	13 (2.6)	49 (5.3)	63 (5.3)
Injection site pain	31 (6.3)	3 (0.3)	3 (0.3)
Injection site reaction	39 (7.9)	1 (0.1)	1 (0.1)
Injection site erythema	119 (24.0)	0 (0.0)	0 (0.0)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled ^a (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)
Infections and infestations	267 (53.8)	658 (71.6)	863 (72.6)
Nasopharyngitis	84 (16.9)	216 (23.5)	289 (24.3)
Urinary tract infection	42 (8.5)	164 (17.8)	215 (18.1)
Upper respiratory tract infection	58 (11.7)	145 (15.8)	203 (17.1)
Sinusitis	36 (7.3)	101 (11.0)	133 (11.2)
Oral herpes	7 (1.4)	81 (8.8)	98 (8.2)
Influenza	27 (5.4)	78 (8.5)	97 (8.2)
Bronchitis	16 (3.2)	65 (7.1)	92 (7.7)
Herpes zoster	4 (0.8)	39 (4.2)	57 (4.8)
Pharyngitis	7 (1.4)	36 (3.9)	53 (4.5)
Injury, poisoning and procedural complications	98 (19.8)	240 (26.1)	337 (28.4)
Contusion	29 (5.8)	92 (10.0)	137 (11.5)
Fall	15 (3.0)	32 (3.5)	46 (3.9)
Investigations	133 (26.8)	264 (28.7)	358 (30.1)
CD4 lymphocytes decreased	6 (1.2)	49 (5.3)	58 (4.9)
CD8 lymphocytes decreased	9 (1.8)	49 (5.3)	56 (4.7)
Lymphocyte count decreased	8 (1.6)	36 (3.9)	50 (4.2)
Body temperature increased	2 (0.4)	23 (2.5)	37 (3.1)
Alanine aminotransferase increased	31 (6.3)	5 (0.5)	8 (0.7)
Musculoskeletal and connective tissue disorders	197 (39.7)	434 (47.2)	587 (49.4)
Pain in extremity	49 (9.9)	123 (13.4)	178 (15.0)
Arthralgia	45 (9.1)	116 (12.6)	152 (12.8)
Back pain	41 (8.3)	114 (12.4)	163 (13.7)
Muscular weakness	54 (10.9)	71 (7.7)	101 (8.5)
Muscle spasms	31 (6.3)	64 (7.0)	94 (7.9)
Myalgia	28 (5.6)	62 (6.7)	98 (8.2)
Musculoskeletal pain	27 (5.4)	37 (4.0)	49 (4.1)
Nervous system disorders	344 (69.4)	675 (73.4)	898 (75.6)
Headache	114 (23.0)	487 (53.0)	671 (56.5)
Multiple sclerosis relapse	216 (43.5)	250 (27.2)	320 (26.9)
Paraesthesia	51 (10.3)	118 (12.8)	153 (12.9)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled ^a (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)
Dizziness	30 (6.0)	92 (10.0)	144 (12.1)
Hypoaesthesia	58 (11.7)	91 (9.9)	130 (10.9)
Dysgeusia	49 (9.9)	86 (9.4)	119 (10.0)
Migraine	25 (5.0)	35 (3.8)	46 (3.9)
Psychiatric disorders	154 (31.0)	288 (31.3)	404 (34.0)
Insomnia	75 (15.1)	160 (17.4)	217 (18.3)
Depression	57 (11.5)	72 (7.8)	106 (8.9)
Anxiety	34 (6.9)	65 (7.1)	98 (8.2)
Respiratory, thoracic and mediastinal disorders	94 (19.0)	356 (38.7)	492 (41.4)
Oropharyngeal pain	24 (4.8)	104 (11.3)	139 (11.7)
Dyspnoea	8 (1.6)	86 (9.4)	129 (10.9)
Cough	20 (4.0)	84 (9.1)	117 (9.8)
Skin and subcutaneous tissue disorders	130 (26.2)	716 (77.9)	968 (81.5)
Rash	27 (5.4)	445 (48.4)	621 (52.3)
Urticaria	9 (1.8)	157 (17.1)	237 (19.9)
Pruritus	12 (2.4)	152 (16.5)	215 (18.1)
Rash generalised	4 (0.8)	73 (7.9)	95 (8.0)
Erythema	14 (2.8)	52 (5.7)	72 (6.1)
Alopecia	10 (2.0)	30 (3.3)	46 (3.9)
Rash pruritic	0 (0.0)	23 (2.5)	37 (3.1)
Vascular disorders	53 (10.7)	192 (20.9)	244 (20.5)
Flushing	23 (4.6)	88 (9.6)	111 (9.3)

Source: ISS p. 182-184

- MedDRA version 13.1 was used for coding.
- Percentages are based on the number of treated subjects in the corresponding treatment group.
- A subject is counted only once within each SOC/PT.
- SOC's are presented alphabetically, and within SOC the PT's are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

^aNote that some events occurred at an incidence of $\geq 5\%$ in the alemtuzumab 24 mg/day group only.

SC = subcutaneous; IFNB-1a = interferon beta-1a; SOC = system organ class; PT = preferred term

Common Adverse Events excluding Infusion-Associated Reactions

Infusion-associated reactions (IARs)¹⁸⁴ occurred in 91.6% of alemtuzumab-treated subjects; IARs are discussed in Section 7.3.5.3. This section discusses adverse events excluding IARs.

Sponsor Table 6-7 displays the incidence of AEs, excluding IARs, reported in $\geq 5\%$ of subjects in any treatment group in controlled trials (Pool E). When IARs were excluded from the analysis of most common AEs, the most common events ($>10\%$ of subjects) in the alemtuzumab 12 mg/day treatment group were MS relapse (27.0%), headache (23.5%), nasopharyngitis (23.3%), UTI (17.7%), RTI (15.8%), fatigue (14.9%), rash (13.5%), sinusitis (11.0%), pain in extremity (10.8%), paraesthesia (10.7%), and arthralgia (10.6%).

¹⁸⁴ IARs refer to AEs that occur between the start and 24 hours after the stop of any alemtuzumab infusion. Infusion-associated reactions were not determined for IFNB-1a-treated subjects since the product was administered subcutaneously.

Table 83. Sponsor Table 6-7: Incidence of Adverse Events Excluding IARs Reported in $\geq 5\%$ of Subjects in Any Treatment Group. Controlled Trials (Pool E)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled ^a (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)
Any Event	469 (94.6)	842 (91.6)	1097 (92.3)
Blood and lymphatic system disorders			
Lymphopenia	10 (2.0)	51 (5.5)	65 (5.5)
Gastrointestinal disorders			
Diarrhoea	25 (5.0)	84 (9.1)	128 (10.8)
Nausea	37 (7.5)	81 (8.8)	121 (10.2)
Vomiting	19 (3.8)	61 (6.6)	81 (6.8)
Abdominal pain ^a	17 (3.4)	36 (3.9)	53 (4.5)
Constipation	28 (5.6)	34 (3.7)	49 (4.1)
General disorders and administration site conditions			
Fatigue	69 (13.9)	137 (14.9)	188 (15.8)
Pyrexia	42 (8.5)	69 (7.5)	103 (8.7)
Oedema peripheral	12 (2.4)	34 (3.7)	48 (4.0)
Influenza like illness	105 (21.2)	33 (3.6)	48 (4.0)
Pain	14 (2.8)	27 (2.9)	41 (3.5)
Injection site erythema	83 (16.7)	0 (0.0)	0 (0.0)
Injection site reaction	35 (7.1)	0 (0.0)	0 (0.0)
Infections and infestations			
Nasopharyngitis	84 (16.9)	214 (23.3)	286 (24.1)
Urinary tract infection	42 (8.5)	163 (17.7)	213 (17.9)
Upper respiratory tract infection	57 (11.5)	145 (15.8)	203 (17.1)
Sinusitis	35 (7.1)	101 (11.0)	133 (11.2)
Influenza	27 (5.4)	77 (8.4)	96 (8.1)
Oral herpes	7 (1.4)	75 (8.2)	90 (7.6)
Bronchitis	16 (3.2)	63 (6.9)	90 (7.6)
Injury, poisoning and procedural complications			
Contusion	28 (5.6)	90 (9.8)	132 (11.1)
Fall	15 (3.0)	31 (3.4)	45 (3.8)
Investigations			
CD4 lymphocytes decreased	6 (1.2)	49 (5.3)	58 (4.9)

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab Pooled ^a (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)
CD8 lymphocytes decreased	8 (1.6)	48 (5.2)	55 (4.6)
Lymphocyte count decreased	7 (1.4)	35 (3.8)	49 (4.1)
Musculoskeletal and connective tissue disorders			
Pain in extremity	43 (8.7)	99 (10.8)	145 (12.2)
Arthralgia	40 (8.1)	97 (10.6)	130 (10.9)
Back pain	37 (7.5)	78 (8.5)	112 (9.4)
Muscle spasms	29 (5.8)	53 (5.8)	79 (6.6)
Muscular weakness	52 (10.5)	48 (5.2)	73 (6.1)
Myalgia	23 (4.6)	27 (2.9)	43 (3.6)
Nervous system disorders			
Multiple sclerosis relapse	213 (42.9)	248 (27.0)	316 (26.6)
Headache	82 (16.5)	216 (23.5)	299 (25.2)
Paraesthesia	47 (9.5)	98 (10.7)	128 (10.8)
Hypoaesthesia	53 (10.7)	83 (9.0)	117 (9.8)
Dysgeusia	5 (1.0)	50 (5.4)	67 (5.6)
Dizziness	25 (5.0)	45 (4.9)	81 (6.8)
Psychiatric disorders			
Insomnia	45 (9.1)	76 (8.3)	107 (9.0)
Depression	56 (11.3)	72 (7.8)	103 (8.7)
Anxiety	32 (6.5)	49 (5.3)	73 (6.1)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	24 (4.8)	80 (8.7)	107 (9.0)
Cough	18 (3.6)	68 (7.4)	92 (7.7)
Skin and subcutaneous tissue disorders			
Rash	24 (4.8)	124 (13.5)	172 (14.5)
Pruritus	11 (2.2)	45 (4.9)	59 (5.0)
Alopecia	10 (2.0)	26 (2.8)	40 (3.4)

Source: ISS p. 101-193

-MedDRA version 13.1 was used for coding.

-Percentages are based on the number of treated subjects in the corresponding treatment group.

-A subject is counted only once within each SOC/PT.

-SOCs are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

^a Some events occurred at an incidence of $\geq 5\%$ higher in the alemtuzumab 24 mg/day group only.

SC = subcutaneous; IFNB-1a = interferon beta-1a; SOC = system organ class; PT = preferred term

Menstrual disorders

In controlled trials, menstrual disorders were reported more frequently in the alemtuzumab group (112 subjects, 14.3% of females) than in the IFN β -1a group (24 subjects, 7.4% of females). No subjects were discontinued from treatment because of a menstrual disorder AE. The most frequent events ($\geq 2\%$ in either treatment group) were menorrhagia (5.6 % in the alemtuzumab 12 mg/day group versus 1.5% in the IFN β -1a group), menstruation irregular (3.3% versus 1.5%), an dysmenorrhea (2.4% versus 1.5%). SAEs occurred in 8 of 783 (1.0%) female alemtuzumab subjects, compared to 3 of 323 (0.9%) female IFN β -1a subjects.

Skin disorders: Rash and urticaria

In controlled trials (Pool E), rash was reported as an AE in 621 of 1188 (52.3%) of alemtuzumab subjects, compared to 27 of 496 (5.4%) IFN β -1a subjects; 172 of 1188 (14.5%) alemtuzumab subjects had an AE of rash that was not an infusion reaction.

In controlled trials (Pool E), urticaria was reported as an AE in 237 of 1188 (19.9%) alemtuzumab subjects, compared to 9 of 496 (1.8%) IFN β -1a subjects; 44 of 1188 (3.7%) alemtuzumab subjects had an AE of urticaria that was not an infusion reaction.

7.4.2 Laboratory Findings

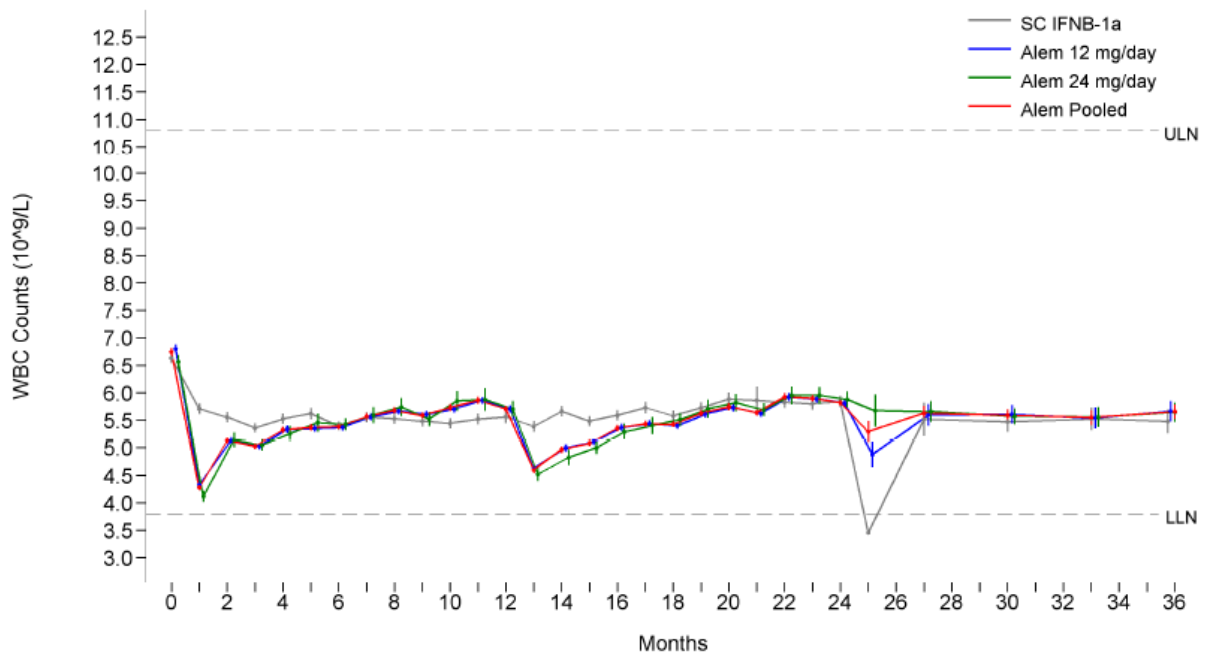
7.4.2.1. Hematologic laboratory evaluations

Leukocytes

Alemtuzumab binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages. There is thought to be little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells.¹⁸⁵ Alemtuzumab acts through antibody-dependent cellular cytotoxicity and complement-mediated lysis following cell surface binding to B and T lymphocytes. Figure shows changes in leukocyte count in controlled trials (Pool E).

¹⁸⁵ Proposed LEMTRADA prescribing information. Submitted to sBLA103948 on November 27, 2012.

Figure 5. Sponsor Figure 13.5.8.7. Mean (\pm s.e.) WBC Counts over Time. Pool E



Source: ISS Appendix 14-4-5, p. 5211.

Note: Normal Range (from Phase III central lab) in $10^9/L$: LLN=3.8, ULN=10.8

Because alemtuzumab has differing effects on leukocyte subsets, changes leukocyte subsets are evaluated in this section.

Lymphocytes

A rapid depletion of circulating T and B lymphocytes, caused by the anti-CD52 mechanism of alemtuzumab action, results in nearly all subjects in MS clinical trials experiencing lymphopenia following treatment. In analyses of worst post-baseline platelet count by CTC grade, alemtuzumab-treated subjects had lower frequencies of grade 1 and grade 2 changes in lymphocytes, compared to IFNB-1a subjects, because the majority of alemtuzumab subjects had grade 3 or grade 4 abnormalities.

Table 84. Sponsor Table 13.5.4.2 Lymphocytes. CTC Grade for Hematologic Laboratory Parameters for Baseline and Worst Post-Baseline Values. Pool E

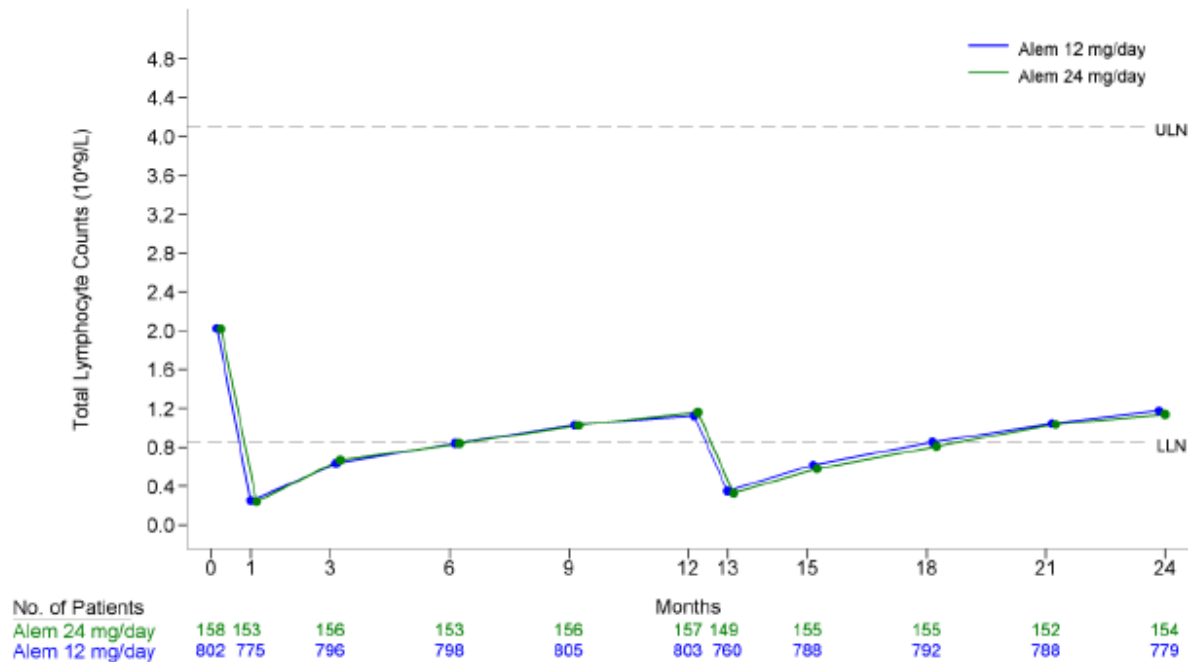
Parameter: Lymphocytes($10^9/L$)		SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
Time Period	CTC Grade	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Baseline	0	486/494 (98.4)	910/918 (99.1)	263/269 (97.8)	1173/1187 (98.8)
	1	4/494 (0.8)	4/918 (0.4)	5/269 (1.9)	9/1187 (0.8)
	2	4/494 (0.8)	3/918 (0.3)	0/269 (0.0)	3/1187 (0.3)
	3	0/494 (0.0)	0/918 (0.0)	0/269 (0.0)	0/1187 (0.0)
	4	0/494 (0.0)	1/918 (0.1)	1/269 (0.4)	2/1187 (0.2)
Overall - Post Baseline	0	289/492 (58.7)	1/919 (0.1)	0/269 (0.0)	1/1188 (0.1)
	1	41/492 (8.3)	0/919 (0.0)	0/269 (0.0)	0/1188 (0.0)
	2	134/492 (27.2)	30/919 (3.3)	8/269 (3.0)	38/1188 (3.2)
	3	27/492 (5.5)	409/919 (44.5)	80/269 (29.7)	489/1188 (41.2)
	4	1/492 (0.2)	479/919 (52.1)	181/269 (67.3)	660/1188 (55.6)

Source: ISS Appendix 14-4-5, p. 5250.

Lymphocytes CTC Grade Ranges in $10^9/L$ Units: 0: $\geq LLN$, 1: $< LLN - 0.8$, 2: $< 0.8 - 0.5$, 3: $< 0.5 - 0.2$, 4: < 0.2 .

Sponsor Figure 4-1 displays the mean total lymphocyte counts over 2 years in Phase 3 studies (Pool B).

Figure 6. Sponsor Figure 4-1: Mean (+/- SE) Total Lymphocyte Counts over Time. Pool B

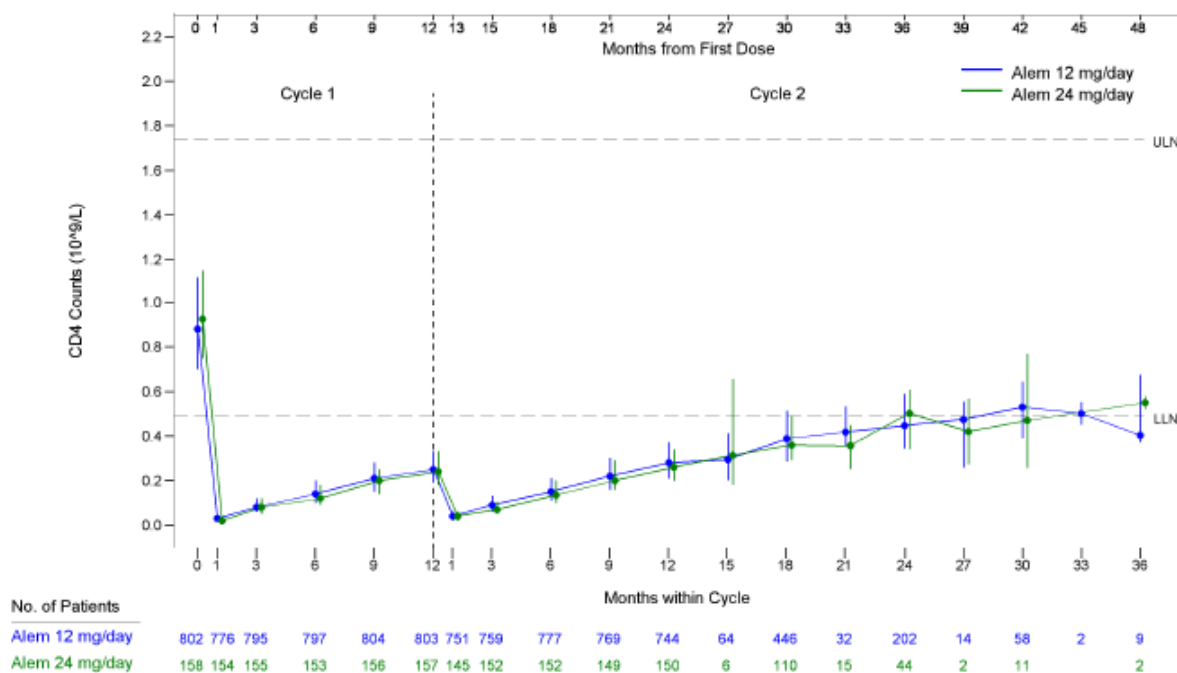


Source: ISS Appendix 14-7, p. 10.

Depletion of CD4+ lymphocytes was especially profound. Mean CD4+ counts were reduced to 40 cells/ μ L at Month 1¹⁸⁶ from a baseline value of 960 cells/ μ L, and were 55% of LLN by 12 months after Cycle 1 (270 cells/ μ L) (see figure below).

Sponsor Table 3.5.4.10 (below) displays the distribution of time to first event and time to resolution for CTC Grade 3 or 4 for hematologic laboratory parameters in all alemtuzumab studies (Pool C). CTC Grade 3 or 4¹⁸⁷ decreases in CD4 lymphocytes (CD4+ lymphocyte count <200 cells/ μ L) occurred in 1447 of 1485 alemtuzumab-treated subjects. After a median of approximately 2 years of follow-up, 845 of 1447 subjects did not have a CD4+ lymphocyte count greater than that subjects baseline value or the LLN (whichever is lower).

Figure 7. Sponsor Figure 4-2: Median (IQR) CD4+ Cell Counts over Time for Alemtuzumab-Treated Subjects in the Phase 3 Studies and Extension study CAMMS03409 (Baseline through Complete Follow-up in CAMMS0409)



Source: ISS Appendix 14-7, p. 14.

¹⁸⁶ Month 1 is the time of nadir median CD4+ lymphocyte count. No post-infusion laboratory measurements were routinely performed prior to 1 month, so the actual nadir value may have occurred prior to 1 month post-infusion.

¹⁸⁷ For CD4+ lymphocytes, CTC Grade 3 changes are <200 cells/ μ L – 50 cells/ μ L; CTC Grade 4 changes are <50 cells/ μ L.

Table 85. Sponsor Table 3.5.4.10. Distribution of Time to First Event and Time to Resolution for CTC Grade 3 or 4 Results in Hematologic Laboratory Parameters Pool C

	Alemtuzumab Pooled (N=1485)				
	Hemoglobin	Neutrophils	Platelets	Lymphocytes	CD4
Time to first CTC Grade 3 or 4 toxicity (months)					
n	13	81	29	1405	1447
Median	21.1	12.9	22.0	1.0	1.0
Min, Max	1.0, 51.2	0.3, 60.1	0.3, 58.1	0.0, 24.8	0.1, 17.3
Q1, Q3	14.0, 38.2	1.2, 23.3	17.3, 29.8	0.7, 1.0	1.0, 1.1
Time to resolution of first CTC Grade 3 or 4 toxicity (months)					
n	12	78	26	1315	602
Median	1.6	1.1	0.5	4.9	25.9
Min, Max	0.1, 14.3	0.1, 12.6	0.1, 5.7	0.1, 84.7	1.6, 84.1
Q1, Q3	0.8, 3.1	0.5, 2.6	0.3, 1.0	2.5, 8.2	11.0, 29.5
Duration of unresolved follow-up from first CTC Grade 3 or 4 toxicity (months)					
n	1	3	3	90	845
Median	12.6	6.2	0.0	5.0	23.4
Min, Max	12.6, 12.6	1.0, 7.0	0.0, 1.2	0.0, 92.3	0.0, 93.4
Q1, Q3	12.6, 12.6	1.0, 7.0	0.0, 1.2	3.7, 8.2	11.8, 29.5

Source: ISS Appendix 14-4-3, p. 6233

Note: Resolution of a CTC Grade 3 or 4 toxicity is defined as a subsequent lab value that is greater than that subject's baseline value or the LLN, whichever is lower

-Hemoglobin CTC Grade Ranges in G/L Units: 0: \geq LLN; 1: \geq 100 - <LLN; 2: \geq 80 - <100; 3: \geq 65 - <80; 4: <65.

-Neutrophils CTC Grade Ranges in $10^9/L$ Units: 0: \geq LLN; 1: \geq 1.5 - <LLN; 2: \geq 1.0 - <1.5; 3: \geq 0.5 - <1.0; 4: <0.5.

-Platelet CTC Grade Ranges in $10^9/L$ Units: 0: \geq LLN; 1: \geq 75 - <LLN; 2: \geq 50 - <75; 3: \geq 25 - <50; 4: <25.

-Lymphocytes CTC Grade Ranges in $10^9/L$ Units: 0: \geq LLN, 1: < LLN - 0.8, 2: <0.8 - 0.5, 3: <0.5 - 0.2, 4: <0.2.

-CD4 CTC Grade Ranges in $10^9/L$ Units: 0: \geq LLN, 1: < LLN - 0.5, 2: <0.5 - 0.2, 3: <0.2 - 0.05, 4: <.05.

Altered lymphocyte populations have been discussed as a potential basis for secondary autoimmune disease after alemtuzumab treatment.¹⁸⁸⁻¹⁸⁹ Expanded lymphocyte phenotyping substudies of Phase 3 trials resulted in high-level observations, including the following:¹⁹⁰

- Consistent with alemtuzumab's intended lymphocyte-depleting pharmacodynamic effect, the absolute count of nearly all lymphocyte subsets was reduced at Month 1 compared with Baseline. The exception were immature B cells (and subsets thereof), whose absolute count was consistently higher post-treatment than at baseline.

¹⁸⁸ Costelloe L, et al. Secondary autoimmune diseases following alemtuzumab therapy for multiple sclerosis. *Expert Rev. Neurother.* 12(3), 335–341 (2012).

¹⁸⁹ Weetman A. Immune reconstitution syndrome and the thyroid. *Best Practice & Research Clinical Endocrinology & Metabolism* 23.6 (2009): 693-702.

¹⁹⁰ ISS Appendix 14-7 Section 4.4

- While the absolute abundance of nearly all lymphocyte subsets was reduced by alemtuzumab treatment, differential depletion and repopulation led to post-treatment shifts in the relative proportions of various lymphocyte subsets.
- Lymphocyte repopulation began early, since Month 3 values were generally higher than Month 1, and continued until next alemtuzumab exposure caused re-depletion.
- The extent of depletion and the degree and rates of repopulation following a second cycle were comparable to the first cycle.
- CD4+ and CD8+ subsets showed similar patterns of depletion and repopulation.
- Naïve cells were depleted by alemtuzumab to a relatively greater extent than Memory cells.

Reviewer comment: If alemtuzumab is approved, this reviewer recommends description of changes in lymphocytes in prescribing information. Abnormal B or T cell counts were exclusion criteria in Phase 3 studies. This reviewer recommends caution in using alemtuzumab in patients with baseline abnormalities in leukocyte counts. In the proposed prescribing information submitted by Genzyme, Human Immunodeficiency Virus (HIV) infection is listed as a contraindication.

Neutrophils

In analyses of worst post-baseline platelet count by CTC grade, alemtuzumab-treated subjects had a lower incidence of grade 1, grade 2, and grade 3 changes in neutrophils (see table below). Alemtuzumab-treated subjects had a higher incidence of grade 4 changes in neutrophils (2.3%), compared to IFNB-1a subjects (1.4%).

Table 86. Sponsor Table 13.5.4.2. Neutrophils. CTC Grade for Hematologic Laboratory Parameters for Baseline and Worst Post-Baseline Values. Pool E

Parameter: Neutrophils(10 ⁹ /L)		SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
Time Period	CTC Grade	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Baseline	0	480/493 (97.4)	889/915 (97.2)	254/269 (94.4)	1143/1184 (96.5)
	1	6/493 (1.2)	13/915 (1.4)	6/269 (2.2)	19/1184 (1.6)
	2	5/493 (1.0)	7/915 (0.8)	7/269 (2.6)	14/1184 (1.2)
	3	2/493 (0.4)	3/915 (0.3)	1/269 (0.4)	4/1184 (0.3)
	4	0/493 (0.0)	3/915 (0.3)	1/269 (0.4)	4/1184 (0.3)
Overall - Post Baseline	0	249/492 (50.6)	685/919 (74.5)	169/269 (62.8)	854/1188 (71.9)
	1	92/492 (18.7)	100/919 (10.9)	35/269 (13.0)	135/1188 (11.4)
	2	103/492 (20.9)	93/919 (10.1)	37/269 (13.8)	130/1188 (10.9)
	3	41/492 (8.3)	27/919 (2.9)	15/269 (5.6)	42/1188 (3.5)
	4	7/492 (1.4)	14/919 (1.5)	13/269 (4.8)	27/1188 (2.3)

Source: ISS Appendix 14-4-5, p. 5248.

Neutrophils CTC Grade Ranges in 10⁹/L Units: 0: ≥LLN; 1: ≥1.5 - <LLN; 2: ≥1.0 - <1.5; 3: ≥0.5 - <1.0; 4: <0.5.

Platelets

In analyses of worst post-baseline platelet count by CTC grade, alemtuzumab-treated subjects had a lower incidence of grade 1 changes in platelets (19.7%), compared to IFNB-1a subjects (8.8%) (see table below). The frequencies of grade 2 and grade 3 changes in platelets were comparable between groups. Alemtuzumab-treated subjects had a higher incidence of grade 4 changes in platelets (1.2%), compared to IFNB-1a subjects (0.4%). With the exception of Subject 1089-5126, who had an isolated platelet count $<25 \times 10^9/L$ that returned to normal on repeat measurement 3 days later, all Grade 4 values in alemtuzumab-treated in controlled trials were reported in subjects with ITP. Low platelet counts associated with ITP are discussed in greater detail in Section 7.3.5.1.3.

Table 87. Sponsor Table 13.5.4.2. Platelets. CTC Grade for Hematologic Laboratory Parameters for Baseline and Worst Post-Baseline Values. Pool E

Parameter: Platelet($10^9/L$)					
		SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
Time Period	CTC Grade	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Baseline	0	490/495 (99.0)	912/918 (99.3)	267/269 (99.3)	1179/1187 (99.3)
	1	5/495 (1.0)	6/918 (0.7)	2/269 (0.7)	8/1187 (0.7)
	2	0/495 (0.0)	0/918 (0.0)	0/269 (0.0)	0/1187 (0.0)
	3	0/495 (0.0)	0/918 (0.0)	0/269 (0.0)	0/1187 (0.0)
	4	0/495 (0.0)	0/918 (0.0)	0/269 (0.0)	0/1187 (0.0)
Overall - Post Baseline	0	390/492 (79.3)	827/919 (90.0)	236/269 (87.7)	1063/1188 (89.5)
	1	97/492 (19.7)	81/919 (8.8)	24/269 (8.9)	105/1188 (8.8)
	2	1/492 (0.2)	1/919 (0.1)	0/269 (0.0)	1/1188 (0.1)
	3	2/492 (0.4)	3/919 (0.3)	2/269 (0.7)	5/1188 (0.4)
	4	2/492 (0.4)	7/919 (0.8)	7/269 (2.6)	14/1188 (1.2)

Source: P. 5249 ISS Appendix 14-4-5.

Platelet CTC Grade Ranges in $10^9/L$ Units: 0: $\geq LLN$; 1: $\geq 75 - < LLN$; 2: $\geq 50 - < 75$; 3: $\geq 25 - < 50$; 4: < 25 .

Hemoglobin

In analyses of worst post-baseline platelet count by CTC grade, alemtuzumab-treated subjects had a lower incidence of grade 1 changes in hemoglobin (39.1%), compared to IFNB-1a subjects (44.3%) (see table below). The incidence of grade 2 changes in hemoglobin was comparable between groups. Alemtuzumab-treated subjects had a higher incidence of grade 3 changes in hemoglobin (0.5%), compared to IFNB-1a subjects (0.0%). Alemtuzumab-treated subjects had a higher incidence of grade 4 changes in hemoglobin (0.2%), compared to IFNB-1a subjects (0.0%).

Table 88. Sponsor Table 13.5.4.2. Hemoglobin. CTC Grade for Hematologic Laboratory Parameters for Baseline and Worst Post-Baseline Values. Pool E

Parameter: Hemoglobin(G/L)					
Time Period	CTC Grade	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
		n/N (%)	n/N (%)	n/N (%)	n/N (%)
Baseline	0	453/495 (91.5)	830/919 (90.3)	248/269 (92.2)	1078/1188 (90.7)
	1	40/495 (8.1)	85/919 (9.2)	20/269 (7.4)	105/1188 (8.8)
	2	2/495 (0.4)	4/919 (0.4)	1/269 (0.4)	5/1188 (0.4)
	3	0/495 (0.0)	0/919 (0.0)	0/269 (0.0)	0/1188 (0.0)
	4	0/495 (0.0)	0/919 (0.0)	0/269 (0.0)	0/1188 (0.0)
Overall - Post Baseline	0	256/492 (52.0)	527/919 (57.3)	148/269 (55.0)	675/1188 (56.8)
	1	218/492 (44.3)	357/919 (38.8)	107/269 (39.8)	464/1188 (39.1)
	2	18/492 (3.7)	30/919 (3.3)	11/269 (4.1)	41/1188 (3.5)
	3	0/492 (0.0)	5/919 (0.5)	1/269 (0.4)	6/1188 (0.5)
	4	0/492 (0.0)	0/919 (0.0)	2/269 (0.7)	2/1188 (0.2)

Source: ISS Appendix 14-4-5, p. 5247

Hemoglobin CTC Grade Ranges in G/L Units: 0: \geq LLN; 1: \geq 100 - <LLN; 2: \geq 80 - <100; 3: \geq 65 - <80; 4: <65.

7.4.2.2. Clinical Chemistry Laboratory Evaluations

Changes in liver function tests are discussed in Section . Other than laboratory changes seen in cases of nephropathy (Section 7.3.5.1.5), changes in renal chemistry assessments were comparable in alemtuzumab subjects and IFNB-1a subjects.

In controlled trials (Pool E), there were no other notable differences in mean changes and changes from baseline according to CTC grade between alemtuzumab subjects and IFNB-1a subjects.¹⁹¹

Urinalysis

Urinalysis results for Phase 3 trials (CAMMS323 and CAMMS324) are discussed in this section.¹⁹² As part of monitoring for anti-GBM disease, alemtuzumab-treated subjects received monthly urinalyses. IFNB-1a subjects received quarterly urinalyses. Analyses of all measurements are affected by more frequent measurements in alemtuzumab subjects.

¹⁹¹ Pool E laboratory changes from baseline are summarized in ISS Appendix 14-4-5 Table 13.5.4.1 (p. 4792-4854). Pool C laboratory changes from baseline are summarized in ISS Appendix 14-4-3 Table 3.5.10 (p. 5867-4643).

¹⁹² Urinalysis was introduced late in the course of CAMMS223, so results are not included. CAMMS03409 had criteria for clinically significant changes in urinalysis that were different from Phase 3 trials, so results from CAMMS03409 were not pooled.

Based on all available quarterly and monthly assessments, post-baseline shifts in occult blood to "positive, clinically significant" were reported with greater incidence for alemtuzumab 12 mg/day subjects than IFNB-1a subjects (5.0% versus 2.2% in Year 1; 7.3% versus 1.4% in Year 2). When only quarterly assessments were used, incidence of shifts from baseline to "positive, clinically significant" were similar for alemtuzumab 12 mg/day subjects and IFNB-1a subjects in Year 1 (1.4% versus 2.0%), and incidence was increased in the alemtuzumab 12 mg/day group in Year 2 (3.1% versus 1.4%).

Based on all available quarterly and monthly assessments, post-baseline shifts in protein to "positive, clinically significant" were reported for a larger proportion of alemtuzumab 12 mg/day subjects than IFNB-1a subjects in the Phase 3 studies (4.6% versus 2.2% in Year 1; 5.0% versus 1.1% in Year 2). When only quarterly assessments were used, shifts in urine protein results from baseline to "positive, clinically significant" were reported for similar proportions of alemtuzumab 12 mg/day subjects and IFNB-1a subjects (1.7% versus 2.0% in Year 1; 1.5% versus 1.1% in Year 2).

Reviewer comment: With analysis of only quarterly measurements in both treatment groups, this reviewer considers the incidence of urinalysis changes to be similar in alemtuzumab and IFNB-1a groups.

7.4.3 Vital Signs

Sponsor Table 13.4.3 provides the incidence of vital sign changes from baseline in controlled trials (Pool E). The incidence of systolic blood pressure (BP) increase ≥ 20 mm Hg was less frequent in alemtuzumab-treated subjects (24.8%), compared to IFNB-1a subjects (29.2%); the incidence of systolic BP increases ≥ 40 mm Hg was comparable between groups. The incidence of systolic blood pressure (BP) decrease ≥ 20 mm Hg was more frequent in alemtuzumab-treated subjects (27.4%), compared to IFNB-1a subjects (20.1%); the incidence of systolic BP decreases ≥ 40 mm Hg was comparable between groups.

The incidence of pulse increase ≥ 15 bpm was less common in alemtuzumab subjects (38.0%), compared to IFNB-1a subjects (39.8%). The incidence of pulse increase ≥ 30 bpm was more common in alemtuzumab subjects (7.2%), compared to IFNB-1a subjects (4.9%). The incidence of pulse decrease ≥ 15 bpm was more common in alemtuzumab subjects (25.3%), compared to IFNB-1a subjects (19.5%). The incidence of pulse decrease ≥ 30 bpm was more common in alemtuzumab subjects (2.9%), compared to IFNB-1a subjects (2.2%).

Table 89. Sponsor Table 13.4.3. Incidence of Abnormal Vital Signs Change From Baseline. Pool E

Vital Sign Parameter Relative to Baseline	SC IFNB-1a	Alemtuzumab 12 mg/day	Alemtuzumab 24 mg/day	Alemtuzumab Pooled
Systolic BP				
Increase \geq 20 mm Hg	144/493 (29.2)	226/919 (24.6)	69/269 (25.7)	295/1188 (24.8)
Increase \geq 40 mm Hg	11/493 (2.2)	14/919 (1.5)	6/269 (2.2)	20/1188 (1.7)
Decrease \geq 20 mm Hg	99/493 (20.1)	233/919 (25.4)	92/269 (34.2)	325/1188 (27.4)
Decrease \geq 40 mm Hg	7/493 (1.4)	12/919 (1.3)	5/269 (1.9)	17/1188 (1.4)
Diastolic BP				
Increase \geq 10 mm Hg	270/493 (54.8)	453/919 (49.3)	129/269 (48.0)	582/1188 (49.0)
Increase \geq 20 mm Hg	80/493 (16.2)	128/919 (13.9)	40/269 (14.9)	168/1188 (14.1)
Decrease \geq 10 mm Hg	245/493 (49.7)	514/919 (55.9)	150/269 (55.8)	664/1188 (55.9)
Decrease \geq 20 mm Hg	66/493 (13.4)	119/919 (12.9)	54/269 (20.1)	173/1188 (14.6)
Pulse				
Increase \geq 15 bpm	196/493 (39.8)	348/919 (37.9)	103/269 (38.3)	451/1188 (38.0)
Increase \geq 30 bpm	24/493 (4.9)	58/919 (6.3)	27/269 (10.0)	85/1188 (7.2)
Decrease \geq 15 bpm	96/493 (19.5)	222/919 (24.2)	79/269 (29.4)	301/1188 (25.3)
Decrease \geq 30 bpm	11/493 (2.2)	23/919 (2.5)	11/269 (4.1)	34/1188 (2.9)

Source: ISS Appendix 14-4-5, p. 4618.

-Subjects are counted once regardless of the number of times achieving the threshold change.

-Percentages are calculated from the total number of subjects in each group with a baseline value for that parameter and at least one valid post-baseline measurement

Reviewer comment: The first post-treatment vital signs were performed 1 month after infusion. This analysis does not include vital sign changes during and after alemtuzumab infusion, during which vital sign abnormalities occur most frequently. Also, this reviewer was unable to locate an analysis of mean changes in vital signs overall.¹⁹³

7.4.4 Electrocardiograms (ECGs)

The QT substudy is discussed in Section 7.4.5.2. Outside of the QT substudy, EKGs were not routinely performed in alemtuzumab studies.

7.4.5 Special Safety Studies/Clinical Trials

7.4.5.1 Semen Analysis in Male Subjects

An isoform of the CD52 antigen is present in the male reproductive tract (epididymis and seminal vesicles) and on mature spermatozoa, but not on spermatogenic cells nor spermatozoa within the seminiferous tubules¹⁹⁴. This finding raises the possibility that alemtuzumab, which binds CD52, could impact sperm quantity, quality, or function. Clinical data from 13 alemtuzumab-treated male subjects participating in the Phase 3 studies (CAMMS323 and CAMMS324) showed no adverse impact of alemtuzumab treatment on sperm quality, quantity, or motility.

¹⁹³ ISS Appendix 14-4-5 Table 13.4.4 displayed mean changes in vital signs were provided for 3 month intervals.

¹⁹⁴ Schröter, 1999, *J Biol Chem*

Sixteen men in the Phase 3 studies (13 in the alemtuzumab group and 3 from the IFNB-1a group) participated in a semen substudy designed to evaluate the effects of alemtuzumab on sperm concentration, motility and agglutination (see Module 5.3.5.3). Samples were collected prior to initiating methylprednisolone and study drug at Baseline and at Months 1, 3, and 6. For subjects entering the substudy after initiating therapy, samples were collected prior to initiating methylprednisolone and study drug at Month 12 and at Months 13, 15, and 18. Two samples were collected and analyzed at each time point to account for sample variability that frequently occurs in normal, healthy volunteers. If the sperm count and/or motility were abnormal in either sample tested at Month 6 (or Month 18, for late enrollees), 2 additional samples were collected and tested at Month 9 (or Month 21, for second cycle enrollees). Among the 13 alemtuzumab-treated subjects examined, none developed aspermia, azoospermia, or consistently depressed sperm count. Additionally, there was no evidence of motility disorders or an increase in sperm morphological abnormalities between treatment arms or within a treatment arm over time. While a degree of sperm agglutination was present in some samples, this agglutination did not persist within any subject over time. Similarly, in 1 subject a transient incident of increased anti-sperm antibody binding to sperm occurred, in conjunction with increased sperm agglutination, but this finding was not persistent over time.

7.4.5.2. Substudy of CAMMS03409 to assess QT Interval

In 2007, FDA approved a supplement for Campath which expanded the product label to include first-line use of Campath in the treatment of B-CLL. As a condition of approval, Genzyme agreed to conduct a postmarketing commitment study to assess the potential effect of alemtuzumab on QT/QTc interval prolongation.¹⁹⁵

At selected sites, subjects who received alemtuzumab for the first time and who met all eligibility criteria for participating in the CAMMS03409 Extension Study, were screened for this QT substudy. Subjects were required to provide informed consent and meet all eligibility criteria in order to participate in the substudy. The sub-study continued to enroll subjects until it had accrued approximately 55 evaluable participants.

Subjects in the QT sub-study underwent a minimum 7-day washout period from their last disease-modifying therapy for MS (interferon beta-1a [IFNB-1a] or glatiramer acetate), steroids, and any prior medication with known potential to prolong the QT/QTc interval. Following the washout period, a screening ECG was obtained to establish eligibility. If a subject failed this screening ECG, it could be repeated to re-assess eligibility.

A moxifloxacin lead-in period was used as a positive control to demonstrate sensitivity to changes in QTcF (see Section 3.4.2). After a 3- to 6-day washout period from moxifloxacin, subjects received their first cycle of alemtuzumab which consisted of 5 consecutive daily IV infusions of 12 mg/day.

¹⁹⁵ QT substudy report. Submitted to sBLA103948 on February 27, 2013

The FDA Interdisciplinary Review Team for QT Studies (QT-IRT) was consulted regarding this substudy. Their summary of QT-IRT findings and recommendations are copied below.

1.1 OVERALL SUMMARY OF FINDINGS

No large changes (i.e., > 20 ms) in QTc were detected in this study following alemtuzumab 12 mg/day for 5 days in 53 patients with multiple sclerosis. The largest upper bound of the 2-sided 90% CI for the change from baseline was 10.8 ms on Day 3 at 0.2 hours. The largest lower bound of the two-sided 90% CI for the Δ QTcF for moxifloxacin was greater than 5 ms. However, assay sensitivity was not established because moxifloxacin was not administered in a randomized fashion or concurrent with study treatment. In our previous review of the protocol (July 20, 2010), we provided comments to the Sponsor alerting them that the inclusion of moxifloxacin in this study would not establish assay sensitivity.

In this study, 53 subjects received alemtuzumab and a single oral dose of moxifloxacin 400 mg. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Alemtuzumab and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Day	Time (hour)	Δ QTcF (ms)	90% CI (ms)
Alemtuzumab 12 mg/day	3	0.2	7.7	(4.7, 10.8)
Moxifloxacin 400 mg*	-1	3	13.7	(11.8, 15.7)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 11.1 ms.

An increase in heart rate was observed in this study. The largest upper bound of the 2-sided 90% CI for the mean change from baseline was 28.1 bpm at 1 hour post-dose on Day 1. The mean change from baseline was in the range of 22 to 26 bpm during the two hour period following the initial infusion of alemtuzumab on Day 1. The increase in heart rate was not observed at subsequent doses with higher exposure of alemtuzumab. This finding can reasonably be explained by a cytokine-release syndrome, which has been observed with several monoclonal antibodies (Bugelski PJ et al., Expert Rev Clin Immunol 5(5), 499-521; 2009) including alemtuzumab (Wing MG et al., J Clin Invest 98(12), 2819-2826; 1996) and is usually a first-dose phenomenon. This finding is consistent with clinical studies of alemtuzumab in which tachycardia occurred more frequently after the first dose in a cycle as compared to subsequent doses (Integrated Summary of Safety).

The studied dosing regimen (12 mg/day for 5 days) is the proposed therapeutic dosing regimen for MS indication studied for treatment-naïve patients in the Phase 2 (CAMMS223) and Phase 3 (CAMMS323) studies, and for most treatment-experienced patients in the Phase 3 study (CAMMS324). The sponsor did not identify any intrinsic/extrinsic factors that will significantly affect alemtuzumab PK.

2 PROPOSED LABEL

QT-IRT proposed labeling language is a suggestion only. We defer final labeling decision to the Division.

12.6 Cardiac Electrophysiology

The effect of multiple doses of alemtuzumab (12 mg/day for 5 days) on the QTc interval was evaluated in a single arm study in 53 patients with multiple sclerosis. No large changes in the mean QTc interval (i.e., > 20 ms) were detected in the study. A mean increase in heart rate of 22 to 26 beats/min was observed for at least 2 hours following the initial infusion of alemtuzumab. This increase in heart rate was not observed with subsequent doses.

Neurology Reviewer comment: This reviewer agrees with the findings and recommendations in the QT-IRT consultation report outlined above.

Two adverse events of prolonged QT occurred in Genzyme studies of alemtuzumab in MS outside of the QT substudy (see table below).

Table 90. Cases of prolonged QT outside of the QT substudy. Genzyme studies of alemtuzumab in MS.

USUBJID	Study	Phase 2-3 Treatment	PT	SAE	Comment
CAMMS324/1059-5483	CAMMS 324	Alemtuzumab 12 mg/d	Electrocardiogram QT prolonged	N	Pt. had an SAE of Grade 3 iron deficiency anemia. Prolonged QT in the setting of diphenhydramine use. Resolved within 1 day.
CAMMS324/1090-5236	CAMMS 03409	Alemtuzumab 24 mg/d	Electrocardiogram QT prolonged	N	Syncope during exercise stress test with long QT on EKG.

QT-IRT comments on cases in Table 90 included the following:

- Subject 1059-5483: *“The reported event, a grade 1 QT prolonged, took place when subject was off-drug for many days. Subject’s co-medication included QT-prolongers: diphenhydramine and tizanidine. Subject was bradycardic, a condition that favors QT-prolongation. A Grade 1 QT prolongation corresponds to QTc > 450 ms - ≤ 470 ms; this a normal range value for females.*
- Subject 1090-5236: *“A grade 2 syncopal episode was reported in this subject 16 days after starting the third infusion series with alemtuzumab. At the time of the event subject was taking doxazosin for hypertension that could cause this event. Regarding the QT prolonged episode, it was mild and no baseline ECGs are available.”*

Neurology Reviewer comment: According to QT-IRT, these cases of QT prolongation were mild in severity and occurred in the setting of confounding factors.

7.4.6 Immunogenicity

The development of immunogenicity to alemtuzumab was investigated, using different assays in the Phase 2 trial (CAMMS223) and Phase 3 clinical trials (CAMMS323 and CAMMS324). Because of assay differences, Phase 2 results were not pooled with Phase 3 results.¹⁹⁶

Adverse events were analyzed by anti-alemtuzumab antibody and anti-alemtuzumab inhibitory antibody status (positive or negative) and titer values overall and before and during each cycle to assess whether the presence of anti-alemtuzumab antibodies and alemtuzumab inhibitory antibodies was associated with an increased risk of certain events. Similar analyses were performed for IARs.

A majority (691/811, 85.2%) of patients treated with 12 mg/day alemtuzumab in the Phase 3 studies tested positive for anti-alemtuzumab antibodies. A higher proportion of patients (667/786, 84.9%) tested positive in Cycle 2 as compared with Cycle 1 (579/810, 71.5%).¹⁹⁷

No differences were seen in the overall incidence of AEs when subjects in the alemtuzumab 12 mg/day group who were ever-positive for anti-alemtuzumab antibody (673/691 subjects, 97.4%) were compared with subjects who were always negative for antibody during the study (116/120 subjects, 96.7%).¹⁹⁸ In addition, no trends were noted when the overall incidence of AEs were stratified by peak or pre-cycle anti-alemtuzumab titer quartiles for antibody positive subjects

No difference was seen in the overall incidence of IARs when subjects in the alemtuzumab 12 mg/day group who were ever positive for anti-alemtuzumab antibodies (90.0%) were compared with subjects who were always negative (90.8%),¹⁹⁹ and in general this pattern was also observed when subjects who were ever positive were stratified by peak antibody quartiles.

¹⁹⁶ There were 216 alemtuzumab subjects in Phase 2 (CAMMS223) and 972 alemtuzumab subjects in Phase 3 trials (CAMMS323 and CAMMS324).

¹⁹⁷ Summary of clinical pharmacology, p. 82.

¹⁹⁸ Sponsor Table 2.3.2.7.2 Appendix 14-2-2.

¹⁹⁹ Sponsor Table 2.3.4.8.1 Appendix 14-2-2.

7.5 *Other Safety Explorations*

7.5.1 *Dose Dependency for Adverse Events*

ITP occurred more frequently in subjects who received high dose (24 mg/day) treatment in 223. Beginning with Amendment 2, the alemtuzumab 24 mg/day group was closed to newly enrolling subjects, and all subjects enrolled after approval of Amendment 2 were randomized in a 2:1 ratio to receive alemtuzumab 12 mg/day or IFNB-1a. In CAMMS323, alemtuzumab subjects were only assigned to receive 12 mg/day.

7.5.2 *Time Dependency for Adverse Events*

Evaluations of time dependency for several categories of events (including autoimmunity, malignancy, and infusion reactions) are included in the relevant review sections.

7.5.3 *Drug-Demographic Interactions*

Age

No subjects >60 or <18 years of age were enrolled in Genzyme-sponsored clinical studies of MS. Therefore, there is no clinical safety experience currently available for these MS subjects.

In controlled trials (Pool E), median subject age at time of study enrollment was 33.0 years (min, max: 18, 60). Age group quartiles for Pool E subjects are listed below:

- <25th percentile = <27.0 years
- 25th - <50th percentile = ≥ 27.0 - <33.0 years
- 50th - <75th percentile = ≥ 33.0 - <40.0 years, and
- 75th percentile = ≥ 40.0 years.

In Pool E, younger age quartiles had higher frequencies of adverse events in the Endocrine disorders SOC, all but 1 of which were thyroid-related adverse events. An opposite pattern was seen in IFNB-1a subjects – endocrine disorders were more frequent in older age quartiles (see Table 49 in Section 7.3.5.1).

In all alemtuzumab-treated subjects (Pool C), infusion-associated reactions were reported at a similar incidence across age groups in the alemtuzumab 12 mg/day group (91.5%, 92.7%, 90.4%, and 86.1%, respectively). The incidence of infections in the alemtuzumab 12 mg/day group was not different among the age groups examined (71.2%, 73.0%, 66.7%, and 67.5%, respectively). Cytopenias were reported less frequently in the lower age quartiles for the alemtuzumab 12 mg/day group (16.9%, 18.5%, 21.4%, and 24.3%, respectively).

Sex

In the active-controlled studies approximately two thirds of subjects were female (65.7%). The overall incidence of AEs was not different in males (94.8% IFNB-1a and 97.8% alemtuzumab 12 mg/day) versus females (94.7% IFNB-1a and 97.5% alemtuzumab 12 mg/day).

There was a markedly increased incidence of treatment-emergent malignancy in female alemtuzumab subjects (discussed in Malignancy Section 7.3.5.2).

Female subjects had increased incidences in some categories of autoimmune disease. In the SOC of 'Endocrine Disorders' the incidence of AEs for females in the alemtuzumab 12 mg/day group was 18.7% compared to 7.2% for males.²⁰⁰ Serious thyroid adverse event occurred in 23 of 972 (2.4%) female subjects, compared to 7 of 513 (1.4%) male subjects (Pool C). Eighteen of 972 (1.9%) and 8 of 513 (1.6%) female and male subjects, respectively, had confirmed ITP. Cases of nephropathy or immune kidney disorder in occurred in 5 of 972 (0.5%) female subjects and 1 of 513 (0.2%) male subjects (Pool C).

The incidence of infusion reactions was similar in males and females. Over all available follow up, the incidence of infections was greater in female subjects in the alemtuzumab 12 mg/day treatment group (73.8% versus 61.1% in males). This difference included increased frequency of respiratory and urinary tract infections in females. Herpes zoster was also reported more frequently in females in the alemtuzumab 12 mg/day treatment group (7.1% versus 3.5% in males). Over all available follow up, the incidence of cytopenias was greater in female subjects in the alemtuzumab 12 mg/day treatment group (22.7% versus 16.4% in males).

Race

The number of non-White subjects in the active-controlled studies was small (149 subjects; 8.8% of the total number of subjects) and precluded meaningful interpretation of AE data by race.

Weight

In this ISS analyses by weight examined the following subject groups: <10th percentile, 10th percentile to < 90th percentile, 90th percentile and above. These groups were chosen to examine the extremes of weight in the study population. The weight group percentile results were similar across all analysis pools.

The incidence of IARs was not increased in lower body weight subjects receiving alemtuzumab; 86.6% incidence in alemtuzumab 12 mg/day subjects weighing <10th percentile compared to 91.3% in subjects in the 10th to <90th percentile and 94.7% in subjects with weight ≥90th percentile.

²⁰⁰ Increased endocrine AEs in females is consistent with the epidemiology of thyroid disease.

Over all available follow up, the incidence of infections was higher in the >90th percentile weight category for both the alemtuzumab 12 mg/day (66.9%, 68.7% and 77.6%, respectively) and 24 mg/day treatment groups (79.2%, 83.4% and 87.9%, respectively). In the pooled alemtuzumab dose group the incidence of infections was 79.9% in the >90th percentile weight category compared to 71.3% in the 10th - 90th percentile.

The incidence of thyroid AEs was generally similar across weight groups with similar patterns across the alemtuzumab 12 mg/day (18.6%, 18.7% and 14.5%, respectively) and IFNB-1a treatment groups (8.7%, 4.1% and 10.0%, respectively).

BMI

In this ISS, analyses by BMI examined the following percentiles: <10th percentile, 10th percentile to <90th percentile, 90th percentile and above. The upper and lower percentiles were chosen to examine the extremes of BMI in the study population. The BMI percentile results were similar across all analysis pools.

In all alemtuzumab treated subjects, the incidence of infections was greatest in the highest BMI group for both the alemtuzumab 12 mg/day (66.4%, 68.4% and 78.5%, for each BMI percentile, respectively) and 24 mg/day groups (86.4%, 81.7% and 96.3%, for each BMI percentile, respectively). Respiratory infections, UTIs, and herpes zoster were among the types of infections more prevalent in the highest BMI category. Over all available follow up, the incidence of cytopenias was greatest in the highest BMI category for subjects treated with alemtuzumab 12 mg/day (10.4%, 20.9% and 28.1%, respectively) in contrast to the alemtuzumab 24mg/day group (40.9%, 25.1%, and 29.6%, respectively) where the incidence of cytopenias was greatest in the lowest BMI category.

Geographic Region

Sponsor-defined geographic regions are listed below:

- United States/Canada/Australia
- Latin America (Mexico, Brazil, Argentina)
- EU (Germany, France, UK, Sweden, Poland, Czech Republic)
- Non-EU Europe and Israel (Serbia, Croatia, Israel, Russia, Ukraine)

In active-controlled studies, the majority of subjects (96.3%) were enrolled in 3 geographic regions: United States/Canada/Australia (44.2%), EU (20.9%), and Non-EU Europe and Israel (31.2%). Subject enrollment by geographic region was similar across the 3 treatment groups with the exception of a higher percentage of alemtuzumab 24 mg/day subjects enrolled in the USA/Canada/Australia (see table). To avoid possible effects of this difference, analyses by region in this review section are reported for the alemtuzumab 12 mg/day group.

Table 91. Number and percentage of subjects in the alemtuzumab 24 mg/day treatment group (Safety population. Controlled trials)

Region	n/N (%)
United States/Canada/Australia	151/744 (20.3%)
Latin America	7/62 (11.3%)
EU	53/352 (15.1%)
Non-EU Europe and Israel	58/526 (11.0%)

There was an increased incidence of reported treatment-emergent malignancy in U.S. alemtuzumab subjects (discussed in Malignancy Section 7.3.5.2).

Over all available follow up, the incidence of IARs reported in the 12 mg/day group was similar in the USA/Canada/Australia (94.4%) and the EU (93.3%) and lower in non-EU Europe and Israel (81.7%). Results for the pooled dose group were similar.

In the active-controlled studies, the incidence of infections reported in the alemtuzumab 12 mg/day group was similar across the regions with the exception of a lower incidence in non-EU Europe and Israel (46.5%²⁰¹ compared to 83.7% in USA/Canada/Australia). Similar reporting patterns were observed in the IFNB-1a treatment group (68.9% incidence in USA/Canada/Australia compared to 31.5% in non-EU Europe and Israel). Results for the alemtuzumab 24 mg/day group and the pooled dose group were similar.

In the active-controlled studies, the incidence of thyroid AEs reported in the alemtuzumab 12 mg/day group was similar across the regions with the exception of a lower incidence in non-EU Europe and Israel (14.5% compared to 21.0% in USA/Canada/Australia and 18.3% in the EU). In the IFNB-1a group, the incidence of thyroid AEs in non-EU Europe and Israel was 3.0% compared to 5.7% in USA/Canada/Australia and 7.8% in the EU.²⁰² Generally, there did not appear to be trends across the regions with similar reporting patterns across the alemtuzumab 12 mg/day and IFNB-1a treatment groups. Results for the pooled dose group were similar.

In the active-controlled studies, the incidence of cytopenias was highest in the EU in the alemtuzumab 12 mg/day (28.9%) compared to 21.3% in USA/Canada/Australia and 12.2% in non-EU Europe and Israel. In the IFNB-1a treatment group the same incidence of cytopenias was reported in the EU and Latin America (29.4%) compared to 19.8% in USA/Canada/Australia and 13.9% in non-EU Europe and Israel. The higher incidence of cytopenias in the EU and non-EU Europe and Israel was primarily driven by increased incidences of lymphopenia and leukopenia in the alemtuzumab 12 mg/day group and neutropenia and lymphopenia in the IFNB-1a group.

²⁰¹ The reported incidence of infections in non-EU Europe and Israel was 44.4% less than the reported incidence in USA/Canada/Australia for alemtuzumab and 54.3% less in IFNB-1 subjects.

²⁰² The reported incidence of thyroid disorders in non-EU Europe and Israel was 31.0% less than the reported incidence in USA/Canada/Australia for alemtuzumab and 47.4% less in IFNB-1 subjects.

Reviewer comment: The incidence of reported adverse events with alemtuzumab was consistently lower in the Non-EU Europe and Israel region (Serbia, Croatia, Israel, Russia, Ukraine). In active-controlled studies subjects from the Non-EU Europe and Israel region comprised 31.2% of the overall subject population. Because of this difference, adverse event frequencies reported overall are likely lower than frequencies relevant to the U.S. population. The causes of these regional differences are not well characterized. Baseline demographics were similar between regions.

Prior MS Treatment Status

Reviewer comment: This section compares subjects who received prior MS treatment to treatment-naïve subjects.

Over all available follow up, the overall incidence of IARs in previously treated subjects in the alemtuzumab 12 mg/day group (89.8%) and the 24 mg/day group (98.1%) was similar to the incidence in subjects who were treatment-naïve (90.3% and 99.1%, respectively).

Over all available follow up, the incidence of infections was similar in previously treated subjects and treatment-naïve subjects in the alemtuzumab 12 mg/day group (70.4% and 68.5%, respectively). The incidence of infections in previously treated subjects in the 24 mg/day group was higher (88.8%) compared with subjects who were treatment-naïve (75.9%).

Over all available follow up, a similar incidence of cytopenias was observed in previously treated and treatment-naïve subjects in both the 12 mg/day and 24 mg/day treatment groups (20.8% versus 20.2% and 26.7% versus 27.8%, respectively).

7.5.4 Drug-Disease Interactions

No formal studies of subjects with hepatic or renal impairment were performed.

7.5.5 Drug-Drug Interactions

No formal drug interaction studies have been conducted with alemtuzumab.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Cases of malignancy seen with alemtuzumab are discussed in Section 7.3.5.2.

7.6.2 Human Reproduction and Pregnancy Data

A total of 99 pregnancies in 78 alemtuzumab-treated subjects have been reported in the

MS clinical program as of 26 November 2012. A cumulative summary of available information on subject pregnancies for alemtuzumab-treated subjects through November 26, 2012 is presented in Sponsor Table 6-1.

Two offspring of alemtuzumab subjects have had reported congenital abnormalities:

- Events of fetal cystic hygroma and hypoplastic left heart were reported early in a pregnancy of a female subject, leading to elective abortion (Subject 5501-5560).
- A late-breaking event of congenital talipes equinovarus (club foot) was reported. The partner of a male subject (1067-3442) vaginally delivered a full term live male infant with a unilateral club foot. Presently the infant requires a brace; no surgical intervention is planned at this time. No action was taken with regards to alemtuzumab. Club foot occurs in 1 in 1000 births.

Sponsor Table 1 (below) provides a summary of SAEs in offspring of alemtuzumab-treated subjects. The event of thyrotoxic crisis caused by neonatal Graves' disease (offspring of female subject 1018-3090) is discussed in Section 7.3.5.1.

The offspring of Subject 130-1260 had SAEs of stillbirth and amniotic band syndrome. The fetus had abnormalities of the left hand and blistering lesions on the skin. According to a genetics consult, the most likely cause of fetal demise was a tight nuchal cord, but this was difficult to prove.

Reviewer comment: The case of neonatal Graves' disease raises concern of potential maternal-fetal transfer of other autoimmune antibodies. Two offspring of alemtuzumab subjects have had reported congenital abnormalities. If alemtuzumab is approved, this reviewer recommends a pregnancy registry as a postmarketing requirement. Genzyme proposes to conduct a pregnancy registry as a post-marketing commitment and states that a protocol will be submitted post-approval.

Table 92. Sponsor Table 6-1: Cumulative CAMMS Pregnancy Experience - All Studies (Pool C)

	Alemtuzumab 12 mg/day	Alemtuzumab 24 mg/day	All Alemtuzumab Treated Patients
Pregnancy Outcome	75 pregnancies (61 pts) ^a	24 pregnancies (17 pts)	99 pregnancies (78 pts) ^a
Live Birth^c	40 ^{b, c}	11 ^d	51 ^{c, d}
Elective abortion^e	8	3	11
Spontaneous abortion (<20 weeks)	14	6	20
Stillbirth (≥20 weeks)	1	0	1
Ongoing	8	2	10
Unknown	4	2	6

^a Category includes 8 pregnancies in 8 subjects who were originally treated with INFB-1a who subsequently received alemtuzumab and became pregnant following alemtuzumab exposure. The breakdown of the 8 pregnancies was as follows: 2 full term, 1 elective abortion, 3 ongoing, 2 unknown.

^b One subject was pregnant with twins and miscarried 1 baby, the other baby was delivered full term (data from Genzyme GPE Database)

^c Category includes 2 pregnancies (2 pts) who delivered a preterm baby (defined as >32 weeks and ≤35 weeks)

^d Category includes 2 pregnancies (2 pts) who delivered a preterm baby (defined as >32 weeks and ≤35 weeks)

^e Of the elective abortions, one elective abortion each was due to fetal defects (cystic hygroma and hypoplastic heart, Subject 5501-5560), suspicion of extrauterine pregnancy, and anembryonic gestation; 6 elective abortions were due to subject's personal choice related to family, financial, or other unspecific reasons; and no information is available for the remaining 2 cases.

Source: 4-month safety update report, p. 165. Entered to sBLA 103948 on March 19, 2013.

Data as of November 26, 2012.

Table 93. Sponsor Table 1. Summary of Serious Adverse Events in Offspring of Alemtuzumab-Treated Subjects

Case Number / Subject ID (Parent)	Study ID/ Subject Gender (Parent of Offspring)	Date of First Alemtuzumab Dose	Time from last alemtuzumab dose to pregnancy (female subject or partner pregnancy)	Event (PT) / Event Start Date (Offspring)	Gestational Age at birth/Age at time of Event (Offspring)	Seriousness Criterion (Offspring)	Outcome (Offspring)
CAMP-10359/ 302-1186	CAMMS223 / Female	02 Feb 2004	2 years 2 months	Premature Baby/ (b) (6)	32-33 weeks gestation/ 8 days	Hospitalization	Recovered
CAMP-1000271/ 130-1260	CAMMS223 / Female	12 Apr 2004	3 years 3 months	Amniotic Band Syndrome/ (b) (6)	11 days prior to the estimated due date	Death, Congenital Anomaly	Death in utero
				Skin Exfoliation/ (b) (6)			
				Stillbirth/ (b) (6)			
CAMP-1000299/ 1018-3090	CAMMS323/ Female	12 May 2008	3 ½ months	Thyrototoxic Crisis/ (b) (6)	Full-term/ 20 days	Hospitalization, Life-threatening	Recovered
CAMP-1000670/ 3006-3456	CAMMS323/ Male	08 Dec 2008	7 months	Jaundice Neonatal/ (b) (6)	Full-term/ 2 days	Hospitalization	Recovered
CAMP-1001021/ 1158-3396	CAMMS323/ Male	05 Dec 2008	1 month	Feeding Disorder Neonatal/ (b) (6)	35 week gestation / 0 days	Hospitalization	Recovered
CAMP-1001608/ 1007-3479	CAMMS323/ Female	16 Feb 2009	3 months	Neonatal Respiratory Distress Syndrome/ (b) (6)	37 week gestation / 0 days	Hospitalization	Recovered
CAMP-1001990/ 4903-3588	CAMMS03409/ Male	16 Feb 2009	1 year 7 months	Death Neonatal/ Pregnancy end date (b) (6)	25 weeks/ 2 weeks	Death	Fatal

Data as of May 15, 2012

Source: Genzyme response to FDA information request. Submitted to sBLA 103948 on December 11, 2012.

7.6.3 *Pediatrics and Assessment of Effects on Growth*

Alemtuzumab for MS has not been formally studied in pediatric subjects.

7.6.4 *Overdose, Drug Abuse Potential, Withdrawal and Rebound*

Overdose

In Study CAMMS323, 2 subjects erroneously received up to 60 mg of alemtuzumab, the total dose to be administered over the course of 5 days, in a single infusion. Subject 3006-3281 received 60 mg on Day 1 and experienced headache, rash, and hypotension (BP 83/43) on that day, all of which resolved within 8 hours of onset). Subject 3006-3282 received 48 mg on Day 1 and experienced sinus tachycardia (maximum recorded heart rate 123 beats per minute), headache, and rash on that day, all of which resolved within 10 hours of onset. Neither subject received another infusion of alemtuzumab during Cycle 1. Both subjects were hospitalized for observation and recovered without sequelae.

Doses of alemtuzumab greater than those tested in clinical studies may increase the intensity and/or duration of infusion-associated adverse reactions or its immune effects. There is no known antidote for alemtuzumab overdosage. Treatment consists of drug discontinuation and supportive therapy.

Drug abuse potential

No studies were conducted to evaluate the potential for drug abuse with alemtuzumab. In a search using the MedDRA Drug Abuse SMQ, there were no reports of drug abuse or dependence of alemtuzumab in clinical studies.

Withdrawal and Rebound

In a search using the MedDRA Drug Withdrawal SMQ, there were 2 adverse events in the alemtuzumab subjects:

- 1007-3027: CAMMS03409 subject with an AE Verbatim term 'hydromorphone withdrawal.' *Reviewer comment: This AE is unlikely related to alemtuzumab.*
- 6016-3597: CAMMS324 subject in the 12 mg/day group had an adverse event with the PT 'withdrawal syndrome.' *Reviewer comment: No detail other than the ADAE dataset line listing was provided. It is unclear whether this is related to alemtuzumab.*

7.7 Additional Submissions / Safety Issues

Information from the 120-day safety update has been integrated with the rest of the safety results in this review.

8 Postmarket Experience

Information from the postmarket experience has been integrated with the rest of the safety results in this review.

9 Appendices

Appendix 9.1. Subject 3006-5762. Medwatch case 7154140 reporting systemic vasculitis.

Case Information:

CASE_NMBR	ISR	Serious	Gender	Age (yrs)	FDA Date	Event Date	Report Type
7154140	6409899-0	YES	F	33	10/22/2009	10/01/2009	EXP

CASE_NMBR	Country Occurred	Country Reported	Intl Report	Mfr Date	Mfr Number	Image ID
7154140	BRAZIL	UNITED STATES	UNKNOWN	10/01/2009	US-BAYER-200935341GPV	

Reported Drugs/Vaccines:

CASE_NMBR	Verbatim	Trade name	Trade name LTI	Generic name LTI	Ingredient	Role Code
7154140	ALEMTUZUMAB		Alemtuzumab [Nos]	Alemtuzumab	Alemtuzumab	PS
7154140	IBUPROFEN		Ibuprofen [Nos]	Ibuprofen	Ibuprofen	C
7154140	OMEPRAZOLE		Omeprazole [Nos]	Omeprazole	Omeprazole	C

CASE_NMBR	Route	Dosage	Dechallenge	Rechallenge	Drug Start Date	Drug End Date
7154140	Intravenous	INTRAVENOUS	UNKNOWN	UNKNOWN	06/29/2009	07/03/2009
7154140	None	None	UNKNOWN	UNKNOWN	10/01/2009	
7154140	None	None	UNKNOWN	UNKNOWN	10/01/2009	

CASE_NMBR	NDA Number	OTC	Indication PT	Indication HLT	Indication HLGT
7154140		NO	Multiple sclerosis	Multiple sclerosis acute and progressive	Demyelinating disorders
7154140		NO			
7154140		NO			

CASE_NMBR	Indication SOC
7154140	Nerv
7154140	
7154140	

Reported Events/Symptoms:

CASE_NMBR	PT or SMQ	HLT	HLGT	SOC
7154140	Vasculitis	Vasculitides NEC	Vascular inflammations	Vasc

7154140	Vasculitis (SMQ) [broad]	SMQ	SMQ	SMQ
7154140	Vasculitis (SMQ) [narrow]	SMQ	SMQ	SMQ

Reported Outcomes:

CASE_NMBR	Death	Life Threatening	Hospitalized	Disabled	Congenital Anomaly
7154140	NO	NO	NO	NO	NO

CASE_NMBR	Req Intervention	Other
7154140	NO	YES

Reported Sources:

CASE_NMBR	Reporter Occupation	Health Prof	Foreign	Study	Literature	Consumer
7154140	PHYSICIAN	NO	NO	NO	NO	NO

CASE_NMBR	User Facility	Company Rep	Distributor	Other
7154140	NO	NO	NO	NO

Case Narrative:

This case was received from licence partner Genzyme (Mfr. control no. CAMP-1000413) on 07-Oct-2009. Clinical Trial report received on 01-OCT-2009 from site 3006 regarding a 32-year-old female Multiple Sclerosis patient (30065762/SDS). The patient is currently participating in protocol number CAMMS32400507 entitled "A Phase III Randomized, Rater- and Dose-blinded Study Comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzumab to 3-times Weekly Subcutaneous Interferon Beta-1a (Rebif) in Patients with Relapsing/remitting Multiple Sclerosis Who Have Relapsed on Therapy". The patient received her first cycle of alemtuzumab from 29-JUN- to 03-JUL-2009 administered via intravenous route at a dose of 12 mg, qdx5. The patient's medical history was not available. Baseline labs were unremarkable. Lab results remained unremarkable with the exception of 3+ occult blood, RBCs of 25-30, and few bacteria seen in the urine on 01-SEP-2009. From 18-SEP-2009, the patient experienced cutaneous vasculitis, and then from 24-SEP-2009, the patient experienced polyarthritis and skin lesions in the upper limbs. The platelet count was normal and the patient had no history of bleeding. On 01-OCT-2009, approximately 95 days after starting alemtuzumab, the patient experienced grade 3 Systemic Vasculitis, considered non-serious. Symptoms included purpuric - nodular skin lesions, polyarthritis, nausea, headache, and confusional state (encephalopathy). The patient was to be re-evaluated by a hematologist on 02-OCT-2009. The hematologist suggested the patient have a Mantoux test performed. Alemtuzumab was last administered prior to the reported event on 03-JUL-2009. No action was taken with alemtuzumab. As of the date of receipt of this report the patient outcome was not yet recovered. Concomitant medications reported include IBUPROFEN and OMEPRAZOLE. The Investigator assessed the relationship between Systemic Vasculitis and alemtuzumab as probable. Prior SAEs or MEOIs: None

Source Data: CBAERS data

End of 7154140 as of 08/27/2012 00:00:00

Appendix 9.2. Genzyme Table 13.3.3.7 from ISS Appendix 14-4-5. Incidence of all treatment-emergent adverse events leading to treatment withdrawal by MedDRA SOC and Preferred Term in controlled trials.

Genzyme Corporation – CAMMS ISS

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TABLE 13.3.3.7
Incidence of Treatment-Emergent Adverse Events Leading to Treatment Withdrawal by MedDRA SOC and Preferred Term
Pool E

System Organ Class Preferred Term	SC IFNβ-1a (N=496) n (%)	Alemtuzumab 12 mg/day (N=919) n (%)	Alemtuzumab 24 mg/day (N=269) n (%)	Alemtuzumab Pooled (N=1188) n (%)
Any Event	39 (7.9)	22 (2.4)	7 (2.6)	29 (2.4)
Blood and lymphatic system disorders	5 (1.0)	3 (0.3)	1 (0.4)	4 (0.3)
Autoimmune thrombocytopenia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Idiopathic thrombocytopenic purpura	0 (0.0)	1 (0.1)	1 (0.4)	2 (0.2)
Lymphopenia	2 (0.4)	1 (0.1)	0 (0.0)	1 (0.1)
Neutropenia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	3 (0.3)	1 (0.4)	4 (0.3)
Cardiovascular disorder	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Coronary artery disease	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Myocardial infarction	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Tachycardia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Sinus tachycardia	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Endocrine disorders	1 (0.2)	3 (0.3)	0 (0.0)	3 (0.3)
Hypothyroidism	1 (0.2)	2 (0.2)	0 (0.0)	2 (0.2)
Goitre	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Eye disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Eye pain	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vision blurred	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Note: MedDRA version 13.1 was used for coding.

Note: Percentages are based on the number of treated patients in the corresponding treatment group.

Note: A patient is counted only once within each SOC/PT.

Note: SOC's are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

TABLE 13.3.3.7
 Incidence of Treatment-Emergent Adverse Events Leading to Treatment Withdrawal by MedDRA SOC and Preferred Term
 Pool E

	SC IFNB-1a (N=498)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.1)
Abdominal discomfort	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Abdominal pain	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	11 (2.2)	4 (0.4)	1 (0.4)	5 (0.4)
Non-cardiac chest pain	0 (0.0)	3 (0.3)	0 (0.0)	3 (0.3)
Infusion related reaction	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)
Chills	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Chest discomfort	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Influenza like illness	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site erythema	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site pain	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reaction	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site swelling	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic failure	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis acute	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis toxic	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Jaundice	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Liver disorder	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Note: MedDRA version 13.1 was used for coding.

Note: Percentages are based on the number of treated patients in the corresponding treatment group.

Note: A patient is counted only once within each SOC/PT.

Note: SOC are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

TABLE 13.3.3.7
Incidence of Treatment-Emergent Adverse Events Leading to Treatment Withdrawal by MedDRA SOC and Preferred Term
Pool E

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)
Immune system disorders	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Drug hypersensitivity	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Infections and infestations	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Pulmonary tuberculosis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Investigations	5 (1.0)	1 (0.1)	0 (0.0)	1 (0.1)
CD8 lymphocytes decreased	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Alanine aminotransferase increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Bilirubin conjugated increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Blood alkaline phosphatase increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin unconjugated increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Blood urea decreased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Gamma-glutamyltransferase increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Haematocrit decreased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Haemoglobin decreased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic enzyme increased	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Liver function test abnormal	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Note: MedDRA version 13.1 was used for coding.

Note: Percentages are based on the number of treated patients in the corresponding treatment group.

Note: A patient is counted only once within each SOC/PT.

Note: SOC's are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

TABLE 13.3.3.7
 Incidence of Treatment-Emergent Adverse Events Leading to Treatment Withdrawal by MedDRA SOC and Preferred Term
 Pool E

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)
Musculoskeletal and connective tissue disorders	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle spasms	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	1 (0.1)	1 (0.4)	2 (0.2)
Thyroid cancer	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Acute myeloid leukaemia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Nervous system disorders	7 (1.4)	3 (0.3)	0 (0.0)	3 (0.3)
Multiple sclerosis relapse	5 (1.0)	2 (0.2)	0 (0.0)	2 (0.2)
Multiple sclerosis	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Burning sensation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Migraine	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	5 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Mood altered	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Psychotic disorder	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (0.2)	1 (0.1)	0 (0.0)	1 (0.1)
Haematuria	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Chromaturia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Note: MedDRA version 13.1 was used for coding.

Note: Percentages are based on the number of treated patients in the corresponding treatment group.

Note: A patient is counted only once within each SOC/PT.

Note: SOC's are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

TABLE 13.3.3.7
 Incidence of Treatment-Emergent Adverse Events Leading to Treatment Withdrawal by MedDRA SOC and Preferred Term
 Pool E

	SC IFNB-1a (N=496)	Alemtuzumab 12 mg/day (N=919)	Alemtuzumab 24 mg/day (N=269)	Alemtuzumab Pooled (N=1188)
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)
Reproductive system and breast disorders	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Cervical dysplasia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	3 (0.3)	1 (0.4)	4 (0.3)
Dyspnoea	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)
Pharyngeal oedema	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Asthma	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Pulmonary embolism	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.4)	4 (0.4)	0 (0.0)	4 (0.3)
Dermatitis allergic	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Purpura	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Rash	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Urticaria	1 (0.2)	1 (0.1)	0 (0.0)	1 (0.1)
Alopecia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Note: MedDRA version 13.1 was used for coding.

Note: Percentages are based on the number of treated patients in the corresponding treatment group.

Note: A patient is counted only once within each SOC/PT.

Note: SOC are presented alphabetically, and within SOC the PTs are presented by decreasing incidence in the Alemtuzumab 12 mg/day group.

Appendix 9.3. Subject 4001-6041 Medwatch form for autoimmune epitheliopathy of the retina (Manufacturer report # CAMP-1000590).

U.S. Department of Health and Human Services
 Food and Drug Administration

Genzyme Corporation
 For use by user-facilities,
 importers, distributors and manufacturers
 for MANDATORY reporting

Relays International, Inc., FDA Facsimile Approval: 26-APR-2007

MEDWATCH
 3500A Facsimile

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Mfr Report #	CAMP-1000590
UPI/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier (b) (6)	2. Age at Time of Event: 34 Years or Date of Birth: (b) (6)	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 208.6 lbs or 94.6 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: (mm/dd/yyyy) <input type="checkbox"/> Life-threatening (mm/dd/yyyy) <input checked="" type="checkbox"/> Hospitalization - initial or prolonged <input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices) <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Congenital Anomaly/Birth Defect <input type="checkbox"/> Other Serious (Important Medical Events)			
3. Date of Event (mm/dd/yyyy) 02/14/2010		4. Date of This Report (mm/dd/yyyy) 02/29/2012	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Acute Multifocal Plaque Pigment Epitheliopathy of the Retina [Retinal pigment epitheliopathy]			
Case Description: Clinical Trial report received on 24 Feb 2010 from an investigator regarding a 34 year old male Multiple Sclerosis patient (Site 4001, Patient 40016041/ (b) (6)). The patient is currently participating in protocol number CAMMS32400507 entitled "A Phase 3, Randomized, Rater- and Dose-Blinded Study comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1(Rebif) in Patients with Relapsing-Remitting Multiple Sclerosis Who Have Relapsed On Therapy". The patient was randomized to the Alemtuzumab arm and received his month 0 dose from 10 Aug 2009 to 14 Aug 2009 continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
#1 (b) (6) Antineutrophil cyto (continued)			
#2 Antinuclear antibody (continued)			
#3 07/21/2008 CD4 lymphocytes (continued)			
#4 09/08/2009 CD4 lymphocytes (continued)			
#5 02/09/2010 CD4 lymphocytes (continued)			
#6 02/23/2010 CD4 lymphocytes (continued)			
continued in additional info section...			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Unknown #1 UNK, Relevant History, Herpes zoster (Affecting left side of chest.) #2 UNK, Concomitant Disease, Migraine with aura (Grade 1)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) (Regimens Continued)			
#1. Alemtuzumab (alemtuzumab) Solution for infusion			
#2.			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 12 mg, qdx5, Intravenous		#1. 08/10/2009 to 08/14/2009	
#2.		#2.	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Multiple sclerosis (Continued)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2.		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. UNKNOWN	#1. UNK	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
#1. METHYLPREDNISOLONE (METHYLPREDNISOLONE) 08/10/2009 to 08/12/2009 continued in additional info section...			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Genzyme Jill Robinson R. PH, MBA 675 West Kendall Street Cambridge, MA 02142 UNITED STATES		01 617-768-9000 Ext 2	
4. Date Received by Manufacturer (mm/dd/yyyy) 09/19/2011		3. Report Source (Check all that apply)	
5. (A)NDA # IND # BB-IND 10717		<input checked="" type="checkbox"/> Foreign GBR	
6. If IND, Give Protocol # CAMMS32400507		<input checked="" type="checkbox"/> Study	
7. Type of Report (Check all that apply)		<input type="checkbox"/> Literature	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day		<input type="checkbox"/> Consumer	
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic		<input checked="" type="checkbox"/> Health Professional	
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial		<input type="checkbox"/> User Facility	
<input type="checkbox"/> 15-day <input type="checkbox"/> Follow-up #		<input type="checkbox"/> Company Representative	
Combination Product <input type="checkbox"/> Yes		<input type="checkbox"/> Distributor	
Pre-1938 <input type="checkbox"/> Yes		<input type="checkbox"/> Other:	
OTC Product <input type="checkbox"/> Yes			
9. Manufacturer Report Number CAMP-1000590		8. Adverse Event Term(s) Retinal pigment epitheliopathy	
E. INITIAL REPORTER			
1. Name and Address		Phone # (b) (6)	
		(b) (6)	
continued in additional info section...			
2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Investigator	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Unk	

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

MEDWATCH

3500A Facsimile (Back) (Continued)

Page 2 of 5

MDR Report #	CAMP-1000590
UI/Importer Report #	
FDA Use Only	

ADDITIONAL INFORMATION

B5. EVENT DESCRIPTION (Continued)

administered via intravenous route at a dose of 12 mg, qdx5. The patient's medical history included Shingles and Migraine with aura. Reported concomitant medications included methylprednisolone, paracetamol and Amoxicillin. Laboratory results at screening on 21 Jul 2009 were unremarkable and within normal range values.

On 14 Feb 2010, approximately 189 days after starting Alemtuzumab, the patient experienced retinitis of unknown etiology that was grade 3 in intensity and required hospitalization according to the investigator. At the month 1 visit on 08 Sep 2009, laboratory results revealed decreased white blood cell count (WBC) at $3.1 \times 10^9/L$, decreased absolute lymphocyte count at $0.12 \times 10^9/L$ and decreased CD4 count $<20/mm^3$. At the month 6 visit on 09 Feb 2010, laboratory results revealed normal WBC at $4.4 \times 10^9/L$, decreased absolute lymphocyte count at $0.66 \times 10^9/L$ and decrease CD4 count at $130/mm^3$. On 14 Feb 2010, the patient developed a small homonymous scotoma. The investigator assessed the patient on 16 Feb 2010 and due to his history of migraine diagnosed a migrainous aura. A urinary tract infection was also diagnosed. The field defect enlarged and the patient developed further monocular defects. The patient was referred urgently to an ophthalmologist who noted retinal changes and diagnosed retinitis with possible viral, fungal or inflammatory etiology. The patient was doing well with no fever or other symptoms. He was admitted to the hospital for further evaluation of (b) (6). Laboratory tests done on that day revealed normal WBC $4.6 \times 10^9/L$, normal lymphocyte count at $0.86 \times 10^9/L$ and decreased CD4 count at $206/mm^3$. No action was taken in regards with Alemtuzumab. At the time of the report, the outcome of the patient was not yet recovered. The investigator assessed the relationship between retinitis and Alemtuzumab as probable.

Prior SAEs or MEOIs: None reported.

Follow-up information was received on 23 Mar 2010: According to the investigator, the patient was discharged on an unknown date after undergoing several tests and diagnostic procedures: Cytomegalovirus Immunoglobulin G (IgG) and IgM were negative, Epstein-Barr Virus Antibody to Viral Capsid Antigen (EBV VCA) IgG was positive at 644, EBV VCA IgM was negative, Epstein-Barr Nuclear antigen (EBNA) IgG 126, with all results being suggestive of past but not recent infection. Respiratory complement-fixation tests (CFTs) were negative, syphilis test was negative, Varicella zoster virus (VZV) IgG was 857, and Herpes simplex virus (HSV) IgG was negative. Antinuclear (ANA) and antineutrophil cytoplasmic (ANCA) tests were negative. CT Scan of chest, abdomen and pelvis done on an unknown date was normal as well as a chest X-Ray. MRI of the brain was also normal other than a few Multiple Sclerosis lesions. On 16 Mar 2010, the patient underwent a right aqueous tap which showed no CMV, VZV, HSV or EBV DNA. As of 23 Mar 2010, the patient was doing well at home with no systemic symptoms (no pyrexia, no weight loss) and no abnormal symptoms except for his eyes. The patient was still complaining of areas of altered vision in both visual fields, the ones in the left eye improving but the one in the right one slowly enlarging. The patient was being closely monitored by an ophthalmologist who changed the final diagnosis to acute multifocal placoid pigment epitheliopathy (AMPPE). The patient was not receiving any treatment due to the inflammatory and self-resolving nature of the disease. At the time of the report, the outcome was not yet recovered. Additional information has been requested.

Follow-up information was received on 15 Apr 2010: The patient started treatment with oral Aciclovir on 31 Mar 2010 at a dose of 800 mg, 5 times per day. The event was still ongoing at the time of the report. Additional information has been requested.

Follow-up information was received on 29 Apr 2010: MRI of the brain and Chest X-Ray were performed on (b) (6) and CT Scan of chest, abdomen and pelvis was done on (b) (6). The patient was discharged from the hospital on (b) (6) while the event was still ongoing. According to the investigator the patient was seen by the ophthalmologist on 31 Mar 2010 who noted that there had been resolution of some retinal lesions and appearance of new ones. After new review by the ophthalmologist on 23-Apr-2010, the patient outcome was recovered without sequelae on that day as all lesions were declared inactive and fading. The treatment plan as of 23 Apr 2010 was a total course of 6 weeks of Aciclovir at a dose of 800 mg five times daily to be followed by 400 mg, tid indefinitely. Additional information has been requested.

Follow-up information was received on 06 May 2010: The investigator indicated that CMV and EBV tests were performed on (b) (6) (b) (6) HIV, VZV, Herpes simplex, ANA and ANCA tests were done on (b) (6) Syphilis test was done on (b) (6) and respiratory CFTs were obtained on (b) (6). A lumbar puncture done on (b) (6) showed 8 lymphocyte, protein 0.46 and substantial oligoclonal bands. The patient received treatment with 4 doses of paracetamol given orally at a dose of 1 g between (b) (6) (b) (6) and (b) (6) while hospitalized. Additional information has been requested.

Follow-up information was received on 02 Jun 2010: According to the investigator, the Aciclovir the patient received was used empirically and not based on evidence of herpes infection. The clostridium difficile infection mentioned on the discharge summary was reported in error and was removed from the discharge summary. According to the investigator, the patient still had some minor visual field deficits.

Follow-up information was received on 07 Jul 2010: During a follow-up visit with the ophthalmologist on 27 Jun 2010, a new lesion

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was noted and dose of aciclovir was increased back to 800 mg, 5 times a day orally starting on 28 Jun 2010 indefinitely. The patient had been on a reduced dose of 400 mg, tid from 04 Jun 2010 to 27 Jun 2010. As a result of the new lesion finding, the event outcome was re-assessed as not yet recovered according to the investigator. Additional information has been requested.

Follow up information was received on 26 Aug 2010: According to the investigator, the ophthalmologist consult declared the patient's disease 'inactive'. A second ophthalmological opinion agreed and indicated it was unlikely that the condition was caused by a viral infection and more likely to have been autoimmune in origin. Based on the information provided by the consultation, the Aciclovir treatment of 800 mg, 5 times a day orally was stopped on 17 Aug 2010 and the patient received month 12 dose of alemtuzumab from 18 Aug 2010 to 20 Aug 2010. The event outcome was assessed as recovered without sequelae on 18 Aug 2010.

Follow up information was received on 19 Sep 2011. The investigator amended the event term from Acute Multifocal Plaquoid Pigment Epitheliopathy to Acute Multifocal Plaquoid Pigment Epitheliopathy of the Retina.

Manufacturer's Comment:

The benefit-risk relationship of alemtuzumab is not affected by this report.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	(b) (6)	Antineutrophil cytoplasmic antibody Negative ANCA test = Negative.	See comments NA	
2		Antinuclear antibody Negative ANA test = Negative.	See comments NA	
3		CD4 lymphocytes Normal	885 /mm3	1740 490
4		CD4 lymphocytes Decreased	<20 /mm3	1740 490
5		CD4 lymphocytes Decreased	130 /mm3	1740 490
6		CD4 lymphocytes Decreased Month 6 re-test.	206 /mm3	1740 490
7		Cytomegalovirus test Negative CMV IgG and IG M + Negative	See comments NA	
8		Epstein-Barr virus antibody EBV VCA IgG positive at 622; IgM negative; EBNA IgG: 126 Suggestive of past infection.	See comments NA	
9		Herpes simplex Negative IgG negative.	See comments NA	
10		HIV antibody Negative Negative	See comments NA	
11		Immunology test Negative Respiratory CFTs = negative.	See comments NA	

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12	(b) (6)	Lumbar puncture	See comments NA
		Lymphocytes: 8, Protein 0.46, Substantial oligoclonal bands	
13	07/21/2008	Lymphocyte count Normal	1.90 10e9/l 4.10 0.85
14	09/08/2009	Lymphocyte count Decreased	0.12 10e9/l 4.10 0.85
15	02/09/2010	Lymphocyte count Decreased	0.66 10e9/l 4.10 0.85
16	02/23/2010	Lymphocyte count Normal Month 6 re-test.	0.86 10e9/l 4.10 0.85
17	(b) (6)	Treponema test Negative	See comments NA
18	09/08/2009	Urine analysis	See comments NA
		Color: Straw Appearance: Clear Specific Gravity: 1.013 (range: 1.001-1.035) Reaction PH: 7.0 (range: 4.8-8.0) Protein: Negative Glucose: Negative; Ketone: Negative; Bilirubin: Negative; Occult blood: Negative	
19	02/09/2010	Urine analysis	See comments NA
		Color: Straw Appearance: Cloudy Specific Gravity: 1.027 (range: 1.001-1.035) Reaction PH: 6.5 (range: 4.8-8.0) Protein: Negative Glucose: Negative; Ketone: Negative; Bilirubin: Negative; Occult blood: Negative; RBC/HPF: None seen WBC/HPF: 25-50 (range: M=0-5) Bacteria: Many.	
20	02/23/2010	Urine analysis	See comments NA
		Color: Yellow Appearance: Clear Specific Gravity: 1.024 (range: 1.001-1.035) Reaction PH: 7.0 (range: 4.8-8.0) Protein: Trace Glucose: Negative; Ketone: Negative; Bilirubin: Negative; Occult blood: Negative; RBC/HPF: None seen	

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Mr Report #	CAMP-1000590
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WBC/HPF: 50-100(range: M=0-5)
 Bacteria: Few.

21	(b) (6)	Varicella virus test	See comments NA
		IgG = 857	
22	07/21/2008	White blood cell count Normal	6.0 10e9/l 10.8 3.8
23	09/08/2009	White blood cell count Decreased	3.1 10e9/l 10.8 3.8
24	02/09/2010	White blood cell count Normal	4.4 10e9/l 10.8 3.8
25	02/23/2010	White blood cell count Normal Month 6 re-test.	4.6 10e9/l 10.8 3.8

C4. DIAGNOSIS FOR USE (Continued)
 #1: Multiple sclerosis (Not Coded)

C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

#2. PARACETAMOL (PARACETAMOL) 01/02/2010 to 01/07/2010
 #3. AMOXYCILLIN (AMOXICILLIN) 02/09/2010 to 02/13/2010

E1. NAME AND ADDRESS (Continued)
 KINGDOM
 Phone: +44-1223-216189 Fax: +44-1223-679318

Block C - Additional Dosage Regimens

Suspect Product	2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)	6. Lot #	7. Exp. date
#1 Alemtuzumab Regimen # 12 mg, qdx3, Intravenous 2		08/18/2010 to 08/20/2010	UNK	UNK

CLINICAL REVIEW

Application Type	BLA Labeling Supplement
Application Number(s)	sBLA-103948-5139
Priority or Standard	Standard

Submit Date(s)	November 27, 2012
Received Date(s)	November 27, 2012
PDUFA Goal Date	December 27, 2013
Division / Office	Division of Neurology Products
Reviewer Name(s)	John R. Marler, M.D.
Review Completion Date	October 1, 2013

Established Name	Alemtuzumab
(Proposed) Trade Name	Lemtrada
Therapeutic Class	Monoclonal antibody
Applicant	Genzyme Corporation

Formulation(s)	10 mg/ml concentrate for dilution
Dosing Regimen	Month 0: 12 mg/day for 5 days Month 12: 12 mg/day for 3 days
Indication(s)	Multiple sclerosis
Intended Population(s)	Adults

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1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The sponsor has not submitted evidence from adequate and well-controlled studies to support the safety and effectiveness of alemtuzumab for treating multiple sclerosis. The application does present clinical trial results that show significant differences in the relapse rates between the two treatment arms. However, as described in detail below and the statistical review by Sharon Yan, it is not possible to determine whether these differences are due to an effect of alemtuzumab or other factors including the placebo effect and observer bias because of the subjective nature of the clinical outcomes and the failure to blind patients and treating physicians.

There is evidence to suggest that unblinding influenced the behavior of patients and treating physicians. For instance, drop-out rates were higher in the interferon- β -1a treatment group after treatment started and early in the trial after randomization but before investigators administered treatment. There is also the fact that there was bias across treatment groups in the change from pre-randomization screening to post-randomization baseline EDSS scores in the 324 trial. This bias affects the comparison of disability progression in the two treatment groups and suggests that EDSS scores determined by blinded raters were influenced by the preferences and expectations of the unblinded patients.

Evidence to support a claim that alemtuzumab slows the accumulation of physical disability is particularly weak. For disability progression, there is the same uncertainty about placebo effect and observer bias that casts doubt on the claim of a reduced relapse rate. In addition, taking no account of the bias in the EDSS scores, results of the pivotal 323 trial failed to confirm the positive results of the 324 trial which showed an increased time to SAD. Finally, when the statistical reviewer looked at the effect of setting the baseline EDSS after randomization in the 324 trial, she found evidence of bias that leads to an overestimate of the reduction in time to sustained accumulation of disability in patients treated with alemtuzumab. Her re-analysis using the screening EDSS determined by blinded raters before the patients were assigned to treatment groups fails to show a statistically significant difference in time to SAD. Correcting for bias and placebo effect in the post-treatment EDSS scores would be likely to further reduce the estimate of the effect of alemtuzumab on disability.

The role of placebo effect and reporting bias in the determination of relapse rate is more difficult to demonstrate. However, almost all information used to determine whether a

relapse event occurred derives from the unblinded patients and treating physicians. The clinical trials lacked required procedures to ensure relapse event reporting procedures were uniform in the two treatment groups. In fact, the protocols had several features that increased the opportunity for bias and placebo effect to influence the difference observed between treatment groups. The low p-value for the reported difference in relapse rates for the 323 and 324 trials may create the impression that the results are so large that placebo effect and reporting bias could explain only a small part of the effect. Post-hoc statistical tests show that it is likely that if bias and placebo effect altered 10% of the reports of relapse events, statistical significance of any difference in the number of subjects who were relapse free would be lost.

The results of the different trial outcomes reported by the sponsor were not robust. The only MRI outcome pre-specified as a secondary outcome is one example. Perhaps the seemingly most objective and unbiased finding from the clinical trials, the lack a statistically significant change over two years in the MRI T₂ lesion volume, was inconsistent with the reduced relapse rate findings in both phase 3 trials, consistent with the lack of effect on disability in the 323 trial, and inconsistent with the beneficial effect on disability in the 324 trial.

A decision to recommend approval must be based on regulatory requirements. Given the lack of evidence from well-controlled trials, the broad range of opinion from clinicians, statisticians, and clinical trial methodologists with a full understanding of the facts and the potential risks and benefits becomes a particularly important consideration. Therefore, a final recommendation regarding approval will be made after the Advisory Committee meeting on November 13, 2013.

1.2 Risk Benefit Assessment

The certainty of the risks of potentially lifelong hypothyroidism, serious infusion reactions, melanoma and other malignancies, Graves's ophthalmopathy and other autoimmune disorders, and prolonged increased susceptibility to infection may not be balanced by the uncertainty that exists in the limited evidence of the potential clinical benefits from clinical trials that were not well-controlled.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

If alemtuzumab were to be approved for the MS indication, then the proven dangers and possible long-term effects on the immune system require continued frequent long-term monitoring of both effectiveness and adverse effects even after the last dose of the

drug. The monitoring should include white blood cell typing to determine whether the immune system returns to the normal pre-treatment state for each individual. In addition, it will be important to require yearly measurements of global disability to screen for the occurrence of disabling adverse events that might otherwise go unreported.

1.4 Recommendations for Post-marketing Requirements and Commitments

Alemtuzumab is already approved for treatment of B-cell lymphoma using higher doses than those used in MS. However, MS is a more chronic disease that progresses more slowly than lymphoma. The submission contains limited data on the safety and effectiveness of alemtuzumab over the longer exposures that are likely in the MS population. If alemtuzumab is approved for MS, all subjects should be monitored for safety for at least 4 years. Safety monitoring should include measures of global disability to avoid missing unexpected serious adverse effects due to off-target drug effects. Longer monitoring may be necessary depending on the safety findings during the 4-year follow-up.

2. Introduction and Regulatory Background

2.1 Product Information

The development of alemtuzumab began as an effort at a University of Cambridge pathology laboratory to replace anti-lymphocyte globulins as an immunosuppressive agent to prevent allograft rejection after transplantation by killing both CD4 helper and CD8 cytotoxic lymphocytes.¹ The Cambridge team identified a group of antibodies to CD52 (an abundant peptide on the lymphocyte surface) that induced cell-mediated lysis of lymphocytes—antibody dependent cytotoxicity (ADCC). An immunogenic rodent antibody (CAMPATH-1G) ablated lymphocytes by binding to CD52. A humanized equivalent, CAMPATH-1H, eventually called alemtuzumab, was less immunogenic and retained the ability to lyse CD-52 lymphocytes.

Ownership of the rights to alemtuzumab passed from Cambridge University to British Technology, Wellcome Biotech, Wellcome PLC, and Glaxo-Wellcome. Glaxo-Wellcome carried out the trials that led to FDA approval as a treatment for B-cell leukemia. Glaxo halted development in 1994. A partnership between Leukosite, ILEX, and Schering AG

¹ Herman Waldman and Geoff Hale, Phil. Trans. R. Soc. B (2005) 360, 1707–1711

sought and obtained FDA approval for alemtuzumab to treat fludarabine-resistant B-cell lymphoma in 2001. Millenium Pharmaceuticals purchased Leukosite and sold their rights to alemtuzumab to ILEX. ILEX began trials in multiple sclerosis in 2002 (See section 2.5.2 below). ILEX was acquired by Genzyme in 2004. A labeling supplement approved alemtuzumab as a first-line treatment for B-CLL on September 20, 2007.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 FDA-Approved Treatments for MS

FDA-Approved Treatments for Multiple Sclerosis					
Approved Drug	Name	Sponsor	Approved	Dose	Frequency
beta interferon 1b	Betaferon	Bayer	1993	0.25 mg --increase by 0.0625 mg every 6 weeks	SQ qod
beta interferon 1a	Avonex	Biogen Idec	1996	30 µg (increase by 7.5 µg q 3 weeks)	IM q week
glatiramer acetate	Copaxone	Teva	1996	20 mg/day	SQ
mitoxanthrone	Novantrone	EMD Serono	2000	12mg/m ² IV over 5 to 15 min	IV q 3 mo
beta interferon 1a	Rebif	EMD Serono Pfizer Inc.	2002	22µg or 44µg	SQ tiw
natalizumab	Tysabri	Elan	2004	300mg IV over 1 hour	every 4 weeks
beta interferon 1b	Extavia	Novartis	2009 (1993)	0.25 mg (increase by 0.0625 mg 6 weeks)	SQ qod
fingolimod	Gilenya	Novartis	2010	0.5 mg	orally once daily
teriflunomide	Aubagio	Sanofi	2012	7 mg or 14 mg	orally once daily
dimethyl fumarate	Tecfidera	Biogen-Idec	2013	120 mg for 7 days then 240 mg	twice daily

2.3 Availability of Proposed Active Ingredient in the United States

Alemtuzumab was approved in the United States on October 13, 2000. It was marketed as Campath for the treatment of B-cell chronic lymphocytic leukemia until Genzyme stopped marketing the drug on September 4, 2012. Campath is continues to be available free of charge through a US distribution program.²

² <http://www.campath.com>

2.4 Important Safety Issues with Consideration to Related Drugs

Please see the safety review by Evelyn Mentari.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Review of the presubmission regulatory activity reveals persistent concerns about the ability of the clinical trials in multiple sclerosis to provide unbiased estimates of alemtuzumab activity.

There are four BLA submissions for alemtuzumab (Table 2). The sponsor of the original BLA was Ilex Oncology. Genzyme acquired Ilex in 2004. The original and second submission related to the CLL indication. Ilex submitted a new IND application for the MS indication on October 8, 2002 (IND 10717). Completion of three clinical trials under the new IND led to two new BLA supplement applications in 2012. FDA refused to file the first application because of problems with data formatting. The second is the subject of this review.

Table 2 Applications for NDA 103948 Alemtuzumab

NDA Submissions			
Date	Type	Status	Indication
2001-05-07	Original Application	Approved	for treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy (CDER/OHOP/DHP)
2007-09-19	Supplement 5070	Approved	for use as a single agent for treatment of B-cell chronic lymphocytic leukemia (B-CLL) (PMC#1 under 103948/0)
2012-08-07	Supplement 5127	Refuse to File	LEMTRADA New Indication: Treatment of patients with relapsing forms of Multiple Sclerosis to slow or reverse the accumulation of physical disability and reduce the frequency of clinical exacerbations.
2012-11-27	Supplement 5139	Pending Application	Efficacy Supplement for use of Lemtrada (alemtuzumab) in Multiple Sclerosis

2.5.1 BLA Submission for B-Cell Chronic Lymphocytic Leukemia (CLL)

FDA based the 2001 original approval for BLA 103948 on three open-label historical-control clinical trials. None of the trials had a comparator group. In the largest trial, investigators treated 93 CLL patients who had failed fludarabine therapy with

alemtuzumab 30mg IV three times per week for 4 to 12 weeks.³ The response rate was 33%. Two other open-label one-arm trials with 32 and 24 patients showed response rates of 21% and 29%. The median duration of the response was 7, 7, and 11 months in the three trials. The original label had three black-box warnings for (1) hematological toxicity, including pancytopenia, marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia; (2) infusion reactions; (3) serious opportunistic infections. The label listed hyperthyroidism as a serious endocrine adverse event.

FDA approved an addition to the label on 5/19/2004: "The following serious adverse events were identified in post-marketing reports: tumor lysis syndrome, Goodpasture's syndrome, Graves disease, Guillain-Barre syndrome, optic neuropathy, and serum sickness."

FDA granted the original approval contingent on performance of a post-marketing unblinded randomized controlled clinical trial to compare alemtuzumab to chlorambucil in B-cell CLL. That trial showed an increase in progression-free survival when alemtuzumab was used as first-line therapy. The label was changed to reflect this finding on 9/19/2007.

2.5.2 IND 10717 Alemtuzumab for Multiple Sclerosis

Ilex Oncology submitted an IND to develop alemtuzumab for MS on October 8, 2002. The first trial proposed was the CAMMS223 trial. After acquiring Ilex Oncology, Genzyme submitted the protocols for the CAMMS323 and CAMMS324 trials.

On **November 7, 2002**, FDA archived minutes of a teleconference with Genzyme. Clinical comments relevant to issues of this review included the following:

"The Agency views the proposed study as an open-label Phase II trial with numerous secondary endpoints. Due to the clinical trial design, the results of this study will not provide substantial support for a BLA. The sponsor acknowledged that this study will not provide substantial support for a BLA."

"The sponsor agreed to revise the trial to improve the reliability and objectivity of the ascertainment of relapse occurrence."

"In an open-label study, variations in the use of steroids could have an impact on the occurrence of relapses. Therefore, the protocol should specify and standardize the treatment that investigators will use to treat a clinically significant relapse."

³ For MS the dose of alemtuzumab is two one-week cycles separated by a year. Each cycle consists of 12mg IV three times per week.

“However, the sponsors acknowledged that variation in the treatment of relapses may confound the interpretation of the study results. The sponsor expressed their commitment to obtain complete data regarding the treatment of relapses during the course of the study”

On **August 13, 2004**, FDA archived minutes of a teleconference with Genzyme. Clinical comments relevant to issues of this review included the following:

“The sponsor requested this telephone conference to discuss the possibility of submitting an sBLA based on the results of a 1-year analysis of the ongoing trial.”

“Because of study design issues (open-label, small sample size), the [CAMMS223 trial] is unlikely to provide substantial support for an sBLA.”

On **August 24, 2004**, FDA called Genzyme to discuss a change in the statistical analysis plan for CAMMS223 to add relapse rate as a co-primary endpoint.

FDA noted that the details of the analysis, such as the method for calculating relapse rate and the allocation of alpha to the two co-primary endpoints, are important. FDA also noted that it is permissible to change the statistical analysis plan as long as the data remains blinded.

On **April 1, 2005**, FDA called Genzyme to discuss amendment #60,⁴ a change in the statistical analysis plan for the CAMMS223 trial.

FDA stated that FDA views the ongoing clinical trial as a Phase 2 study. The trial is moderately sized and open-label. Therefore, the trial will not be a pivotal study to support a license application. However, if the trial is conducted rigorously, the trial may provide evidence to support a subsequent Phase 3 study.

“FDA is uncertain about the clinical meaningfulness of an effect on relapse rate at one year. In order to support a license application, an effect on relapse rate at two years (or longer) is necessary”

On **July 19, 2005**, FDA called Genzyme to discuss amendment #60, a change in the statistical analysis plan for the CAMMS223 trial.

“The sponsor plans to revise the statistical analysis plan to specify that the study statistician will provide the interim results to the Steering Committee, who will then make decisions about the design of the Phase 3 study. With this revised plan, the DSMB will not serve as an intermediary between the statistician and the Steering Committee.”

“FDA expressed concern that the Steering Committee that receives the results of the interim analysis should have no impact or effect on the ongoing clinical trial. FDA also

⁴ There is no corresponding amendment described in the sBLA submission. Amendment 3 had the date December 27, 2005. Amendment 2 had the date November 13, 2003.

stated that FDA had no new comment after reviewing the analysis plan submitted in Amendment 65.”

On September 13, 2005, FDA archived minutes of a teleconference with Genzyme after Genzyme had notified FDA that the DSMB had reviewed safety and efficacy data from the study in MS, and recommended suspending dosing of alemtuzumab due to the occurrence of 3 cases of severe ITP in alemtuzumab patients and none in interferon beta patients. A plan to monitor for ITP was discussed. CDER placed the IND on clinical hold:

“The sponsor may not administer additional dosing of Alemtuzumab under this IND, pending submission and CDER review of a revised protocol and consent form that adequately address CDER concerns regarding the risk of ITP.”

In addition, during the same teleconference, the sponsor and CDER discussed the design of a future Phase 3 study. Clinical comments in the minutes regarding trial design included the following:

“Sponsor and CDER agreed that a Phase 3 trial is necessary to confirm these preliminary results.”

“Sponsor and CDER agreed that the public disclosure [of the CAMMS223 results] should be worded such that it does not undermine subject and/or investigator participation in a subsequent, randomized Phase 3 study.”

“Sponsor and CDER agreed that off-label use of Alemtuzumab would be a problem and should not be encouraged by any public disclosure.”

“A lower dose Alemtuzumab group may be necessary to provide strong double-blind evidence of a treatment effect.”

[The sponsor is proposing that] “the trial will include a single-blind active control group, with blinded assessors.”

“Considering the unblinding (of the sponsor and FDA) that has occurred, minimizing the changes to the analysis plan is essential to preserve the integrity of [CAMMS223].”

On February 2, 2006, Genzyme submitted a complete response to the full clinical hold placed because of concerns about ITP. FDA found the response inadequate and continued the clinical hold on March 17, 2006. **On March 17, 2006**, DNP continued the clinical hold.

On May 18, 2006, Genzyme submitted a second complete response. **On July 7, 2006**, DNP continued the clinical hold.

On October 13, 2006, Genzyme submitted a third complete response. FDA continued the clinical hold on November 9, 2006.

FDA clarified that “the clinical hold is a partial hold, in which new exposure to alemtuzumab is not allowed, but clinical follow-up of patients already treated may otherwise continue, as has been the case up to this date.”

On **November 21, 2006**, FDA met with Genzyme to discuss current and future development plans for alemtuzumab. Clinical comments in the minutes regarding trial design included the following:

“FDA cannot agree at this time that the study [CAMMS223] was successfully completed based on the 2 year interim analysis. We note that the original plan was for two co-primary endpoints (relapse rate and time to sustained accumulation of disability) based on 3 years, and that using the two year interim analysis as the primary analysis is a deviation from the prospective analysis plan. Also, the study had an open-label design, which raises possible issues of bias. We are, however, willing to consider that the study could serve as one source of substantial evidence of effectiveness, but our final decision will depend upon our detailed review of the data.”

“[CAMM223] provides encouraging results regarding the efficacy of alemtuzumab for MS, but also raises serious concerns regarding its safety (see above). If efficacy is showed in a well designed, and well controlled randomized study, with very robust evidence, then the completed study has the potential to provide data contributing to the establishment of substantial evidence of efficacy.”

“Genzyme, through press releases, has already shared a lot of information regarding the safety and efficacy of alemtuzumab. Considering the open-label design, and the information already disseminated, FDA has no objection.”

“FDA responded that a rater blinded (but patient not blinded) study may be adequate if the effect is large. However, a totally blinded study is more likely to be found persuasive if the treatment effect is relatively small.”

“The FDA noted that using a low dose active comparator would assist with the blinding. However, the sponsor was hesitant to have a treatment arm with ineffective therapy, such as placebo or very low dose alemtuzumab. The FDA again noted that they prefer double-blinded, controlled studies, especially for the pivotal trials.”

“In the absence of a valid justification for the proposed study, we believe that any further investigation of alemtuzumab for multiple sclerosis should be carried out under a well designed randomized controlled trial that will provide useful efficacy data as well as adequate safety monitoring. The current trial (CAMMS223) does not meet these criteria.”

The clinical hold may be lifted after positive review of a well designed and well controlled randomized study.

March 16, 2007 and **March 21, 2007** Genzyme submitted two protocols for SPA. June 29, 2007, FDA responded with a No Agreement letter. The letter contained the following FDA comments regarding the trial designs for CAMMS323 and CAMMS324:

"The FDA would not allow an indication for "...relapsing forms of MS..." unless you are able to provide the required substantial evidence of effectiveness, including replication, in all relapsing forms of MS."

"You must show that efficacy is sustained throughout the second year, and you should also randomize patients by site."

"FDA strongly recommends that you use a double-dummy placebo control in your pivotal trials. The acceptability of your rater-blinded study will be a matter of review. If your study results reveal an extremely large effect, then FDA may potentially accept this rater-blinded design for the pivotal trials. Also, you should carefully assess the effectiveness of your blinding during the trial and at its conclusion to determine if the rater blind was maintained."

"The secondary efficacy endpoint of proportion of patients with no MS disease activity is based on relapse, SAD, as well as MRI results. In both phase III studies, MRI will be measured once a year. Since Gd-enhancing lesions could markedly increase in number in a short period such as one month, we believe that MRI needs to be measured more frequently (for example every 3 months), in order to adequately capture disease activity."

"No, you must show replication of the outcome(s). For example, if one study were positive for relapse rate, but not SAD, and the second study was positive for SAD, but not relapse rate, then we would not accept this as adequate evidence for efficacy of these outcomes. Likewise, if both trials are positive for relapse rate, but only one is positive for SAD, then FDA would consider the indication for relapse rate, but not SAD."

"If an interim analysis is planned, you need to take all necessary precautions to ensure the integrity of the study and to avoid unauthorized access for the interim data. All personnel who have access to the unblinded interim data and all contacts with those personnel need to be documented for all occasions. The complete details of the interim analysis and charter documents need to be submitted."

May 3, 2007, FDA removed the clinical hold.

April 23, 2009, Genzyme submitted the statistical analysis plan for CAMMS323. On **August 20, 2009**, FDA responded with comments regarding that plan.

The FDA statisticians agreed with the definition of the full analysis set, the use of the proportional hazards model for the analysis of time to SAD but disagreed with the use of the proportional means model for the relapse endpoint.

"Relapse also causes the censoring of time to SAD due to alternative medications the patient receives, if the patient has not experienced SAD yet. Sensitivity analyses, including a worst-case scenario analysis, of time to SAD for patients who are censored due to relapses should be added to the protocol."

"SAD and relapse rate are co-primary endpoints. The study will be considered positive if both endpoints achieve statistical significance at the 0.05 significance level."

“The co-primary endpoint of relapse rate as defined is problematic. A subject who has a relapse is likely to take alternative medication. The treating physician is unblinded in this study. As described in the protocol, the treating physician will treat the patient who has relapses based on the treatment assignment of the patient. Therefore, subsequent relapses may be dependent on the treatment of the first relapse, causing bias in efficacy evaluations. We recommend you use time to first relapse instead of relapse rate as the co-primary endpoint. The relapse rate estimated as proposed is not acceptable.”

March 17, 2010, FDA met with Genzyme to discuss key design elements and the analysis plan for the alemtuzumab development program. FDA comments in the meeting minutes relevant to this review included the following:

FDA agreed “with the use of relapse rate as an endpoint. However, the proposed analysis (in particular with the elimination of censoring of patients who initiate an alternate therapy) would be very difficult to interpret, because of the open-label design of the study. Any relapse, EDSS assessment and time in study taking place after the initiation of an alternative MS therapy should be excluded from the primary analysis.”

“The Division continues to have concerns about group differences in the treatment of relapses by unblinded physicians and the reporting of relapses by unblinded patients.”

FDA was “concerned by the potential bias introduced by the absence of blinding of patients, the possibility of unblinding of EDSS raters, the initiation of alternative MS therapies after the first relapse, and the elimination of censoring. The interpretation of the results from the statistical analysis will be challenging, and extremely robust findings will be necessary to overcome these issues.”

“Blinding procedures were discussed in detail. For EDSS and relapse reporting, the bias introduced by unblinding of physicians and patients remains a significant problem which will cause serious difficulties in interpreting the results of the trial. Trial procedures leave doubt about the extent of any unblinding of EDSS raters.”

“**Analysis of secondary outcomes will not be done unless the differences in both primary outcomes are statistically significant.** Labeling of any secondary outcome is ultimately a question of review. However, FDA continues to believe that the secondary clinical outcomes of CAMMS323 overlap many of the same domains covered by the primary outcomes.”

“The adjudicated relapses will form the basis for the analysis of the primary relapse rate outcome. **The detection of a relapse still depends entirely on subjective observations by the unblinded patient or an unblinded physician.**”

June 11, 2010, FDA granted Fast Track Designation.

January 24, 2011, FDA met with Genzyme at a pre-BLA meeting. Clinical comments regarding the planned BLA application included the following:

“Beginning with our initial review of the CAMMS323 and CAMMS324 protocols, the lack of double-blinding has consistently concerned us. The lack of blinding remains a major concern. We [FDA] note that, despite these previous concerns that have been communicated to you, there was little discussion of the unblinded design of the trials in the meeting material. We emphasize the importance of presenting a full discussion and analysis of the impact of having the patients and treating physicians unblinded. You need to present data and analyses that evaluate the objectivity of the EDSS and MRI outcomes as well as the relapses. To do so requires full descriptions of the procedures for ensuring the blind and data to support compliance with the different blinding procedures in the protocols. You need to include efficacy data from the ongoing extension study CAMMS03409 because it can provide important information about clinical outcomes after subjects left the CAMMS223, CAMMS323, and CAMMS324 trials.”

August 7, 2012, FDA refused to file the initial sBLA submission because of problems with data formatting. Subsequent to this meeting DNP clinical reviewers and the DBI statistician communicated with Genzyme by email and teleconference, and at meetings to explain the data formatting problems.

November 29, 2012, Genzyme resubmitted supplement sBLA 103948-5139. FDA filed the application—the subject of this review.

2.6 Other Relevant Background Information

On May 02, 2007, the website Drugs.com reported that Genzyme Corporation and Bayer HealthCare Pharmaceutical had announced detailed interim two-year results from the CAMMS223 Phase 2 study which had been presented by Alasdair J. Coles, Ph.D., at the 59th Annual Meeting of the American Academy of Neurology (AAN) in Boston.⁵ This announcement came 4 or more months prior to randomization of the first subject in the unblinded CAMMS323 and CAMMS324 phase 3 trials.

⁵ http://www.drugs.com/clinical_trials/genzyme-bayer-healthcare-announce-detailed-interim-two-year-alemtuzumab-multiple-sclerosis-data-774.html. The 59th Annual Meeting of the American Academy of Neurology, Boston, Massachusetts occurred from April 28 to May 5, 2007.

3. Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

3.1.1 Quality

The submission was complete and there is no reason to believe it did not accurately portray the conduct and results of the clinical trials. The dataset documentation did not clearly delineate the derivations of analysis variables from fields on the case report forms. In general, the application did not convey objectivity and did not explore alternative explanations for the results that were reported. The submission did not explain unusual features of the trial such as the determination of baseline EDSS scores after randomization in many subjects. The discussion of the blinding was incomplete and did not adequately address FDA concerns about the extent of bias introduced by unblinded subjects and treating physicians or estimate the possible effects of unblinding patients and treating physicians on the interpretation of the results.

The quality of the design and conduct of the trials is the subject of sections 5 and 6, below.

3.1.2 Integrity

The sponsor reported problems with data quality at one of the clinical sites. The sponsor asserts that none of the problems could have had a significant impact on the evidence for effectiveness.

3.2 Compliance with Good Clinical Practices

The sponsor has provided statements asserting compliance with Good Clinical Practice.

3.3 Financial Disclosures

In the sBLA application Genzyme certifies that it has financial disclosure statements from all but 34 clinical investigators that demonstrate no proprietary interest in the product or significant equity in Genzyme. 13 sub-investigators in the CAMMS223 trial, 18 in the CAMMS324 trial, and 3 in the CAMMS323 trial did not provide financial disclosure information to the sponsor. The sponsor reports multiple attempts to obtain the information without success. The chief financial officer submitted a statement that Genzyme made no payments to the sub-investigators that did not complete disclosures.

Genzyme paid the 6 members of the adjudication panel. Genzyme states that the amount of compensation did not depend on the outcome of the trials.

Trial sponsorship by Bayer Schering Pharma was not mentioned in the submission but did appear in the published reports of the clinical trials.⁶ In response to a request for information, Genzyme explained that Bayer Schering Pharma collaborated with Genzyme and supported one-third of clinical development costs. In 2009, Genzyme acquired the rights to Campath (alemtuzumab) from Bayer; however, Bayer retained rights to co-promote the drug if approved for use in MS and may receive payments on any annual revenues in MS. Genzyme claims that they were directly responsible for the “design, conduct, monitoring, analysis, oversight, regulatory reporting and decision making relative to the Phase 2, Phase 3 and Extension studies of alemtuzumab per 21 CFR 312.” The financial disclosures for investigators involved in the 223, 323, and 324 trials did not include any financial interests or arrangements with Bayer. FDA requested financial disclosures regarding Bayer from investigators. Genzyme had not provided those disclosures by the time this review was completed.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

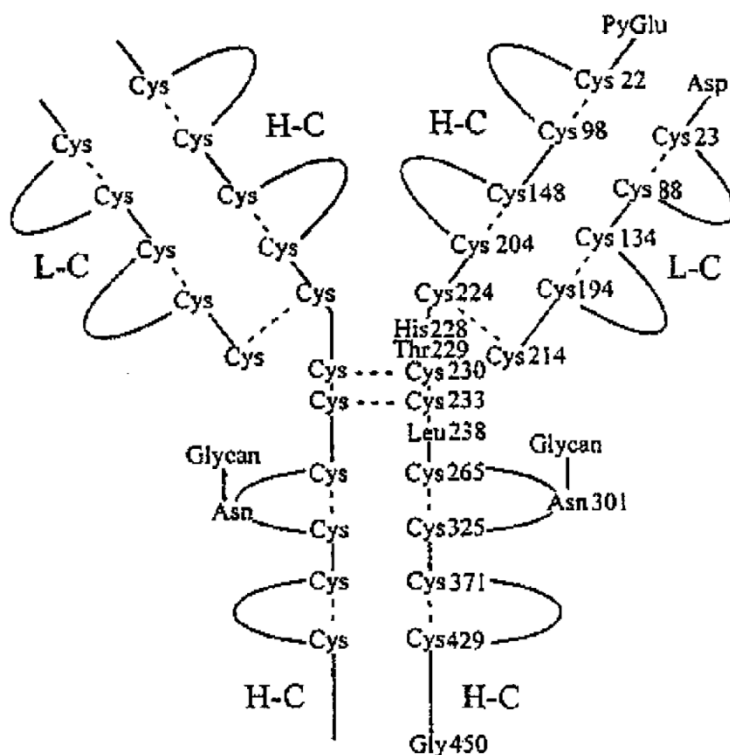
The material in this section summarizes information in the July 19, 2011, version of Genzyme’s Investigator Brochure.

Molecular Structure and Chemical Name

Alemtuzumab is a Y-shaped molecule consisting of two polypeptide chains linked by disulfide bridges.

Drug Molecular Structure

⁶ The CAMMS223 Trial Investigators, *N Engl J Med* 359;17. October 23, 2008; Jeffrey Cohen, CAMMS323, *Lancet*, November 1, 2012; Alastair Coles, CAMMS324, *Lancet*, November 1, 2012.



L-C indicates Light Chain

H-C indicates Heavy Chain

Physical, Chemical, and Pharmaceutical Properties

Alemtuzumab is genetically engineered humanized immunoglobulin G (IgG) monoclonal antibody derived from a rat monoclonal antibody that is specific for the cluster of differentiation 52 (CD52) cell surface glycoproteins found on human lymphocytes. The humanized antibody consists of the heavy and light chain variable domains of the rat monoclonal antibody grafted into a human IgG 1 kappa variable IgG framework to produce a humanized antibody that binds the human CD52 antigen.

4.2 Clinical Microbiology

See CMC Review.

4.3 Nonclinical Pharmacology/Toxicology

Barbara Wilcox, Ph.D. reviewed the nonclinical pharmacology and toxicology. She found no non-clinical issues that would block approval, but did note that there are no

adequate and well-controlled trials in pregnant women (she recommends pregnancy category C⁷ because of effects noted on sperm, increased fetal loss, and the potential for immunotoxicity from alemtuzumab transferred during pregnancy and lactation.) She recommends that women of child-bearing potential should use effective contraceptive measures when receiving a course of treatment and for the four subsequent months. Dr. Wilcox also noted that the sponsor did not submit an adequate pre- and postnatal developmental toxicity study: an additional study of physical and sexual development should be performed.

4.4 Clinical Pharmacology

See also the clinical pharmacology review.

Clinical investigation of alemtuzumab in MS began as early as 1994 with an uncontrolled trial in 7 subjects with secondary progressive MS using new gadolinium-enhancing lesions as a surrogate for disease activity.⁸ The investigators reported an early increase from baseline in the number of MRI Gd-enhancing lesions for three months followed by a significant decline after 6 months. The dose was 60mg given as a single course of 5 daily intravenous infusions of 12 mg per day for five consecutive days.

In 1999 the same investigators reported on the results of alemtuzumab tested using the same 60mg course of alemtuzumab in 27 subjects with clinically definite secondary progressive MS.⁹ Alemtuzumab showed MRI evidence of disease activity for several weeks after treatment but complete suppression of radiological markers of cerebral inflammation and the absence of new symptoms or clinical signs for the ensuing 18 months. The investigators also reported a transient recurrence of previous MS symptoms after the first dose of alemtuzumab. They also noted progressive disability and increasing brain atrophy using MRI spectroscopy. They concluded that

⁷ Pregnancy Category C: "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks."

⁸ Thibault Moreau, John Thorpe, David Miller, Ivan Moseley, Geoff Hale, Herman Waldmann, David Clayton, Mrk Wing, Neil Scolding, Alastair Compston. "Preliminary evidence from magnetic resonance imaging for reduction in disease activity after lymphocyte depletion in multiple sclerosis." *Lancet* 1994; 298-301.

⁹ Monoclonal AJ Coles, MG. Wing, P Molyneux, A Paolillo, CM Davie, G Hale, D Miller, H Waldmann, A Compston. "Antibody Treatment Exposes Three Mechanisms Underlying the Clinical Course of Multiple Sclerosis" *Ann Neurol* 1999;46:296-304

inflammatory mediators caused the early symptomatic reactivation of previously demyelinated lesions, that the anti-inflammatory activity of alemtuzumab prevented the formation of new lesions, but that axonal degeneration continued despite the suppression of new MRI lesions and contributed to progressive disability.

They hypothesized that treatment in multiple sclerosis must be given early in the course, “before the consequences of inflammation are irretrievably established.” In the discussion section of their report they went on to speculate that not all the manifestations of the disease are attributable to demyelination and remyelination and suggested that recovery from relapse is too rapid to be explained by remyelination, and that it is difficult to explain the transition from relapsing-remitting disease to continuous progression of disability by demyelination alone.

4.4.1 Mechanism of Action

Alemtuzumab targets the CD52 cell surface antigen found at high levels on most T and B lymphocytes and to a lesser extent on monocytes, natural killer T-cells, macrophages, and various tissues of the male reproductive system. Alemtuzumab binding to this antigen initiates cell lysis.

4.4.2 Pharmacodynamics

Alemtuzumab reduces lymphocyte count and activity. The sponsor describes clinical studies they claim show that MRI indicators of disease activity are reduced initially but begin to return after 15 to 18 months.

4.4.3 Pharmacokinetics

Figure 1 Estimates of Mean Serum Concentrations of Alemtuzumab from CAMMS-223 Trial¹⁰

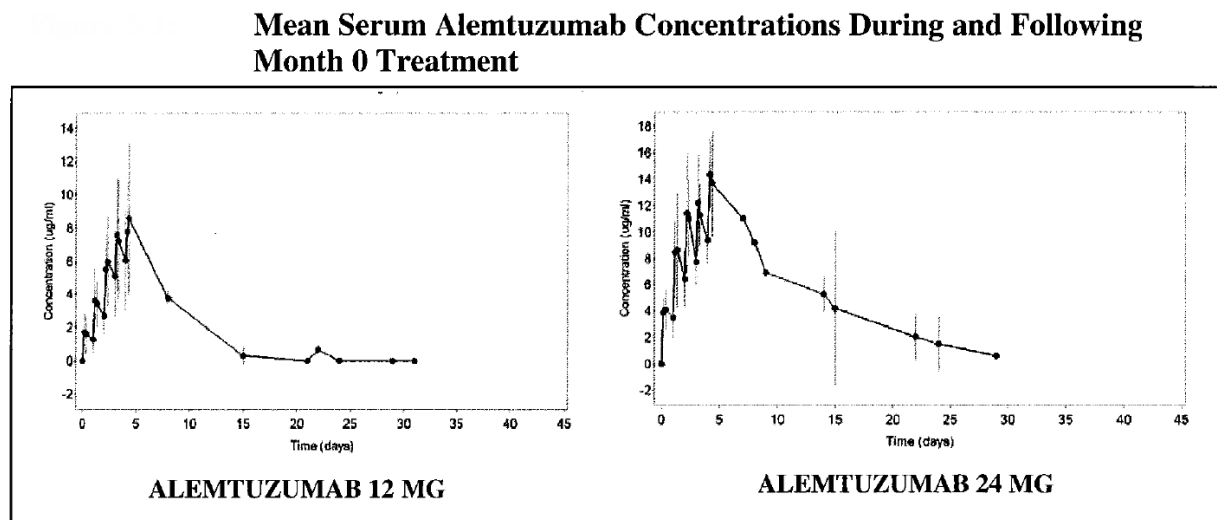


Table 3 Human Pharmacokinetics of Alemtuzumab from the CAMMS-223 Trial¹¹

Alemtuzumab Pharmacokinetic Parameters Through Month 0

	Alemtuzumab 12 mg/day		Alemtuzumab 24 mg/day	
C_{\max} (µg/mL)	N	Mean (SD)	N	Mean (SD)
Day 1	9	1.76 (1.12)	10	4.28 (1.34)
Day 5	9	8.96 (4.61)	9	15.24 (3.23)
Accumulation Ratio	9	5.99 (2.86)	9	3.77 (1.21)
C_{\min} (µg/mL)	N	Mean (SD)	N	Mean (SD)
Day 2	8	1.29 (0.76)	9	3.48 (1.57)
Day 5	8	6.09 (3.06)	7	9.40 (1.90)
Accumulation Ratio	7	5.26 (2.23)	7	3.09 (0.87)

C_{\max} = maximum serum concentration; C_{\min} = trough serum concentration; SD = standard deviation.

5. Sources of Clinical Data for Efficacy Analysis

For evidence of effectiveness for relapsing MS, Genzyme has submitted data and analyses from two phase 3 trials, one phase 2 trial, and, at the request of FDA, outcome data from one ongoing open-label extension safety study with subjects who completed one of the three trials.

¹⁰ Investigational-brochure.pdf 19-July-2011 page 30 of 99.

¹¹ Investigational-brochure.pdf 19-July-2011 page 30 of 99.

The sponsor designed the CAMMS223 phase 2 trial to test preliminary safety and effectiveness of alemtuzumab and guide the design of definitive phase 3 trials. At the time FDA reviewed the 223 trial, FDA notified the sponsor, and the sponsor agreed, that the results of the 223 phase 2 trial would not provide substantial evidence for a supplementary BLA for the treatment of MS.¹² Because of the 50% drop-out rate in the comparator interferon- β -1a group, the multiple starts and stops, multiple interim analyses, the smaller sample size, and the unblinded design, the 223 trial is inadequate to stand alone as evidence of effectiveness. In brief, the weaknesses in the conduct and design of the 223 trial make the results subordinate to those of the 323 trial in similar patients.

This section contains tables that provide an overview of the 223, 323, and 324 trials and detailed presentations of the protocols for each trial and the 3409 extension study.

The three trials were unusual among pivotal trials for FDA-approved MS treatments because there was no blinding of either the trial subject or the treating physician for the two primary clinical outcomes. The degree of bias introduced by the lack of blinding depends on the objectivity of the outcome measures and the consistency and thoroughness of the trial procedures for collecting the outcome data. Therefore, the summaries that follow place emphasis on the procedural aspects of the trial designs in order to help assess the extent to which the results of the trial can be attributed to differences in treatment rather than placebo effect or observer bias.

5.1 Tables of Studies/Clinical Trials

The tables in this subsection serve as an introductory overview for the detailed protocol descriptions in section 5.3. They are based on the last version of the protocol for each trial or study. A history of protocol changes pertinent to the efficacy analyses is provided in the detailed descriptions given below in section 5.3.

Table 4 below gives basic descriptions of the four clinical studies that comprise the sponsor's evidence to support their claim that alemtuzumab is a safe and effective treatment for relapsing remitting multiple sclerosis.

¹² See section 2.5.2, above, November 7, 2002.

Table 4 Sources of Clinical Efficacy Data

Trial Names	Time to Primary Outcome	Arms	N	Primary Outcome	Population
Phase 3 Trials					
323 CAMMS323 CARE-MS I	2 years	Alemtuzumab 12 mg Interferon- β -1a 2:1	581	Relapse Rate Time to SAD	Treatment Naïve RRMS
324 CAMMS324 CAMMS32400507 CARE-MS-II	2 years	Alemtuzumab 12 mg Alemtuzumab 24 mg Interferon- β -1a 2:2:1 then 2:1§	667 (840§)	Relapse Rate Time to SAD	RRMS with Relapse While on Treatment
Phase 2 Trial					
223 CAMMS223	3 years	Alemtuzumab 12 mg Alemtuzumab 24 mg Interferon- β -1a 1:1:1	334	Relapse Rate Time to SAD	Early, Active RRMS
Open Label Extension Study					
EXT Extension CAMMS03409		Alemtuzumab 12 mg	1320	None	Subjects who completed Trials 223, 323, or 324
§ In 324 the sponsor stopped alemtuzumab 24mg treatment arm late in the trial. The sponsor treated any comparisons of efficacy data using outcomes from the 24mg arm as exploratory. ¹³					

The 323 and 324 trials blinded the EDSS raters and had an independent relapse adjudication panel. However, in all three trials, unblinded trial subjects and treating physicians were the primary source of clinical outcome data. In addition to the open-label design there were numerous features of the trial designs that increased the opportunity for preferences and biases of trial subjects and treating physicians to have a significant impact on the trial results.

The three trial designs had many similarities. All three randomized trials used thrice-weekly subcutaneous interferon- β -1a (Rebif) 44 μ g as an active control. Investigators administered alemtuzumab in two courses one year apart, the first consisting of five

¹³ camms-integrated-summary-clin-efficacy-final.pdf, page 65 of 206

daily infusions of 12 or 24 mg (60 or 120mg), and the second consisting of three daily infusions (36 or 72 mg). Total alemtuzumab dose was 96 or 192mg.

All three trials compared annualized relapse rates and sustained accumulation of disability over 6 months (SAD). To help control bias implicit in clinical outcomes with unblinded open-label designs, the protocols for the 323 and 324 trials included blinded examiners for the EDSS, a Relapse Adjudication Panel, and blinded readings of sequential MRI T₂-lesion volume measurements.

The table below compares the selection criteria for the three trials in the submission and provides more detail than is available in Table 4, above. In brief, the 223 and 323 trials enrolled treatment-naïve subjects and the 324 trial enrolled subjects who had failed previous therapy with interferon- β or glatiramer acetate.

Table 5 Sponsor's comparison of Patient Selection for 223, 323, and 324¹⁴

Table 1-3: Overview of Patient Inclusion Criteria

Inclusion Criteria	CAMMS223	CAMMS323	CAMMS324
Patient Age (years)	18 – 50	18 – 50	18 – 55
Criteria for MS Disease Diagnosis	McDonald's update of the Poser criteria	McDonald's criteria	McDonald's criteria
Onset of MS Symptoms Prior to Study	Within past 3 years	Within past 5 years	Within past 10 years
Screening EDSS Score	0.0 to 3.0	0.0 to 3.0	0.0 to 5.0
MS Episode History	At least 2 clinical episodes in the 2 years prior to the study	At least 2 clinical episodes in the 2 years prior to the study plus at least 1 episode in year prior, with objective neurological signs	At least 2 clinical episodes in the 2 years prior to the study plus at least 1 episode in year prior, with objective neurological signs
MS Treatment History	Treatment-naïve	Treatment-naïve	≥ 1 MS relapse during treatment with a beta interferon or glatiramer acetate after having been on that therapy for ≥6 months
MRI Findings	At least 1 Gd-enhancing lesion during any of up to 4 monthly screening MRIs	Cranial MRI scan demonstrating white matter lesions attributable to MS	Cranial MRI scan demonstrating white matter lesions attributable to MS plus at least 1 of the following 1) ≥9 T2 lesions ≥3 mm in any axis, 2) a Gd-enhancing lesion ≥3 mm in any axis plus ≥ 1 brain T2 lesions, 3) a spinal cord lesion consistent with MS plus ≥ 1 brain T2 lesions

EDSS = Expanded Disability Status Scale; Gd = gadolinium; MRI = magnetic resonance imaging;
MS = multiple sclerosis

¹⁴ From the sponsor's ISE page 25/206.

5.2 Review Strategy

Because the three trials lacked blinding, the primary focus of the review is to determine whether the three trials adequately controlled for bias and placebo effect, i.e., they were well controlled. The overall clinical review strategy is to describe and compare the design, results, and protocol compliance for each trial or clinical study before presenting the reviewer's assessment of the degree to which the application provides substantial evidence of safety and effectiveness. That assessment will consider the results as reported by the sponsor, the consistency of the results within each trial and between trials in the application. The evaluation of efficacy summarized in sections 6.12 to 6.15, below.

5.3 Design of Individual Clinical Studies and Clinical Trials

This section describes the design of the 3 efficacy trials and the associated extension study: 323 first, then 324, 223, and extension 3409. For clarity and brevity, after Trial 323 is described in full detail, each subsequent description builds on those that precede it. The section concludes with side by side comparisons of important design features of the trials to facilitate understanding the relationships between the methods presented in The Review of Efficacy in section 6, to follow.

For each trial, the description of the design in this section is based on the final version of the protocol. In addition, there are detailed histories of protocol amendments in relation to key trial milestones because significant changes to the trial designs occurred after randomization of the first subjects. In section 6.12, the summary of efficacy, below, there is a summary of the unusual trial design features that increase the potential for bias to play a significant role in the trial results.

5.3.1 Trial 323: Design

The 581-subject CAMMS323 two-to-one randomized, active-control, and open label trial compared IV alemtuzumab 12mg given daily for 5 days then again one year later for 3 days to thrice weekly subcutaneous injections of interferon- β -1a 44 μ g for two years for reducing relapse rate and time to sustained disability in subjects with newly diagnosed and untreated relapsing remitting multiple sclerosis.

5.3.1.1 323 Primary and Secondary Outcome Measures

The two co-primary outcome measures are

- (1) time to 6-month SAD, and
- (2) relapse rate.

Secondary outcome measures are (in order of hierarchical analysis):

- (1) Proportion of patients who are relapse free at Year 2
- (2) Change from Baseline in EDSS at Year 3
- (3) Acquisition of disability as measured by the MSFC at Year 2
- (4) Percent change from Baseline in MRI-T2 hyperintense lesion volume at Year 2

Seventeen additional tertiary outcomes are listed in Appendix 9.3 on page 89 below.

5.3.1.2 323 Trial Primary Efficacy Analysis

Trial 323 primary outcomes are time to SAD and relapse rate. The final version of the protocol specifies a two-step primary efficacy analysis on the available 2-year follow-up data for all subjects treated with study drug adjusted for multiple comparisons via the Hochberg method. A positive result requires either a statistically significant difference between alemtuzumab and interferon beta-1a in time to SAD at a 5% confidence level, or a reduced relapse rate at a 2.5% confidence level.¹⁵ The protocol specifies that comparison of the SAD endpoint events would use a Cox proportional hazards regression model with treatment group indicator and geographic region as covariates in the model, and that comparison of the relapse rate event would use the proportional means model with the same covariates.¹⁶

The statistical analysis plan¹⁷ described the Hochberg adjustment for multiplicity somewhat differently. Instead of a two-step procedure, p-values were to be estimated for each primary event type. The trial outcome would be positive if the maximum of the two p-values for the difference between alemtuzumab and interferon beta-1a in time to SAD and relapse rate was ≤ 0.05 or the minimum was $\leq .025$. The results of the 323 trial are reported as positive because, although the p-value for SAD is 0.1325, the p-value for relapse rate is less than 0.025 (<0.0001).

The final SAP stipulates a Cox proportional hazards (PH) regression with robust variance estimation (Lin and Wei 1999) to determine the difference between treatments

¹⁵ The statistical review does not describe the two types of event (relapse, SAD) as “co-primary” outcomes because success with either outcome alone is viewed as a “positive” trial if the Hochberg criteria are satisfied, i.e., you can win with positive results for only one of the two primary outcome events.

¹⁶ 323 Trial final protocol (camms323-16-1-1.pdf, page 1526/1688)

¹⁷ Statistical Analysis Plan, Version 3, January 31, 2011 (camms323-16-1-9.pdf, pp. 40-1 of 161)

for the SAD co-primary endpoint using all patient follow up data with treatment group and geographic region as PH covariates. The Wald test of the log hazard ratio (estimated regression coefficient from the model) determines the p-value. In this analysis, the absence of outcome data has no effect on the results.

For the relapse rate outcome, the annualized relapse rate (ARR) is not used. The final SAP stipulates that the treatment group comparison is based on all follow-up data using the proportional means model (equivalent to the Anderson-Gill multiplicative intensity model with robust variance estimation). This model allows for the relapse rate to change over time but assumes that the relapse rate ratio between the treatment groups is constant over time. The time to relapse is measured from the start of treatment and not the time from randomization. Covariates are treatment group and geographic region. This model does not produce an estimate of the annualized relapse rate (ARR). The p-value will express the chances that the logarithm of the rate ratio estimated by the model's regression coefficient differs from 0 due to chance alone.

In order to provide an estimate of the ARR, the sponsor will use a negative binomial model with robust variance estimation to estimate the ARR. The observed number of relapses will be the dependent variable, the log total amount of follow-up from date of first study treatment for each patient will be the offset variable and treatment group indicator and geographic region will be the covariates in the model.

Sample Size¹⁸ The sponsor estimated that 525 subjects were needed to demonstrate a 60% relative treatment effect with 95% or more confidence for the time to SAD. The sample size calculations anticipated the following:

- a logrank test for the test of statistical significance
- 2:1 randomization
- an exponential distribution of the time to SAD
- 20% two-year SAD incidence in subjects on interferon beta-1a (equivalent to a - 0.11 hazard rate assuming an exponential time to SAD distribution)
- a hazard ratio of 0.40 comparing alemtuzumab to SC - interferon beta-1a
- accrual period of approximately 1 year
- analysis of SAD based on the 2-year follow-up data
- 10% dropout rate

¹⁸ The SAP Version 3.0 in Appendix 1 (camms323-16-1-9.pdf, page 62) does not describe the sample size calculation, referring to the protocol. Hence, this sample size description comes from the final 323 protocol, Amendment 5, May 11, 2010, camms323-16-1-1.pdf, page 1424/1688.

-a 2-sided significance level of 5% (first step of Hochberg procedure)

5.3.1.3 Consent

Patients signed consent forms before investigators performed screening tests to determine eligibility. The 20 page consent form template for the trial concludes with a section describing withdrawal from the trial. The consent form contained the following statement:

If your disease becomes worse during treatment, you will be told and the study treatment will be stopped and alternative medical care will be discussed with you.

Subjects could enroll in the trial with the understanding that any report of a relapse or increasing disability could lead to a change in the availability of the study treatment. This knowledge could influence their reporting of relapse events and their performance during testing to determine EDSS ratings.

5.3.1.4 323 Screening and Patient Selection

After giving informed consent, subjects began a screening process that could last as long as 35 days before randomization or 56 days if they experienced a relapse or infection. During the screening process, investigators obtained the following:

- Medical and neurological history including history of previous relapses
- EDSS by the blinded rater
- MSFC (initial and 2 repeats to minimize the impact of practice effects);
- Physical examination
- Reports of AE that occur during screening
- Results of central laboratory assessments including thyroid function, lymphocyte phenotyping, HIV, hepatitis B and C
- Cranial MRI performed with and without gadolinium contrast.

There protocol contains 44 criteria for selecting subjects for randomization and treatment in the 323 trial. Appendix 9.1 below lists all of the criteria.

In brief, the protocol required subjects to have RRMS onset within 5 years, 2 or more MS episodes in the two years prior to starting the screening period, one or more relapses in the year prior to the start of the screening period, EDSS score 0 to 3.0, and no prior MS therapy other than corticosteroids. Except for MS, the subjects had to be in good general health.

A footnote to the schedule in the trial protocol specifies that the screening EDSS is to be performed by a blinded rater, but does not require that the same screening EDSS rater will continue to perform the EDSS after randomization.¹⁹

5.3.1.5 Schedule

The following schedule is adapted from the 323 trial protocol (Table 6). One feature to notice is that randomization is not included in the table—it precedes “Month 0.” “Month 0” is the same as “Baseline.” An important feature of the schedule is that the interferon- β -1a and alemtuzumab groups (R and A in the schedule) had different event schedule.

Table 6 323 Trial Schedule adapted from trial protocol²⁰

Schedule for CAMMS323 and 324 Trial																									
EVENTS	MONTH																								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
EDSS	x			x			x			x			x			x			x			x			x
MSFC plus Sloan charts	x						x						x						x						x
SF-36	x												x												x
FAMS and EQ-5D	x						x						x						x						x
Pregnancy test	x												x												x
Basic or Expanded Imaging	x												x												x
Chemistry	x	R		x			x			x			x			x			x			x			x
Serum creatinine		A	A		A	A		A	A		A	A		A	A		A	A		A	A		A	A	
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Thyroid Function				x			x			x			x			x			x			x			x
Lymphocyte Phenotyping		A		x			x			x			x	A		x			x			x			x
Urinalysis	x	A	A	x	A	A	x	A	A	x	A	A	x	A	A	x	A	A	x	A	A	x	A	A	x
Autoantibody sample	x						x						x						x						x
Sample for antibodies to study drug	x	A		A									A	A		A									x
Pharmacokinetic samples	A	A		A			A						A	A		A			A						
Semen samples	x	x		x			x			x			x	x		x			x			x			
Unblinded physician review/PE/VS	x	R		x			x			x			x	R		x			x			x			x
HRUQ (at selected study centers)	x			x			x			x			x			x			x			x			x
CARE-MS Monthly Monitoring	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Methylprednisolone administration	x												x												
Alemtuzumab administration	A												A												
Initiation of Rebif titration	R																								
Rebif drug accountability				R			R			R			R			R			R			R			R
Assessment of blinding for assessors													x												x

¹⁹ camms323-16-1-1.pdf, page 1550 of 1688.

²⁰ camms323-16-1-1.pdf, page 1548; camms324-16-1-1.pdf, page 1294

Schedule for CAMMS323 and 324 Trial																									
EVENTS	MONTH																								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
AEs and Concomitant Medications	x			x			x			x			x			x			x			x			x
“x” = all patients; “A” = only alemtuzumab patients; “R” = only Rebif (SC interferon-beta-1a) patients																									

5.3.1.6 323 Randomization

At the end of the screening period, investigators randomized eligible subjects.

The protocol specified randomization in a 2:1 ratio (alemtuzumab: interferon- β -1a) stratified by center in blocks of three. The protocol and SAP restricted knowledge of the block size until after the database is locked. The randomization period extended 35 days after the subject gave informed consent unless the subject experienced a relapse or infection. In that case, the randomization period extended to 56 days. Investigators called an interactive voice response system, ClinPhone, managed by Perceptive Informatics, 2 Federal St, Billerica, MA 01821, USA, for treatment arm assignments.

The protocol called for blinding of EDSS, MSFC, and Sloan chart raters. The protocol did not require blinding of trial subjects or the clinical site staff that cared for them.

5.3.1.7 Baseline Period

The baseline period is unusual because baseline measurements including the baseline EDSS and MRI occur after randomization but before the subject gets the first dose of the study treatment. The protocol sets 14 days as the maximum time allowed from randomization to the start of treatment.²¹

However, if a subject experiences a relapse during the baseline period, the start of treatment and completion of baseline assessments is delayed until either 1) day 30 from relapse onset, or 2) the day that an investigator determines that the subject is neurologically stable.

Development of an active infection during the baseline period delays the start of treatment and completion of baseline testing until the infection resolves.

²¹ camms32400507-16-1-1.pdf, Section 9.1.3, Version 4, CAMMS324 Protocol, page 1218 of 1438

5.3.1.8 Treatment

The baseline period ends when treatment starts. A feature of this trial is that the start of treatment marks the end of the variable-length baseline period that follows randomization. The start of treatment then serves as a reference date for the co-primary outcome measures, relapse rate and time to SAD.

The protocol treatment regimen for a subject assigned alemtuzumab is as follows:

- At investigator's discretion:
 - Long-acting non-sedating antihistamine 1 day prior to all infusions
 - Antihistamine 30-60 minutes immediately before alemtuzumab
 - Cimetidine or ranitidine if additional antihistamine activity needed
 - Pretreatment with acetaminophen 30-60 minutes prior to alemtuzumab
- Methylprednisolone 1 gram IV over one hour (Days 1, 2, and 3 of Months 0 and 12).
- Alemtuzumab 12 mg/kg IV infusions over at least 4 hours. (At month 0, Days 1, 2, 3, 4, and 5, and Month 12, Days 1, 2, and 3) in a supervised medical facility.
- Recommended observation for 1 to 2 hours following each infusion
- Acyclovir 200 mg twice daily (or a therapeutic equivalent) starting on the first day of each alemtuzumab cycle and continuing for 28 days after the last day

Section 8.1.4 of the protocol specifies that the start of the Month 0 5-day or Month 12 3-day cycles be delayed if a subject received steroids for treatment of a relapse within 30 days or has an unresolved infection.²² For the Month 0 cycle, the start of treatment should also be delayed if the subject has a relapse in the prior thirty days whether or not treated with steroids. If a cycle is interrupted, an investigator could give missed doses within one month of the start of the cycle. A separate part of the protocol (Section 9.1.3) adds the possibility of completing the baseline evaluation and starting treatment before 30 days after the onset of a relapse if the [unblinded treating] investigator is of the opinion that the subject is neurologically stable.²³

The protocol regimen for a subject assigned interferon- β -1a is as follows:

- Rebif interferon- β -1a 44 μ g by SC injection 3-times weekly for two years
 - Initial titration over 4-weeks
 - 20% dose the first 2 weeks
 - 50% dose the next 2 weeks

²² camms323-16-1-1.pdf, page 1461 of 1688.

²³ camms323-16-1-1.pdf, page 1473 of 1688.

-Full dose until two years.

--Methylprednisolone 1 gram IV over one hour (Days 1, 2, and 3 of Months 0 and 12), preferably at the same time of day and in the morning.

Start of interferon- β -1a treatment is modified, interrupted, or delayed if a subject develops depression, symptoms of liver dysfunction, elevated serum GPT or ALT, or if the full dose is poorly tolerated. If a patient assigned to SC interferon beta-1a has a relapse within 1 month prior to initiation of treatment at Month 0, completion of baseline assessments, premedication with methylprednisolone and initiation of interferon- β -1a treatment should be deferred until the patient is, in the opinion of the Investigator, neurologically stable, or for a maximum of 30 days from the start of the relapse (see also Section 9.1.3).

The treatment regimen differs for the two arms of the 323 trial in the following aspects:

Alemtuzumab vs. interferon- β -1a

Antihistamine vs. no antihistamine

Acyclovir vs. no acyclovir

5.3.1.9 Follow-up Contacts

The sponsor conducted a Monthly Monitoring Survey (MMS) to screen for ITP and hematuria in all subjects. Subjects responded to 12 questions about bruising, petechiae, and bleeding using paper forms, telephone calls to the clinical site, or automatic telephone or internet systems.

Safety monitoring required monthly visits to a laboratory or home visits by a phlebotomy service for drawing blood to test serum platelet counts for all subjects and serum creatinine as well as collecting urine for urinalysis from alemtuzumab subjects. The protocol scheduled these contacts to collect blood and urine samples between the monthly MMS calls.

Every three months the protocol calls for an EDSS score determined by the blinded rater, additional laboratory tests, and examination by the treating physician. Some special testing is done in only the alemtuzumab subjects. Drug accountability is done only for the interferon- β -1a subjects. The protocol required a physical examination and vital signs at the Month 1 visit for interferon- β -1a subjects but not for alemtuzumab subjects.

At months 12, 24, and the end of study (EOS), the blinded raters are expected to perform the EDSS, MSFC and Sloan eye chart tests for all subjects. Other yearly tests include the SF-36, FAMS, EQ-5D and MRI imaging followed by the treating physician

examination. Before administering the month-12 treatment cycle, the investigators screened subjects for disqualifying events or conditions: malignancy, bleeding disorder, major systemic illness, interfering medical or psychiatric condition, low platelet count, abnormal lymphocyte cell type counts, reduced neutrophils, and any sign of infection that could be exacerbated by alemtuzumab.

The protocol required statements from the blinded raters regarding knowledge of the treatment assignment. If a rater acknowledged unblinding in the answer to the rater-blinding question or by notifying the Principal Investigator, a backup rater must perform all subsequent blinded assessments.

5.3.1.10 Discontinuation

The protocol provides a list of acceptable reasons for stopping the trial treatment at any time during the trial regardless of treatment arm:

- Investigator considers it would be in the best interests of the patient
- Patient requests discontinuation
- Unacceptable toxicity of the study drug(s), either alemtuzumab (eg, autoimmune hemolytic anemia, autoimmune thrombocytopenia) or SC interferon beta-1a
- Female patient becomes pregnant
- Patient fails to use adequate birth control
- Patient is unable or unwilling to comply with the protocol²⁴

The protocol states that investigators should encourage subjects who discontinue trial treatment to continue with all safety and efficacy assessments until two years after their enrollment date. At the time of discontinuation subjects are allowed to switch to another approved multiple sclerosis treatment. Subjects become eligible to enroll in the extension study if they complete the full two years of the trial, whether or not they discontinue the trial treatment.

The protocol required investigators to reassess eligibility of all alemtuzumab subjects at the Month 12 visit just prior to the second course of alemtuzumab. If investigators found disqualifying medical or social conditions, they withheld the second course of alemtuzumab and reported that the subject had discontinued trial participation.

Category of discontinuation

Patient or physician determined

²⁴ camms323-16-1-1.pdf, page 1457 of 1688.

Alemtuzumab: failed eligibility reassessment before 12 month course
Status after discontinuation
 No contact
 Follow-up in trial to completion
 Alemtuzumab: safety follow-up
Treatment after discontinuation
 Unknown
 Alternate MS therapy
 No alternate therapy
Trial completion status
 Completed Trial
 Did not complete trial
Extension study status
 Enrolled in extension trial
 Did not enroll in extension trial

The case report forms included a 2-page completion/discontinuation form. The form contained fields for entering a completion/discontinuation date, date of last dose, whether the subject completed the protocol, whether the subject completed the treatment protocol, and whether the subject would participate in the 3409 Extension Protocol.

5.3.1.11 Concomitant medications

The 323 trial protocol allowed no concomitant therapy with any other disease-modifying MS treatments (including interferons, chemotherapeutic agents, natalizumab, mitoxantrone, IV immunoglobulin, glatiramer acetate) without approval. The protocol allowed alternate MS treatments if the subject discontinued the trial treatment. Even if a subject discontinued treatment, investigators were to obtain complete follow-up until 2 years after initiation of treatment at Month 0. The protocol did not allow experimental treatment after discontinuation.

In the relapse assessment section, the protocol allowed the treating neurologist to determine whether to use of corticosteroids to treat relapses. The protocol reiterated that treatment had to start after assessment by the blinded rater. This reiteration emphasizes that the order of assessments during a relapse visit is optional, although, strongly recommended. The datasets did not document the order of assessments or the actual date and time of the assessments. In this same section the protocol permitted corticosteroid use to treat relapses for non-MS-related diseases.

The protocol proscribed the use of live vaccines for alemtuzumab-treated subjects for 30 days prior to the start of treatment and throughout the trial.

The protocol required all subjects to receive one gram of methylprednisolone IV (MP) for three consecutive days beginning at Month 0 and Month 12. Each site chose whether to dilute the MP with 0.9% NaCl or 5% dextrose according to hospital package insert requirements or hospital policies. At their discretion, treating physicians could choose to reduce the dose for subjects intolerant of the full dose. The time for administration was immediately prior to alemtuzumab or approximately the same time, preferably in the morning, for the interferon- β -1a group. This time of administration was not recorded in the concomitant medications dataset.

The protocol allowed physicians to choose to delay MP premedication if an alemtuzumab subject had an infection or had been treated with corticosteroids for a relapse within 30 days. The delay was until the infection resolved or until 30 days after corticosteroid relapse treatment began. For interferon- β -1a subjects, the protocol required omission of the MP infusion.

The protocol required that all assessments precede premedication with MP but did not require data collection to confirm that investigators followed this requirement.

To prevent HSV in alemtuzumab subjects, the investigators chose 28-day courses of acyclovir 200mg daily or a therapeutic equivalent (not specified). These medications were reported along with other concomitant medications.

5.3.1.12 Relapse event

The relapse rate outcome is determined by relapse events. Recognition, management, and reporting of relapse events depended primarily on the unblinded subject, and secondarily the unblinded treating physician. The 323 protocol defines a relapse event as:

*New neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms must be attributable to MS, last at least 48 hours, be present at normal body temperature (ie, no infection, excessive exercise, or excessively high ambient temperature), and be preceded by at least 30 days of clinical stability.*²⁵

This definition of relapse rate is repeated in the statistical analysis plan.

²⁵ CAMMS323 protocol, Amendment 5, page, 1492 of 1688.

The paragraph following the definition of on-study relapse cited above states that

*An exacerbation, or recurrence, of symptoms and signs in a patient with MS that can be reasonably attributed to transient impairment of conduction in previously demyelinated pathways due to drugs (such as rarely occurs a few hours after injections of interferon beta), raised core body temperature (the “Uhthoff phenomenon”), or systemic cytokine release (such as occurs with the first dose of alemtuzumab) will not be considered a relapse. Sensory-only relapses without a change in objective signs on neurological examination will not be considered a relapse post-treatment, except in cases in which the sensory symptoms are part of a paroxysmal attack. Single paroxysmal attacks (e.g., trigeminal neuralgia, tonic spasm) do not constitute a relapse, but multiple episodes occurring over not less than 48 hours do.*²⁶

The protocols, RAP charter, and operations manuals lacked procedures to ensure adequate documentation or consistent interpretation of this second paragraph by the unblinded treating physician.

The On-Site Relapse assessment form (OSRAF) in eCRF describes clinical features of relapse events that are not part of the protocol definition. See Table 7 for a summary of all the fields in the form.

The OSRAF does not contain the date and time that the subject reported the relapse. Therefore it is not possible to determine the extent to which subjects complied with the protocol recommendation to report relapses within 48 hours. In addition, there were no call log records to determine whether investigators reported all possible relapses as clinical events.

The OSRAF changes the protocol relapse definition by requiring objective changes to correspond to current relapse symptoms. If a relapse lasts more than 48 hours but is not assessed before the symptoms resolve, then the lack of “current” symptoms at the time of the assessment requires a judgment from the unblinded investigator assessing the possible relapse and eventually the Relapse Adjudication Panel.

The protocol, training material, and statistical analysis plan do not explain how assessors are to use OSRAF item #8 (onset over hours and days) and item #10 (objective change in “current” relapse symptoms and reference to EDSS) to determine of whether MS caused an event (item #11). In addition, there was no mention of how a fever was to be documented for item #7 or an explanation of the difference between “fever” in the OSRAF and the presence of symptoms when body temperature was elevated. Item #11

²⁶ From camms323-16-1-6.pdf, page 1236 of 1438, section 9.2.3 On-Study Relapse:

contains the data item that indicates the unblinded treating physician's determination of the cause of the clinical event: "MS" or "other." The wording of Item #11 is open to the interpretation that if the clinical event is not a relapse, then the symptoms are attributable to another cause and that cause is reported as an adverse event. The eCRF Completion Guidelines indicate that item 11 cannot be left blank, but does not resolve whether that applies all of the data elements that compose item 11. Specifically, it does not clarify whether there must be an AE and does not indicate that the adverse event number is required for all AEs. This creates uncertainty that MS relapses may have been classified as adverse events rather than clinical events.

Table 7 On-Site Relapse Assessment Form Filled Out by Unblinded Treating Physician

Table of Data Items in On-Site Relapse Assessment Form for 323		
Item Number	Description of Data Field	Choices and options
1	Onset date	
2	End date	
3	Method used to classify event	<i>EDSS and other</i>
4	Assessor	<i>Blinded Neurologist or Other Physician</i>
5,6	Laboratory tests described	
7	Was patient symptomatic over any continuous forty eight hour period in the absence of documented fever?	
8	Was onset acute? (i.e. over hours or days)	
9	Was the current event preceded by at least 30 days of clinical stability? (i.e. no deterioration)	
10	Was there an objective change corresponding to current relapse symptoms? (i.e. increase of one point on two FS scales or two points on one FS scale or increase on EDSS score)	
11	Symptoms attributable to:	<i>MS or Other and AE Number(s)</i>
12	Was patient treated with corticosteroids for this event?	<i>Yes, add to concomitant medications page or No</i>
13	Description of symptoms	

The protocol and RAP Charter did not provide instructions to the Relapse Adjudication Panel implementing the key concepts in the definition of relapse.

5.3.1.13 Relapse Adjudication Panel (RAP)

Genzyme established a Relapse Adjudication Panel consisting of six neurologist experts in MS clinical research to assess the clinical events that the treating neurologists evaluated as suspected on-study relapse events. An independent organization, ACI,

coordinated the activities of the RAP and prepared electronic dossiers for each suspected relapse event.

The charter for the RAP, Version 1.0, August 11, 2010, specifies that two reviewers will review a subset of data from the electronic case report forms and vote whether or not the relapse qualifies as a protocol-defined relapse. If the two disagree, then a third reviewer decides the case.

The charter states that the RAP review will be blinded, but does not describe how eCRF data will be filtered before transfer to the RAP reviewers. An example of a dossier is attached to the charter with test data. That sample includes the treating physician's opinion regarding the cause of the event ("MS" or "other") in addition to a list of adverse events, EDSS scores, and whether the subject received steroids in association with the clinical event. MRI data was not shown in the dossier prototype. The data processes for the RAP are described in the ACI Data Review Guidelines, which were not submitted.

The ISE states that the treating neurologist did not record whether the events were MS relapses. However, the eCRF and OSRAF contained data elements that indicate whether a subject had or is experiencing a relapse and also whether the symptoms of a clinical event are attributable to MS or not.²⁷

The ISE also states that the sponsor transferred data relevant to assessment of relapses to ACI, which prepared blinded case dossiers containing on-site relapse data, vital signs, AEs, physical examinations, EDSS scores, medical history, and clinical episode history. MRI data were not provided to the RAP. The ISE states that ACI performed additional programmatic checks on free text fields pertaining to Adverse Events and Physical Examination findings for data points that were part of the relapse dossier. The application did not document these procedures.²⁸

5.3.1.14 Sustained Accumulation of Disability (SAD) at 6 months

The protocol defines SAD at six months as follows:

SAD: for patients with a Baseline EDSS score of 0.0, SAD is defined as an increase of ≥ 1.5 points sustained over a 6-month consecutive period. For patients with a Baseline EDSS score of ≥ 1.0 , SAD is defined as an increase of ≥ 1.0 point sustained over a 6-month consecutive period.

²⁷ camms-integrated-summary-clin-efficacy-final.pdf, page 44 of 206.

²⁸ camms-integrated-summary-clin-efficacy-final.pdf, page 46 of 206.

To implement this definition, the SAP²⁹ expects, but does not require, three EDSS scores at consecutive scheduled visits to establish the occurrence of a SAD event. The trial schedule requires rater-blinded EDSS assessments every 3 months (± 2 weeks) and when the subject reports a relapse clinical event. According to the SAP, a 6-month SAD event occurs when two consecutive EDSS determinations at least 155 days apart (5.09 months) confirm a change from baseline of either 1 point (baseline ≥ 1) or 1.5 points (baseline = 0). The SAP anticipates that most SAD events will be characterized by three EDSS scores (EDSS at start of SAD event, then at 3 and 6 months to confirm the duration of the event and the fact that it is sustained for more than three months). However, the SAP makes the following exceptions:

1. If a scheduled EDSS assessment is reported, 2 consecutive EDSS assessments at least 6 months apart will be sufficient to establish SAD.
2. When a patient leaves the trial early, or at the time a patient completes 24 months of follow up, if the last 2 EDSS scores are at least 3 months apart and indicate the potential onset of SAD, the convention will be to declare that the patient has reached the SAD endpoint. The unscheduled end of study EDSS visit will be used in this calculation if available.

The SAP does not limit the number of missed Visits between two confirmatory EDSS scores.

The SAP excludes all unscheduled EDSS assessments from SAD determinations unless they are done at the time a subject discontinues participation in the trial. The SAP does not exclude scheduled EDSS visits that coincide with the assessment of a possible relapse.

5.3.1.15 EDSS Measurement

The sustained accumulation of disability (SAD) outcome depends entirely on a sequence of EDSS scores determined by treatment-blind raters. Although not specified in the protocol or operations manual, the co-primary relapse rate may also have depended on the EDSS score to some extent because item #3 in the eCRF for the relapse assessment form included EDSS as a choice for the method used to classify the relapse event (see Table 7). In addition the eCRF and relapse assessment form used a change in the EDSS as an example of an objective change corresponding to current relapse symptoms.

²⁹ camms323-16-1-9.pdf, page 19 of 161

Blinded Rater Qualifications. The 323 protocol states that “all study centers will be attended by at least 2 neurologists: a Treating Neurologist responsible for patient care and a Blinded Neurologist responsible for administering and scoring (or overseeing these tasks) key efficacy assessments and confirming on-study relapses”³⁰ and that “all treating and blinded neurologists will be trained and certified to perform the EDSS in a consistent manner.”³¹ However, the integrated summary of efficacy describes the professional qualifications of the EDSS raters differently: “all EDSS raters were physicians with a minimum of 2 years of neurology training or experience (i.e., had completed 2 years of a neurology residency or fellowship training program) or other licensed health professionals (such as a nurse practitioner, physician assistant, or similar clinician) with at least 2 years prior experience performing similar exams.”³²

Investigators obtained and maintained certification through an internet site, “neurostatus.net.”³³ The Neurostatus system is well known in MS trial community. The ISE did not describe the reliability and validity of the EDSS when raters were certified by Neurostatus. The protocol does not describe criteria or frequency of certification testing. Appendix C of the protocol contains a standardized Neurostatus Scoring Sheet for reporting results and instructions that “[t]he EDSS will be administered as described in the ... [Neurostatus Scoring] form with 2 exceptions: 1. The abdominal reflex test (“Cutaneous” reflex on the Neurostatus form) will not be routinely tested because the presence of abdominal injection marks could inadvertently unblind the blinded assessor. 2. Fatigue will not be included in the EDSS scoring.”

Section 5.3.1 of the 323 Standard Operating Manual states that EDSS certification is obtained through the neurostatus.net internet training site.³⁴ The SOM mentions that Neurostatus grants several levels of qualification to perform the EDSS, but does not describe the level required for the 323 trial or how often the certification expires and must be renewed. In datasets provided in the application, it is mentioned that a test score of 30 or greater out of 50 is a passing score for website certification. Training was conducted by Neurostatus representatives at investigator meetings or could be obtained

³⁰ camms323-16-1-1.pdf, page 1533 of 1688

³¹ camms323-16-1-1.pdf, 1491 of 1688

³² camms-integrated-summary-clin-efficacy-final.pdf, page 31 of 206

³³ “Access to and use of this site ('Neurostatus.net') is provided by Prof. Dr. L. Kappos, Outpatient Clinic Neurology-Neurosurgery, University Hospital Basel & Regarde, Franz Schnyder, Basel”

³⁴ ise-appendix-8-3.pdf, page 34 of 2777.

by completing the Neurostatus training CD/DVD and passing an electronic test. Certification was documented through the Neurostatus web site.

The EDSS is a complex clinicometric tool that is based on the neurological clinical examination. The different elements of the test are categorized by seven functional areas that are combined to determine the EDSS step," a measure of disability. There are 136 elements possible for each EDSS score. 105 are required and 31 are optional tests of neurological function. See Appendix 9.5.

Determination of the baseline EDSS is a key reference datum for subject selection and determination of SAD. The protocol defines Baseline EDSS as "the EDSS at Month 0 or, if there has been a relapse within 1 month prior to Month 0, Baseline EDSS will be the score at 1 month (30 days) after the onset of a relapse." The time to perform the Baseline EDSS can be arbitrary, depending on the treating neurologist to determine that neurologic stability allows the start of treatment sooner than 30 days after relapse onset. In all cases, the baseline EDSS is determined after subjects are randomized and can know their treatment group assignment.

5.3.1.16 Relapse assessment

Protocol amendment 5 *strongly recommends* a 7-step process for any relapse evaluation visit:³⁵

- (1) *Patient calls the center within 48 hours of symptom onset to report suspected relapse and presents for evaluation unless it is very clear that symptoms are not MS related*
- (2) *Patient visits the center within 7 days of symptom onset*
- (3) *Blinded Neurologist performs examination to document the Functional System Scores (FSS) and EDSS, with no reference to previous scores. Conversation between Blinded Neurologist and patient should elicit only the minimum historical information needed to complete these tasks (eg, recent sphincteric dysfunction).*
- (4) *Treating Neurologist or unblinded designee performs physical examination, obtains vital signs, and takes a history of recent symptoms.*
- (5) *Supportive laboratory testing, as indicated, is performed*
- (6) *Treating Neurologist completes Clinical Event source documents. Treating Neurologist also determines whether there is a fever or other disqualifying event.*
- (7) *If the Treating Neurologist determines treatment for relapse or other clinical event is warranted, treatment can be initiated after the Blinded Neurologist's assessment is complete. Apart from the protocol-specified annual 3-day cycle of methylprednisolone, it*

³⁵ camms323-16-1-1.pdf, page 1489 of 1688.

is expected that patients will receive corticosteroids during the study only for treatment of MS relapses or when indicated for non-MS related diseases.

The protocol did not require clinical sites to collect information about calls from subjects to report clinical events. The protocol and operations manual did not require investigators to track and report the time and date of calls, who received calls, or whether the symptoms were clearly not related to MS. In the protocol, it is somewhat ambiguous whether the treating neurologist performs an EDSS or always uses the EDSS from the blinded rater. If the treating neurologist performs the EDSS and determines that the event is a relapse, the second EDSS is not recorded for comparison with the blinded rater. There is no procedure in the protocol or statistical analysis plan that describes any additional data or changes in analysis when relapse assessments are made after 7 days or reported after 48 hours. The protocol did not describe the analysis or disposition of late reports.

The 323 and 324 protocols specify that the blinded rater elicit only the minimum historical information needed to complete the EDSS. The protocol does not clarify whether minimal information included the nature of the exam (unscheduled following a relapse vs. routine exam at 3 month intervals), whether the subject recently had a relapse, or whether there were any recent neurological symptoms.

The revised manual of standard operation procedures (SOP) specified that a full relapse assessment, including a blinded EDSS, must be completed for every potential relapse, even if the symptoms were reported outside the protocol-defined window.³⁶ The manual states that the center should train subjects to report symptoms within 48 hours and that the subject must be evaluated at the research center within 7 days of symptom onset, “unless it is very clear that symptoms are not MS related. (Ex, subject cannot walk due to a broken ankle sustained in a bicycle accident).” A designated blinded EDSS rater for a patient was to perform the blinded EDSS with no reference to previous EDSS scores. In response to an FDA request for information, the sponsor stated that the EDSS scores available to treating physicians and other unblinded site staff. The manual concludes instructions for the relapse evaluation visit with a statement that the treating physician’s “determination as to relapse and the need for treatment” will be sent to the RAP.

There were two eCRF forms, PE and YC, with relapse event data. In the form “Physical Examination/Vital Signs” two entries record:

³⁶ SOM CAMMS323 v4.0 (June 2010) ise-appendix-8-3.pdf page 35-6 of 2777.

- (1) "Has the patient experienced a possible relapse since the last visit?" with a response choice of "No" or "Yes, ensure a relapse assessment eCRF is completed."
- (2) "Is the patient currently experiencing a possible relapse episode?" with a response choice "Yes" or "No".

The option for reporting "Off-Site Relapse Assessment" form was not to be used after May 11, 2010 (Protocol Amendment 5).

5.3.1.17 MRI Outcome Measurement

Percent change from baseline in MRI-T2 hyperintense lesion volume at year 2 is the fourth in the hierarchy of four secondary trial outcomes. Other conventional and non-conventional MRI outcomes were among the 17 tertiary outcome measures listed in the protocol. The final data submitted with the sBLA application reported the MRI measures listed in Table 8. The number and names of MRI parameters to be tested varied in the site imaging manual, the protocol and the NeuroRx charter.

Table 8 MRI Outcome Measures Report for 323 Trial

T2 Lesion Volume (Secondary Outcome)	Brain Parenchymal Fraction
New T1 Lesion Count	Consensus Gad Lesion Count
T1 Lesion Volume (75%)	Cortical T1 Volume
T1 Lesion Volume (85%)	Gad lesions evolving to Blackholes (75%)
T2 Lesion Load Volume	Gad lesions evolving to Blackholes (85%)
New / Enlarging T2 Lesion Count	MRI Activity
New Gad Lesion Count	

ICON Medical Imaging coordinated quality control at each site and collected the MRI scan data and metadata for final analysis at a later time by NeuroRx in Montreal, Canada, and Cleveland Clinic Foundation. ICON provided two imaging manuals to each site. One described the procedures for MRI imaging of trial subjects for baseline, year 1, and year 2 scans. The second provided MRI phantom recognition requirements for the CAMMS323 protocol.

The site imaging manual included some quality control requirements including the following:

- If a subject has been treated with steroids, ensure that the MRI scans are not performed within 3 weeks of administration.
- Standard dosage of the contrast medium should be used. Ensure that the same contrast medium is used throughout the duration of the study. If the contrast medium is double strength, then half the dose should be injected to bring it into standard dosage range.

- After injecting the contrast agent, there should be a wait time of 5 minutes before scanning the 2D T1 post contrast sequence. The 3D sequence can be performed during this 5 minute period after injecting the contrast. Ensure that the patient remains still in the scanner during administration of the contrast so that the slice locations of the post contrast scans are the same as the pre contrast scan locations.

There were no data elements in the data transfer form or eCRF for the MRI scans that confirmed that these requirements had been met. The amount of contrast, the time from contrast to scan, time of any exposure to corticosteroids, and the order of the different scan sequences could be subject to individual variation and the judgment of the technicians and treating physician or radiologist. There was no requirement in the trial protocol or Imaging Manuals for sites to use the same equipment on subjects in both treatment arms and for the baseline, screening, one and two-year scans. The data transfer form did collect information on the manufacturer and model of the MRI scanner used for each scan, but not the specific device.

5.3.1.18 Data Monitoring Committee

The data monitoring committee charter³⁷ states that the primary responsibility of the DMC is to provide independent expert review of safety data to enable early and ongoing risk management during the conduct of the study. Safety data is presented by treatment group. The DMC The charter included the possibility of an efficacy interim analysis. The CAMMS323 protocol stated that DMC would review only safety data. However, the protocol did not address whether relapses reported as adverse events were safety data or not. Despite what is said in the protocol, there were no restrictions in the protocol or DMC charter that specifically prohibited unblinded interim looks at data that would disclose efficacy outcomes.

5.3.1.19 Protocol and SAP Changes After Randomization of First Subject.

There were 6 versions of the protocol, an original and 5 amended versions. Unless stated otherwise, this section describes the 323 trial as it is in the final version, Amendment 5.

The sponsor began to implement Amendment 1 on October 5, 2007, after 6 subjects had been randomized. This amendment reduced the duration of treatment for each subject

³⁷ Charter of the Data Monitoring Committee (DMC) Genzyme Studies CARE-MS I & II (Protocols CAMMS323 & CAMMS32400507 & CAMMS223 & CAMMS03409), Version 4.0, January 10, 2011. camms323-16-1-9.pdf, pages 84ff.

to two years in place of treating all subjects until two years after the last subject enrolled. Subsequent to amendment 1, investigators were to treat each subject for a maximum of two years and then stop treatment or enroll the subject in an open-label extension study.

Amendment 1 also increased the sample size from 450 to 525 and changed the DMC role from monitoring both safety and efficacy to monitoring safety alone.

Amendment 2, took effect July 3, 2008, after 125 subjects (20%) had been randomized. This amendment doubled the number of clinical sites, incorporated guidelines for how subjects should disguise injuries from injection of interferon- β -1a before evaluation by blinded raters, made the EDSS at screening the score for determining inclusion in the trial (previously, it had been unspecified whether screening or baseline), and clarified that the 525 subject sample size calculation assumed a 2-year SAD rate of 20%.

Amendment 2 replaced the Kaplan-Meier method with logistic regression for determining the proportion of subjects relapse free at 2 years (a secondary outcome).

Amendment 2 also added the complicated rules for delaying treatment when there was an active infection or a relapse had occurred less than 30 days before scheduled infusions at Month 0 or Month 12. These rules differed depending on treatment group. Amendment 2 changed the maximum time to complete the Baseline assessments and begin treatment from one to two weeks (14 days). Amendment 2 also removed the baseline EDSS as a covariate in the SAD primary outcome model and deleted the definition of baseline EDSS because the details would be in a separate statistical analysis plan. (See 5.3.1.7.)

Amendment 2 added a requirement that alemtuzumab subjects be rescreened before the second infusion cycle at 12 months to ensure that subjects did not have increased risks. The disqualifying criteria included malignancy, bleeding disorders, and any condition that could interfere with a subjects ability to complete the trial.

Amendment 2 modified the determination of the EDSS score. The change removed fatigue as a factor and forbid testing for the abdominal reflex in order to protect blinding of the rater.

Amendment 3 took effect January 5, 2009 after 386 subjects (66%) had entered the trial. This amendment added acyclovir 200mg bid for 28 days following infusion of alemtuzumab to prevent HSV infection. The analysis of time to SAD was specified as the Cox proportional hazard model.

Amendment 4 is dated July 17, 2009, when all 581 randomized subjects had enrolled and 38% of the total follow-up had occurred. This amendment removed the

requirement for 100% source data verification. In addition the amendment modified the description of the adjudication process.

Amendment 5 bears the date May 11, 2010, when 75% of the follow-up had been completed and in response to FDA comments made at a meeting with the Division of Neurology Products on March 17, 2010. (see 2.5.2) This amendment changed a number of procedures related to the blinded rater and the determination of relapse events late in the trial after most endpoints had already occurred. The amendment specified that investigators must complete a full relapse evaluation even if the subject reported the symptoms outside the 48-hour window. The change also removed the option that a treating physician or other blinded rater could perform the EDSS assessment during a relapse evaluation.

Amendment 5 also changed the blinded rater's report of unblinding. The modified protocol required an unspecified individual or CRF to ask blinded raters whether they were blinded to treatment assignment after each assessment. The protocol asked that the responses be recorded only at the time of the Month 12 and Month 24 early termination visit. In addition, the amendment modified the instructions for the blinded rater question to "The blinded rater should answer 'NO' [they are not aware of treatment arm] if they have been informed or otherwise become aware of the ... treatment assignment." This replaced the instruction to answer 'No' only if the blinded rater "definitively knows" the treatment assignment.

5.3.2 Trial 324 Design: Differences from Trial 323.

The protocols for CAMMS323 and CAMMS324 were very similar. The major difference between the trials was that the CAMMS324 population had failed previous approved therapy with interferon or glatiramer acetate and CAMMS323 subjects were approved-treatment naïve.

This section describes the differences between the 324 and 323 trials

Initially, like the phase 2 trial, the 324 trial had three treatment arms: interferon- β -1a and two doses of alemtuzumab (12mg and 24mg). Fourteen months after investigators randomized the first subject, Genzyme amended the protocol to stop randomization in the 24mg arm of the 324 trial. After this amendment, the design of the 324 trial is very similar to the 323 trial except for the subject population. The population for the 323 trial is treatment-naïve; the population for 324 has experienced disease progression while on approved treatment for MS. The mutually exclusive trial populations allowed the trials to run concurrently at the same sites.

The 324 trial had the same organizational structure as 323. The relapse adjudication panel (RAP) members, the data monitoring committee (DMC), and many of the trial investigators were the same in both trials. The DMC had one charter that applied to both trials.

5.3.2.1 Subject Selection for Trial 324

Investigators excluded subjects from the 323 trial if they gave a history of treatment with any experimental or approved MS therapy other than steroids. Compared to the subjects in the 323 trial those in the 324 trial had previously taken treatment and relapsed while on treatment, could be older, and had more findings on MRI scans. Specifically, compared to 323 trial subjects, at baseline 324 trial subjects had:

- one or more MS attacks during treatment with a beta-interferon therapy or glatiramer acetate for at least 6 months. (The protocol excluded subjects if they had taken any other approved or experimental MS agent unless the exposure had occurred more than 6 months before giving consent and Genzyme approved the enrollment);
- MRI scans that demonstrated white matter lesions attributable to MS and meeting at least 1 of the following criteria: (1) nine or more T2 lesions at least 3 mm in any axis; (2) a gadolinium-enhancing lesion at least 3 mm in any axis and more than one or more brain T2 lesions, or (3) a spinal cord lesion consistent with MS and one or more brain T2 lesions;
- a greater maximum baseline EDSS score (5.0 compared 3.0);
- a longer maximum time since diagnosis (10 years instead of 5 years);
- the same history of more than two MS attacks with objective signs occurring in the previous 24 months and one or more in the previous 12 months;
- an older maximum age of 55 instead of 50 years old.

5.3.2.2 Washout

The protocol required subjects eligible for 324 and still taking interferon or glatiramer acetate to undergo a washout period of at least 28 days prior to randomization.

5.3.2.3 Interim analysis and monitoring

The CAMMS324 trial protocol included plans for interim futility and efficacy analyses not mentioned in the CAMMS323 protocol.

Section 11.6 of the protocol described plans for a futility analysis that may be performed 2 years after the first subject is randomized by an independent statistical group would perform the analysis. Before the futility analysis is performed, the protocol requires development of a charter and statistical analysis plan.

Section 11.7 of the protocol stated that an interim analysis based on unblinded co-primary endpoint data may be conducted under the auspices of the DMC when approximately 50% of the subjects have completed at least 2 years of follow-up. The protocol specified that there would be a statistical analysis plan and charter for the interim efficacy analysis that specified standard sequential monitoring methods and stopping rules.

The protocol or DMC charter did not state a definition for “unblinded” to clarify whether an analysis of adverse events by treatment group without identify the specific treatment was considered unblinded or not.

5.3.2.4 Protocol and SAP Changes to 324 Protocol After Randomization of First Subject.

Amendment #1 added the section that described an interim efficacy analysis to the CAMMS324 but not the CAMMS323 trial. The sponsor chose not to perform this interim analysis.

Amendment #2 made several significant changes. This amendment stopped recruitment in the 24mg treatment arm. The last subject in the 24mg arm was the 713th subject of 840 (84.88%) on the 641st day of the 699-day randomization period. Genzyme also changed the sample size and design parameters with this amendment. As a result of dropping the 24mg arm and changing assumptions the original 1200-subject (240+480+480) sample size shrank to 573 (191+382). The original sample size was based on a 45% treatment effect; the new sample size assumed a 50% treatment effect and the same 20% 2-year SAD rate for interferon- β -1a subjects. The sponsor attributed this change to interim results from the ongoing phase 2 CAMMS223 trial.

5.3.3 Trial 223 Design

Genzyme approved the final version of the phase 2 CAMMS223 trial on March 19, 2009. This section first describes the final version of the protocol and then summarizes the 10 amendments to the protocol after randomization of the first subject in December 2002.

The 223 phase 2 trial began with the primary objective to test efficacy based on time to the onset of 6-month sustained accumulation of disability with later changes in the

sample size and redefinition of the primary outcome as it progressed. The trial was interrupted by a clinical hold from September 13, 2005 to May 3, 2007 because of safety concerns about several cases of serious cases of idiopathic thrombocytopenic purpura. The hold was placed by FDA at a time when randomization was 100% and 3-year follow-up over 63% completed. During the 20-month hold, investigators gave no additional treatment with alemtuzumab but did continue scheduled visits for randomized subjects. During the hold, the sponsor used data from interim analysis of the 223 trial 2-year results to design the two phase three trials, 323 and 324, described above.

5.3.3.1 CAMMS223 Trial Population

The protocol describes the 223 population as subjects with “early active RRMS.” The subjects were similar to those in the phase 3 323 trial population characterized as “treatment naïve.” Both 323 and 223 admitted only subjects who reported no prior treatment for MS other than steroids. On the other hand, the 324 protocol specified subjects with more advanced MS that had experienced relapses while on interferon- β or glatiramer.

Compared to the 323 trial population, the 223 population had MS onset within 3 years of screening instead of 5 years. Trial 223 subjects had to have at least one Gd-enhancing MRI lesion in at least one of 4 MRI scans done in the three months prior to randomization compared to any scan in the previous 5 years compatible with the diagnosis of MS. Both trials required 2 or more attacks in the previous 2 years, but the 323 trial required objective neurological signs confirmed by a neurologist or nurse practitioner, at the time of screening or retrospectively.

5.3.3.2 CAMMS223 Trial Design

When completed, the 223 Trial was a 334-subject, randomized, controlled, open-label trial that compared once yearly 12 and 24mg doses of alemtuzumab to thrice weekly 44 μ g doses of subcutaneous interferon- β -1a. The primary outcomes were relapse rate and sustained accumulation of disability at three years. The investigator’s concerns about reducing the incidence of Graves disease were given as the reason for testing 2 doses in this phase 2 trial.

Unlike the phase 3 trials, which had no planned interim efficacy analyses, the 223 protocol specified interim analyses one and two years after the randomization of the last subject. The protocol specified that the DSMC review the interim analyses.

Like the 323 and 324 trials, the 223 trial had blinded raters determine EDSS ratings. Unlike the phase 3 trials, trial 223 had no relapse adjudication panel. Instead, the blinded raters examined the subject, asked about intercurrent events, and accessed prior records to determine if there was a new relapse event.

Randomization was stratified by site, age, sex, and baseline EDSS. Randomization was stratified only by site in the phase 3 trials.

The relapse assessment differed significantly from that described in the 323 and 324 protocols. The major difference was that the 223 trial blinded assessors made the determination of whether any clinical event was a relapse or a pseudorelapse. In the phase 3 trials the treating neurologists determined whether an event was a relapse or not. The Relapse Adjudication Panel then confirmed or did not confirm the relapse determination by the unblinded treating neurologist.

5.3.3.3 CAMMS223 Extension Phases

The time from the first subject entering the 223 until the last subject last was approximately 7.25 years.³⁸ By the time that the 223 trial ended, the 323 and 324 trials were fully enrolled and following their entire cohort. The last subject was randomized in 223 on July 21, 2004. Subjects continued participation in the 223 trial until after the CAMMS3409 extension trial began. The purpose of the extension trial was to provide safety follow-up.

5.3.3.4 CAMMS223 Summary of Protocol Amendments

There were 11 versions of the protocol, an original and 10 amended versions. Genzyme approved the original on October 4, 2002 and Amendment 10 on March 18, 2010.³⁹

The sponsor signed off on Amendment 1 on March 6, 2003, 92 days after the trial began randomization and 21 subjects had been randomized. Several features of this amendment resulted from FDA comments on the original protocol. The sponsor added a specific procedure for determining and managing on-study relapses to improve the reliability and objectivity of on-study relapse data. Amendment 1 re-prioritized the eleven secondary efficacy endpoints in the original protocol. The result was that there were 3 secondary endpoints in the revised protocol and the other eight were made tertiary. The order of the secondary outcomes was 1) relapse rate, 2) percent change in

³⁸ Maximum Length of Participation in Four Clinical Studies from ADSLRAND.jmp

³⁹ Section 8.8.1 Changes in the Conduct of the Study, camms223-body.pdf, page 81ff.

cerebral atrophy, and 3) percent change in median T₂ lesion volume. The amended protocol also contained a modified secondary objective to include determination of alemtuzumab dose effect regarding Graves' disease and other thyroid diseases.

The specific process for evaluating relapses added in Amendment 1 is as follows:

"When a patient believes he/she is experiencing a relapse (ie, new neurologic symptoms), the patient will phone the investigational site as soon as possible, but in any event within 48 hours of onset of the potential relapse. If, in the opinion of the treating neurologist, an MS relapse may have occurred, the patient will be directed to come to the investigational site within 7 days of onset of symptoms, and be evaluated by both the treating neurologist and the masked assessor. The assessor will document an examination and an EDSS. The assessor may ask the patient about intercurrent events. After completing the neurological assessment, and only then, the assessor may refer to records of previous neurological examinations to determine if a relapse or a pseudorelapse has occurred. The treating neurologist will review this information and decide whether treatment with a standardized corticosteroid regimen is appropriate, by judging whether the relapse is disabling. Examination visits outside the specified exam/visit windows are permitted in the event of a potential relapse. Patients will be strongly encouraged to return to the investigational site if a relapse is suspected; however, if a patient cannot or does not come to the investigational site for examination, then the patient will be encouraged to see his/her local neurologist. In this event, the investigational site will obtain the documentation from the local neurologist's examination, and the treating neurologist will make a judgment based on that documentation as to whether the episode is a relapse or a pseudorelapse."

In addition to the above, Amendment 1 to the 223 trial design:

- Revised safety endpoints to include more rigorous thyroid function monitoring
- Exclude subjects with forms of MS other than RRMS.
- Increased the number of study sites.
- Added an interim analysis at 6 months that amendment 3 later removed.
- Prohibited live viral vaccines in alemtuzumab-treated subjects.

Genzyme approved Amendment 2 on November 13, 2003, after 142 (43%) of the subjects were randomized and subjects had completed 6% of the 3-year follow-up. Amendment 2:

- Increased the sample size and number of study sites to allow detection of a clinically significant improvement in the 3-year progression rate to SAD of 12% for higher dose alemtuzumab versus 30% for IFNB-1a, with 80% power. Originally, the sample

size planned was 180 subjects. The amendment increased the sample size to 285 patients, 95 per treatment arm, anticipating that a 16% dropout rate of 16% would leave 80 patients per arm (240 total patients) for the primary analysis after completing 3 years of therapy.

Excluded patients who had previously received intravenous immunoglobulin (IVIG).

Amendment 3 reflected the FDA clinical hold and suspension of alemtuzumab administration, as recommended by the DSMB, that began on September 16, 2005, following the report of 3 cases of ITP. The sponsor signed this amendment three years after the randomization of the first subject and after completion of 93% of two-year follow-up and 72% of 3-year follow-up. Changes included the following:

- Added safety assessments for ITP surveillance.

- Added a rationale for ending retreated with the higher 24 mg dose because there was no apparent additional efficacy beyond the lower 12 mg dose.

- Continued safety and efficacy assessments for all subjects through Month 36, including monthly CBCs for all alemtuzumab-treated patients for at least 3 years from their last alemtuzumab treatment.

- Changed efficacy endpoints changed to include 2 co-primary endpoints of relapse and SAD (whereas the primary endpoint had been time to SAD in the original protocol).

- Added 2 MRI assessments as efficacy endpoints: MRI-T2 lesion count and gadolinium enhanced MRI-T1 to measure the number of enhancing brain lesions.

- Removed the interim analysis planned for 6 month after the last subject entered the trial on July 27, 2004. The 6-month analysis could have been done after January 2005. A one-year interim analysis was performed on September 8, 2005, almost three months before this amendment.

- Redefined treatment failure to include patients with SAD or who discontinued due to AEs.

The sponsor proposed but did not implement Amendments 4 and 5 (31 Jan 2006 and 15 May 2006, respectively).

The sponsor implemented Amendment 6 (30 Aug 2006) while the trial was on partial clinical hold. Changes to the protocol include the following:

- Changes made to clarify that there would be no additional alemtuzumab treatment for the remainder of the study.

- Added a 2-year follow-up period (through Month 60) for all patients subsequent to the 3-year treatment period (replacing the 2-year follow-up proposed in Amendment 3), for a total study duration of 5 years. Efficacy and safety data collection were to continue uninterrupted. However, Genzyme no longer provided interferon- β -1a after 36 months.

Provided educational packets to patients regarding signs and symptoms of ITP, including photographs of ecchymoses and petechiae, and implemented monthly ITP sign and symptom questionnaire (offset by 2 weeks from the monthly CBC).

Required investigators to contact alemtuzumab-treated patients who ended their study participation prior to Amendment 3 regarding re-entry into the study for safety monitoring. The amendment required that investigators perform extensive safety assessments at re-entry including expanded hematology and chemistry panels, anti-platelet antibody testing, thyroid function monitoring, lymphocyte phenotyping, and anti-alemtuzumab antibody testing (the latter 2, for alemtuzumab-treated patients only).

Added 3-year assessment of blinding status for the blinded assessor.

The sponsor did not implement Amendment 7 (17 Oct 2007)

Amendment 8 (07 Apr 2008) made the following changes:

Imposed a Jun 2010 date for the last alemtuzumab retreatment dose; the total time on study for any patient was not to exceed 10 years. Patients not retreated were to be followed for 3 years after signing the consent form for this amendment.

During the retreatment period patients receiving alemtuzumab were observed for adverse reactions for 1 to 2 hours post-infusion.

Patients who developed ITP on alemtuzumab were followed for safety for at least 4 years from the time the ITP either resolved or stabilized.

Corrected prior definition of relapse rate by specifying that the number of relapses within a given time period was standardized to that time period (e.g., 1, 2, or 3 years).

Moved objective of demonstrating a reduction in tissue damage on MRI to secondary objectives (not primary). Added objectives for the retreatment/follow-up period.

Rationale for retreatment with 12 mg/day alemtuzumab dosing only was added, as there did not seem to be an efficacy advantage with the higher dose, based on the interim analysis (Coles 2008, N Engl J Med).

Clarified that for the retreatment period, consenting alemtuzumab patients were randomized 1:2 to either the fixed (annual) or as-needed retreatment arms using IVRS.

Confirmed that on-study relapses during the retreatment period were to be treated the same as on-study relapses in the initial 3-year treatment period (i.e., with 1 g IV methylprednisolone over 1 hour for 3 days).

Added retreatment criteria for screening for HIV, hepatitis B and C, and latent TB.

For consistency across all MS protocols, monthly CBCs and ITP monitoring surveys were added.

To improve patient safety, the criterion for resuming monthly monitoring of CBCs following evidence of thrombocytopenia was made more stringent (cut-off of $< 50,000 \times 8$ weeks increased to $< 100,000 \times 8$ weeks).

The sponsor did not implement Amendment 9 (22 Dec 2008)

Amendment 10 (18 Mar 2009):

Permitted subjects or investigators to choose the retreatment regimen felt to be most appropriate for a patient, rather than patients being randomized to the “as needed” or “fixed” alemtuzumab retreatment, per patient/investigator request.

Clarified that patients would receive 2 annual 3-day cycles of alemtuzumab (12 mg/day) in the “fixed” retreatment group or up to 2, 3-day cycles of alemtuzumab (12 mg/day) in the “as-needed” retreatment group.

Clarified that during the retreatment period, IFNB-1a treated patients could continue on this treatment or switch to DMTs at their own expense.

Added disqualifying criteria for the second annual alemtuzumab retreatment; patients meeting any disqualifying criteria could not receive alemtuzumab retreatment until the condition had resolved and/or prior approval was obtained from the Sponsor.

The retreatment screening period was increased from 14 to 30 days.

Implemented a course of acyclovir (or therapeutic equivalent) with each alemtuzumab cycle during the retreatment period, after the review of interim data suggested that patients were at increased risk for HSV infection within 1 month of an infusion.

Redefined the follow-up period as 4 years from the last dose of alemtuzumab for retreated alemtuzumab patients; and 4 years from the date ICF was signed for the follow-up period for IFNB-1a patients and patients who declined/did not qualify for retreatment

Required follow-up of alemtuzumab patients who developed ITP for 4 years from ITP diagnosis, rather than from the date of stabilization or resolution of ITP (per Amendment 8).

Added monthly serum chemistries and urinalysis as part of anti-GBM monitoring for all alemtuzumab patients and added anti-GBM as an MEOI if it did not otherwise meet seriousness criteria (i.e., to be reported within 5 days of occurrence).

5.3.4 The CAMMS3409 Extension Trial (EXT)

Genzyme organized an extension trial to gain additional experience with long-term drug safety.⁴⁰

⁴⁰ From iss-14-5.pdf, page 3 of 10

5.3.4.1 Study Design

This extension trial (EXT) is an open-label, rater-blinded, safety monitoring trial for subjects who had completed participation in the 223, 323, and 324 trials. After enrollment investigators could treat alemtuzumab-naïve subjects with two annual courses of alemtuzumab, the first one at the time of enrollment and the second one year later. The EXT trial is ongoing.

Investigators could re-treat subjects previously given alemtuzumab in 223, 323, or 324 if they still met the selection criteria and they had evidence of resumed disease activity defined as:

more than 1 protocol-defined relapse *or*
more than 2 new or enlarging brain or spinal lesions on MRI

and if they did not:

take alemtuzumab in the past 48 weeks
have EDSS >6.5 sustained for more than 3 months.

5.3.4.2 Selection Criteria

Subjects randomized in any of the three randomized trials, 223, 323, or 324 could participate in the extension trial (EXT) if they:

- 1) Took alemtuzumab in CAMMS323 or CAMMS324, completed the 2-year follow-up period, and did NOT subsequently take treatments for MS other than glatiramer acetate or interferon beta; *or*
- 2) Took interferon- β -1a in CAMMS323 or CAMMS324, completed the 2-year follow-up period, and did NOT subsequently take treatments for MS other than glatiramer acetate or interferon beta; *or*
- 3) Participated in CAMMS223

6. Review of Efficacy

The review of the efficacy in this section addresses the following questions:

- What were the results of the three trials submitted by the sponsor as substantial evidence of effectiveness and what was the indication the sponsor claims the results support? See sections 6.1 through 6.7, pages 60-68.
- Were the trials submitted as substantial evidence of effectiveness adequate and well-controlled according to CFR §314.126 (b)? See section 6.12, page 77.

--Were the treatment effects demonstrated in the trials so large that there is no need for the trial design to distinguish the effect of alemtuzumab (and its concomitant treatments) from other influences such as spontaneous change in the course of the disease, placebo effect, and biased observation? See section 6.13, page 80.

--Were the results of the trials internally consistent and free of evidence of bias in the performance of the trial? See section 6.14, page 82.

6.1 Indication

The sponsor's proposed indication for LEMTRADA in the original application was relapsing forms of MS to slow or reverse the accumulation of physical disability and reduce the frequency of clinical exacerbations.⁴¹ On August 21, 2013, the application was modified to change the indication. The requested indication is now "the treatment of patients with relapsing forms of multiple sclerosis."⁴²

6.2 Methods

The sponsor supports its claim of safety and effectiveness with clinical data from two confirmatory open-label clinical trials, Trials 323 and 324 as corroborated by results from an open-label Phase 2 trial, Trial 223.

In their integrated summary of efficacy, the sponsor focused their application on the primary analysis that compared interferon- β -1a to the 12mg dose of alemtuzumab. The sponsor did not use the efficacy data from the 173 subjects in the alemtuzumab 24mg arm in the 324 trial or 110 subjects in the alemtuzumab 24mg arm of the 223 trial except for subsidiary exploratory analyses.

6.3 Demographics and Baseline Clinical Characteristics

Despite the uneven dropout before randomization in some of the trials (see section 6.4, below), the demographic characteristics of the Full Analysis populations for the two arms of the trials were similar. Typical of the disease, two thirds of the subjects were females. The average subject was at the beginning or middle of her fourth decade.

⁴¹ coverletter.pdf, page 2 of 17, original submission.

⁴² coverletter.pdf, page 1 of 2, [\\Cdsub1\bla\CTD_Submissions\STN103948\0170\m1\us](#), August 21, 2013.

As the sponsor intended, the subjects in the 223 and 323 early intervention trials were younger and had fewer relapses prior to randomization than the subjects in the 324 trial who had failed prior treatment with either interferon or glatiramer. See Table 9.

Table 9 Demographics Of Subjects in 223, 323, 324 by Treatment Arm

Baseline Demographics: Full Analysis Sets						
Trial	CAMMS324		CAMMS323		CAMMS223^a	
Treatment Arm	interferon (N = 202)	almtzmb 12 (N = 426)	interferon (N = 187)	almtzmb 12 (N = 376)	interferon (N = 111)	almtzmb 12 (N = 112)
Age (years)						
Mean (SD)	35.8 (8.77)	34.8 (8.36)	33.2 (8.48)	33.0 (8.03)	32.8 (8.82)	31.9 (8.01)
Sex, n (%)						
Female	131 (64.9)	281 (66.0)	122 (65.2)	243 (64.6)	71 (64.0)	72 (64.3)
Race, n (%)						
White	187 (92.6)	385 (90.4)	180 (96.3)	352 (93.6)	100 (90.1)	102 (91.1)
Black	8 (4.0)	24 (5.6)	3 (1.6)	11 (2.9)	3 (2.7)	5 (4.5)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	1 (0.9)	1 (0.9)
Hispanic	NA	NA	NA	NA	7 (6.3)	4 (3.6)
Am Indian, Alaska Native	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.5)	NA	NA
Other	7 (3.5)	15 (3.5)	4 (2.1)	6 (1.6)	NA	NA
Geographic Region, n (%)						
US, Canada, & Australia	102 (50.5)	216 (50.7)	54 (28.9)	111 (29.5)	56 (50.5)	50 (44.2)
Latin America	13 (6.4)	26 (6.1)	4 (2.1)	11 (3.0)	0 (0.0)	0 (0.0)
EU	44 (21.8)	91 (21.4)	40 (21.4)	81 (21.5)	21 (18.9)	26 (23.0)
Non EU, Israel ^b	43 (21.3)	93 (21.8)	89 (47.6)	173 (46.0)	34 (30.6)	37 (32.7)
US	82 (40.6)	186 (43.7)	39 (20.9)	89 (23.7)	56 (50.5)	50 (44.2)
non US	120 (59.4)	240 (56.3)	148 (79.1)	287 (76.3)	55 (49.5)	63 (55.8)
^a For CAMMS223, geographic region is based on randomized patients						
^b Israel in CAMMS324 only						

The baseline clinical characteristics were similar for subjects in the treatment arms of each trial. The subjects with the history of least prior disease activity were those in the 223 trial. However, these same subjects had more evidence of MRI activity in terms of T2-lesion volume and the number of Gd-enhancing lesions. As described above in Section 5, an unusual feature of the trials was that the baseline EDSS score was determined after randomization when subjects were aware of their treatment assignment.

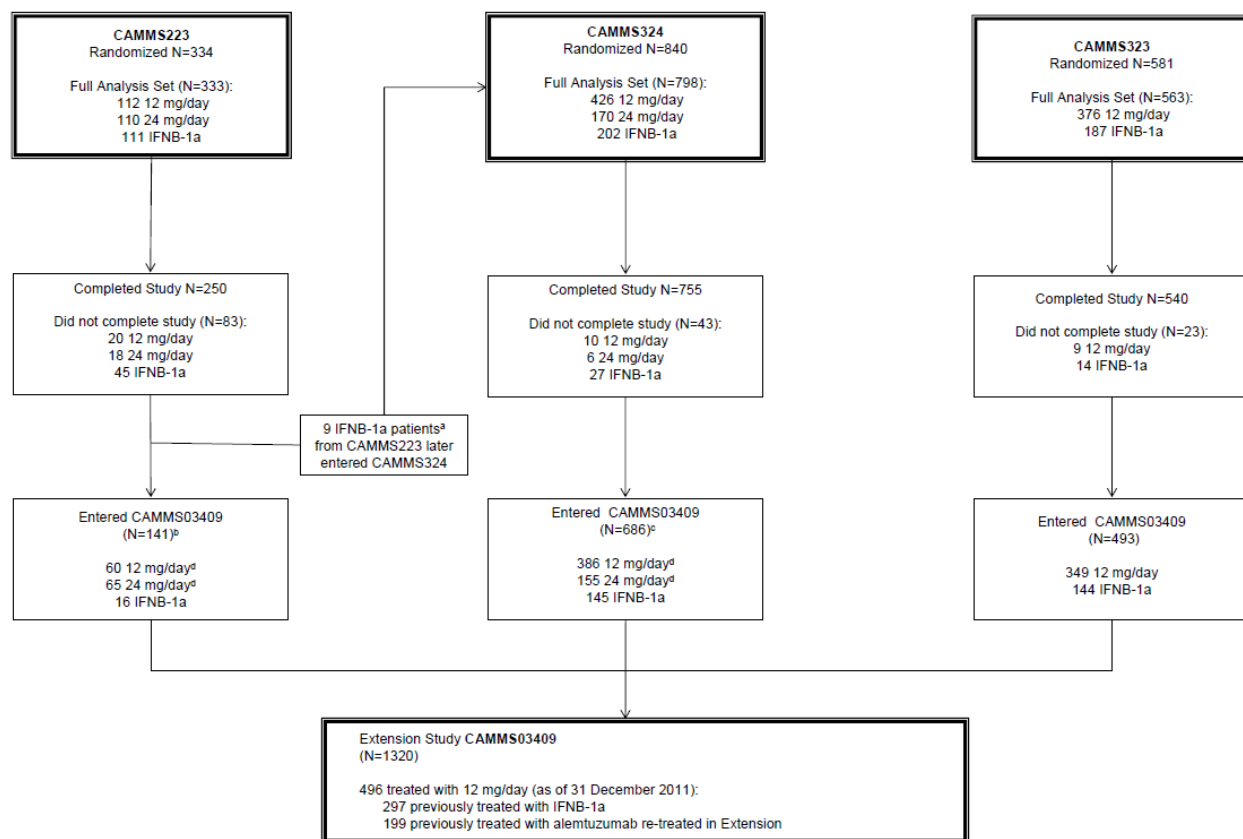
Table 10 Clinical Characteristics at Baseline (After Randomization)

Baseline Clinical Characteristics: Full Analysis Sets						
Trial	CAMMS324		CAMMS323		CAMMS223 ^a	
Treatment Arm	interferon (N = 202)	almtzmb 12 (N = 426)	interferon (N = 187)	almtzmb 12 (N = 376)	interferon (N = 111)	almtzmb 12 (N = 112)
EDSS Score (%)						
Mean (SD)	2.7 (1.21)	2.7 (1.26)	2.0 (0.79)	2.0 (0.81)	1.9 (0.81)	2.0 (0.73)
Median	2.5	2.5	2.0	2.0	2.0	2.0
Min, Max	0.0, 6.0	0.0, 6.5	0.0, 3.5	0.0, 4.0	0.0, 3.5	0.0, 3.0
MS History (time since first episode, years)						
Mean (SD)	4.7 (2.86)	4.5 (2.68)	2.0 (1.32)	2.1 (1.36)	1.6 (1.01)	1.4 (0.84)
Median	4.1	3.8	1.5	1.7	1.4	1.3
Min, Max	0.4, 10.1	0.2, 14.4	0.2, 5.0	0.1, 5.2	0.2, 6.3	0.1, 3.5
Number of Episodes in Prior 1 Year						
0	5 (2.5)	6 (1.4)	4 (2.1)	6 (1.6)	5 (4.5)	9 (8.0)
1	107 (53.0)	211 (49.5)	66 (35.3)	145 (38.6)	46 (41.4)	38 (33.9)
2	68 (33.7)	151 (35.4)	94 (50.3)	169 (44.9)	47 (42.3)	44 (39.3)
≥ 3	22 (10.9)	58 (13.6)	23 (12.3)	56 (14.9)	13 (11.7)	21 (18.8)
Number of Episodes in Prior 2 Years						
0	0	0	0	0	0	2 (1.8)
1	7 (3.5)	15 (3.5)	3 (1.6)	12 (3.2)	8 (7.2)	5 (4.5)
2	109 (54.0)	215 (50.5)	118 (63.1)	215 (57.2)	73 (65.8)	58 (51.8)
≥ 3	86 (42.6)	196 (46.0)	66 (35.3)	149 (39.6)	30 (27.0)	47 (42.0)
Patients with Gadolinium-enhancing Lesions						
N (%)	87 (43.7)	178 (42.4)	94 (51.4)	171 (46.1)	100%	100%
T2 Lesion Volume cm³						
Mean (SD)	9.04 (10.42)	9.94 (12.25)	7.33 (9.86)	7.44 (9.02)	15.8 (15.23)	17.2 (23.84)
Median	5.6	6.0	3.8	4.	10.2	8.5
Min, Max	0.0, 70.3	0.0, 77.6	0.1, 55.5	0.0, 49.0	0.1, 82.6	0.2, 192.3
Note: All subjects in CAMMS223 Trial were required to have Gd-Enhancing Lesions						

6.4 Subject Disposition

Figure 2, below, shows the overall disposition of the populations in the 223, 323, 324, and EXT trials/studies for all arms in the trials.

Figure 2 Sponsor's Consort Diagram for the Three Randomized Trials



^a 1 subject entered CAMMS324 without completing CAMMS223.

^b 8 subjects entered EXT without completing 223 (one 12 mg/day, three 24 mg/day, four IFNB-1a).

^c 1 subject entered EXT without completing 324. This subject enrolled in 223. The eligibility criteria for EXT allowed all who enrolled in 223 to enroll in EXT.

^d Alemtuzumab subjects who entered EXT are broken out by the treatment group that they were randomized to in their original study.

Analysis Populations

The statistical analysis plans for the three trials based the primary outcomes on the Full Analysis (FA) subset that comprises all randomized subjects exposed to at least one dose of study drug. The plan mandates comparison of primary, secondary, and tertiary outcomes by assigned treatment arm without regard for the study treatment actually received or the extent of study drug exposure. Table 11 below shows the size of the randomized intent-to-treat population (ITT) and the modified intent to treat (mITT) FA population. The plan also defined Per-Protocol and Safety subsets of the population. Outcomes for these sub-populations were not considered in the review of effectiveness.

Reviewer comment: The usual justification for the use of the mITT population assumes that drop-out prior to any treatment will be uncommon and balanced between groups, i.e.

“uninformed.” Dropout prior to treatment in the 324 trial was unbalanced ($p \sim 0.001$) and adds uncertainty to the results of the mITT analysis using the Full Analysis subset of randomized patients.

Table 11 Size of Primary Analysis (ITT and mITT=Full Analysis) Populations for Trials 223, 323 and 324⁴³

ITT Population All Randomized Subjects			
Trial	Treatment Arm		Total
	Interferon- β -1a	Alemtuzumab 12mg	
223	111	113	224
323	195	386	581
324	231	436	667
FA Population for Primary Analyses All Treated Subjects (mITT population)			
Trial	Treatment Arm		Total
	Interferon- β -1a N (% of ITT)	Alemtuzumab 12mg N (% of ITT)	
223	107 (96%)	108 (96%)	215
323	187 (96%)	376 (98%)	563
324	202 (87%)*	426 (98%)*	628*
* $p < 0.001$ (X^2 estimated by reviewer)			

6.4.1 Dropout and Discontinuation

Dropout Prior to Starting Treatment

The difference between the FA and ITT populations is the number of subjects who drop out soon after randomization and do not begin any study treatment. See Table 12, above.

In the 223 trial dropout after randomization and before treatment began was 3.6% in the interferon- β -1a arm and 4.4% in the 12mg alemtuzumab arm. In the 323 trial dropout before treatment was 4.1% in the interferon- β -1a group and 2.6% in the alemtuzumab 12mg group. The difference in early dropout rates between treatment groups was

⁴³ camms-integrated-summary-clin-efficacy-final.pdf, Table 3-3, page 91 of 206. Does not include 9 subjects who crossed over from the 24mg treatment arm in trial 324.

much larger in the 324 trial. Of the 667 subjects enrolled in trial 324, 39 dropped out soon after randomization and never received the study treatment. The drop-out rate was 12.6% in the interferon- β -1a group compared to 2.3% in the alemtuzumab 12mg group. The sponsor attributes this difference in dropout rate to subjects who had previously failed interferon treatment refusing further treatment with the same drug.

Table 12 Early Dropouts After Randomization and Before Any Treatment in 223, 323 and 324⁴⁴

Percent of Randomized Subjects Who Dropped Out Before Taking Study Medication		
Trial	Treatment Arm	
	Interferon- β -1a	Alemtuzumab 12mg
223 3-Yrs	3.6%	4.4%
323 2-Yrs	4.1%	2.6%
324 2-Yrs	12.6%	2.3%

Discontinuation of Treatment After First Dose

The FA analysis population discontinuation rates differed across the treatment arms in all three trials.

In the 223 trial, 47.7% of treated subjects in the interferon- β -1a group discontinued the study treatment during the 3-year portion of the trial compared to 5.6% of the treated subjects in the 12mg alemtuzumab arm. The high drop-out rate and the imbalance between the treatment groups makes interpretation of the 223 trial results very difficult. The results are useful only to corroborate but not support a claim of efficacy.

In trial 323, more interferon-treated subjects also discontinued treatment: 11.8% compared to 2.1%. In trial 324, 21.8% of the 202 subjects who began treatment with interferon- β -1a discontinued treatment compared to 7.1% of the 426 alemtuzumab 12mg subjects. The ratio of interferon to alemtuzumab discontinuation rates was 8.50, 2.86, and 3.07 in the 223, 323, and 324 trials respectively. See Table 13.

⁴⁴ camms-integrated-summary-clin-efficacy-final.pdf, Table 3-3, page 91 of 206.

Table 13 Discontinuation of Treatment for 223, 323 and 324 Trials by Treatment Arm

Percent of Treated Subjects Who Discontinued Treatment after One or More Doses of Study Drug Trials 223, 323 and 324			
Trial	Treatment Arm ⁴⁵		Discontinuation Rate Ratio ⁴⁶
	Interferon- β -1a	Alemtuzumab 12mg	
223	47.7%	5.6%	8.5.
323	11.8%	2.1%	5.6.
324	19.0%	5.0%	3.8

Trial completion

The sponsor also reported that the number of subjects who completed each trial, whether or not they discontinued treatment was also unbalanced between treatment arms. See Table 14. An imbalance across treatment arms is most noticeable in the 324 trial.

Clinical site staff made the determination whether or not each subject completed the trials by recording the following on the “Completion/Discontinuation” case report form:

- completion or discontinuation date
- date of the last dose of medication
- whether the subject completed the protocol (“yes” or “no”)
- if “no”, the primary reason the subject did not complete the protocol.

The form instructions defined the completion/discontinuation date as the date of the last trial assessment. There was no detailed definition of trial “completion” in the protocol or statistical analysis plan to guide clinical site staff.

⁴⁵ Review estimates X² test yields p=0.0003 for 323 and p<.0001 for 324 and 223

⁴⁶ Estimated by clinical reviewer.

Table 14 Completion Rates for 223 Randomized Subjects in 223, 323 and 324 Trials by Treatment Arm⁴⁷

Percent of Subjects Randomized Who Completed Trial Protocol for 323, 223, and 324		
Trial	Treatment Arm	
	Interferon- β -1a	Alemtuzumab 12mg
223 3-Yrs	59.5%	81.4
323 2-Yrs	88.7%	95.1%
324 2-Yrs	75.8%	95.4%

After discontinuation of the assigned study treatment, some trial subjects continued to participate in the trial but replaced the study treatment with an alternative therapy. Table 15, below, documents the use of alternative therapy during the three trials. Notably, in trial 324, alternative therapy was used in 5.9% of subjects taking interferon- β -1a compared to 2.6% taking alemtuzumab.

Table 15 Alternative Therapy After Discontinuation of Study Drug⁴⁸

Generic Name	CAMMS324		CAMMS323		CAMMS223	
	SC IFNB-1a (N = 202)	Alem 12 mg/day (N = 426)	SC IFNB-1a (N = 187)	Alem 12 mg/day (N = 376)	SC IFNB-1a (N = 111)	Alem 12 mg/day (N = 112)
Patients with Alternative MS Medications, n(%)	12 (5.9)	11 (2.6)	3 (1.6)	4 (1.1)	4 (3.7)	4 (3.7)
Fampridine	5 (2.5)	6 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immunoglobulin	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Fingolimod	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interferon beta-1a	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	2 (1.9)
Interferon beta-1b	1 (0.5)	1 (0.2)	1 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)
Rituximab	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.9)
Glatiramer Acetate	3 (1.5)	0 (0.0)	2 (1.1)	3 (0.8)	2 (1.9)	1 (0.9)
Immunoglobulin Human Normal	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Natalizumab	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

⁴⁷ camms-integrated-summary-clin-efficacy-final.pdf, Table 3-3, page 91 of 206.⁴⁸ camms-integrated-summary-clin-efficacy-final.pdf, page 96 of 206.

6.5 Analysis of Primary Endpoints

All three trials had results that met the primary efficacy objectives specified in the protocols and statistical analysis plans prior to the locking of the trial datasets. This section presents the sponsor's analysis of the trial outcomes. A later section assesses the credibility of these results. (Section 6.12 - 6.15, starting on page 77)

Table 16 Primary Results of Clinical Trials 223, 323, 324⁴⁹

Co-Primary Outcomes For Trial 223, 323, and 324							
Endpoint	Trial						
	CAMMS223 ^a			CAMMS323 ^a		CAMMS324 ^a	
	Rebif N=111	Alem 12 N=113	Alem 24 N=110	Rebif N=195	Alem 12 N=386	Rebif N=231	Alem 12 N=436
Co-Primary Endpoints							
Relapse rate, N (%)	111 (100)	112 (99.1)	110 (100)	187 (95.9)	376 (97.4)	202 (87.4)	426 (97.7)
ARR	0.37	0.12	0.09	0.39	0.18	0.52	0.26
Rate ratio		0.33	0.23		0.45		0.51
p-value		<0.0001	<0.0001		<0.0001		<0.0001
Time to 6-mo SAD, N (%)	111 (100)	112 (99.1)	110 (100)	187 (95.9)	376 (97.4)	202 (87.4)	426 (97.7)
Proportion 6-mo SAD	0.27	0.08	0.09	11.12	8.00	21.13	12.71
Hazard ratio	0.24	0.24	0.31)		0.70		0.58
p-value		0.0006	<0.0021		0.2173		0.0084

⁴⁹ Response to Information Request, Sequence 122, May 13, 2012, Table 3, page 26 of 123. Table reports proportion as percentage in some columns and decimal in others.

Table 17 Cross Trial Comparison of K-M Curves for SAD and Relapse for 223, 323 and 324 Trials

Trial 223	<p>Time to SAD</p> <p>Cumulative Plot of Time to Sustained Accumulation of Disability (SAD) CAMMS223 Full Analysis Set From Randomization through Year 2</p> <p>HR: 0.18 (0.062,0.546) p-value: 0.0023</p> <p>No. at Risk</p> <table><tr><th>Follow-Up Month</th><th>0</th><th>3</th><th>6</th><th>9</th><th>12</th><th>15</th><th>18</th><th>21</th><th>24</th></tr><tr><td>SC IFNB-1a</td><td>111</td><td>107</td><td>93</td><td>87</td><td>83</td><td>79</td><td>76</td><td>72</td><td>68</td></tr><tr><td>Alemtuzumab 12 mg/day</td><td>112</td><td>108</td><td>106</td><td>104</td><td>103</td><td>99</td><td>98</td><td>98</td><td>97</td></tr></table>	Follow-Up Month	0	3	6	9	12	15	18	21	24	SC IFNB-1a	111	107	93	87	83	79	76	72	68	Alemtuzumab 12 mg/day	112	108	106	104	103	99	98	98	97	<p>Time to First Relapse</p> <p>Kaplan Meier Plot of Time to First Relapse CAMMS223 Full Analysis Set From Randomization through Year 2</p> <p>HR: 0.32 (0.178,0.556) p-value: <.0001</p> <p>No. at Risk</p> <table><tr><th>Follow-Up Month</th><th>0</th><th>3</th><th>6</th><th>9</th><th>12</th><th>15</th><th>18</th><th>21</th><th>24</th></tr><tr><td>SC IFNB-1a</td><td>111</td><td>101</td><td>82</td><td>69</td><td>65</td><td>61</td><td>56</td><td>50</td><td>46</td></tr><tr><td>Alemtuzumab 12 mg/day</td><td>112</td><td>104</td><td>100</td><td>94</td><td>92</td><td>91</td><td>91</td><td>91</td><td>86</td></tr></table>	Follow-Up Month	0	3	6	9	12	15	18	21	24	SC IFNB-1a	111	101	82	69	65	61	56	50	46	Alemtuzumab 12 mg/day	112	104	100	94	92	91	91	91	86
	Follow-Up Month	0	3	6	9	12	15	18	21	24																																																				
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SC IFNB-1a	111	101	82	69	65	61	56	50	46																																																					
Alemtuzumab 12 mg/day	112	104	100	94	92	91	91	91	86																																																					
Trial 323	<p>Time to SAD</p> <p>Cumulative Plot of Time to Sustained Accumulation of Disability (SAD) CAMMS323 Full Analysis Set</p> <p>HR: 0.70 (0.40, 1.23) p-value: 0.2173</p> <p>No. at Risk</p> <table><tr><th>Follow-Up Month</th><th>0</th><th>3</th><th>6</th><th>9</th><th>12</th><th>15</th><th>18</th><th>21</th><th>24</th></tr><tr><td>SC IFNB-1a</td><td>187</td><td>185</td><td>181</td><td>177</td><td>170</td><td>164</td><td>162</td><td>158</td><td>149</td></tr><tr><td>Alemtuzumab 12 mg/day</td><td>376</td><td>376</td><td>372</td><td>368</td><td>363</td><td>357</td><td>352</td><td>345</td><td>336</td></tr></table>	Follow-Up Month	0	3	6	9	12	15	18	21	24	SC IFNB-1a	187	185	181	177	170	164	162	158	149	Alemtuzumab 12 mg/day	376	376	372	368	363	357	352	345	336	<p>Time to First Relapse</p> <p>Kaplan Meier Plot of Time to First Relapse CAMMS323 Full Analysis Set</p> <p>HR: 0.45 (0.33, 0.61) p-value: <.0001</p> <p>No. at Risk</p> <table><tr><th>Follow-Up Month</th><th>0</th><th>3</th><th>6</th><th>9</th><th>12</th><th>15</th><th>18</th><th>21</th><th>24</th></tr><tr><td>SC IFNB-1a</td><td>187</td><td>175</td><td>156</td><td>137</td><td>127</td><td>118</td><td>116</td><td>109</td><td>101</td></tr><tr><td>Alemtuzumab 12 mg/day</td><td>376</td><td>366</td><td>358</td><td>340</td><td>321</td><td>313</td><td>306</td><td>299</td><td>287</td></tr></table>	Follow-Up Month	0	3	6	9	12	15	18	21	24	SC IFNB-1a	187	175	156	137	127	118	116	109	101	Alemtuzumab 12 mg/day	376	366	358	340	321	313	306	299	287
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Trial 324	<p>Time to SAD</p> <p>Cumulative Plot of Time to Sustained Accumulation of Disability (SAD) CAMMS324 Full Analysis Set</p> <p>HR: 0.58 (0.38, 0.87) p-value: 0.0084</p> <p>No. at Risk</p> <table><tr><th>Follow-Up Month</th><th>0</th><th>3</th><th>6</th><th>9</th><th>12</th><th>15</th><th>18</th><th>21</th><th>24</th></tr><tr><td>SC IFNB-1a</td><td>202</td><td>200</td><td>184</td><td>175</td><td>167</td><td>162</td><td>155</td><td>145</td><td>131</td></tr><tr><td>Alemtuzumab 12 mg/day</td><td>426</td><td>426</td><td>412</td><td>404</td><td>392</td><td>384</td><td>380</td><td>375</td><td>354</td></tr></table>	Follow-Up Month	0	3	6	9	12	15	18	21	24	SC IFNB-1a	202	200	184	175	167	162	155	145	131	Alemtuzumab 12 mg/day	426	426	412	404	392	384	380	375	354	<p>Time to First Relapse</p> <p>Kaplan Meier Plot of Time to First Relapse CAMMS324 Full Analysis Set</p> <p>HR: 0.53 (0.41, 0.69) p-value: <.0001</p> <p>No. at Risk</p> <table><tr><th>Follow-Up Month</th><th>0</th><th>3</th><th>6</th><th>9</th><th>12</th><th>15</th><th>18</th><th>21</th><th>24</th></tr><tr><td>SC IFNB-1a</td><td>202</td><td>190</td><td>139</td><td>125</td><td>109</td><td>101</td><td>94</td><td>90</td><td>79</td></tr><tr><td>Alemtuzumab 12 mg/day</td><td>426</td><td>402</td><td>377</td><td>354</td><td>325</td><td>313</td><td>303</td><td>291</td><td>266</td></tr></table>	Follow-Up Month	0	3	6	9	12	15	18	21	24	SC IFNB-1a	202	190	139	125	109	101	94	90	79	Alemtuzumab 12 mg/day	426	402	377	354	325	313	303	291	266
	Follow-Up Month	0	3	6	9	12	15	18	21	24																																																				
SC IFNB-1a	202	200	184	175	167	162	155	145	131																																																					
Alemtuzumab 12 mg/day	426	426	412	404	392	384	380	375	354																																																					
Follow-Up Month	0	3	6	9	12	15	18	21	24																																																					
SC IFNB-1a	202	190	139	125	109	101	94	90	79																																																					
Alemtuzumab 12 mg/day	426	402	377	354	325	313	303	291	266																																																					

Table 18 Mean EDSS over Two Years 223, 323, and 324

	Mean EDSS 0-24 Months																														
Trial 223	<p>Estimated Mean EDSS Score and 95% Confidence Interval at Each Assessment Through Year 2 CAMMS223 Full Analysis Set</p> <p>No. of Obs.</p> <table><tr><th>Follow-Up Month</th><th>0</th><th>3</th><th>6</th><th>9</th><th>12</th><th>15</th><th>18</th><th>21</th><th>24</th></tr><tr><td>SC IFNB-1a</td><td>110</td><td>104</td><td>100</td><td>96</td><td>91</td><td>89</td><td>83</td><td>79</td><td>73</td></tr><tr><td>Alem 12 mg/day</td><td>112</td><td>107</td><td>107</td><td>105</td><td>103</td><td>99</td><td>99</td><td>98</td><td>99</td></tr></table>	Follow-Up Month	0	3	6	9	12	15	18	21	24	SC IFNB-1a	110	104	100	96	91	89	83	79	73	Alem 12 mg/day	112	107	107	105	103	99	99	98	99
Follow-Up Month	0	3	6	9	12	15	18	21	24																						
SC IFNB-1a	110	104	100	96	91	89	83	79	73																						
Alem 12 mg/day	112	107	107	105	103	99	99	98	99																						
Trial 323	<p>Estimated Mean EDSS Score and 95% Confidence Interval at Each Assessment CAMMS323 Full Analysis Set</p> <p>No. of Obs.</p> <table><tr><th>Follow-Up Month</th><th>0</th><th>3</th><th>6</th><th>9</th><th>12</th><th>15</th><th>18</th><th>21</th><th>24</th></tr><tr><td>SC IFNB-1a</td><td>187</td><td>186</td><td>184</td><td>179</td><td>179</td><td>177</td><td>173</td><td>173</td><td>173</td></tr><tr><td>Alem 12 mg/day</td><td>376</td><td>376</td><td>373</td><td>375</td><td>375</td><td>372</td><td>372</td><td>366</td><td>366</td></tr></table>	Follow-Up Month	0	3	6	9	12	15	18	21	24	SC IFNB-1a	187	186	184	179	179	177	173	173	173	Alem 12 mg/day	376	376	373	375	375	372	372	366	366
Follow-Up Month	0	3	6	9	12	15	18	21	24																						
SC IFNB-1a	187	186	184	179	179	177	173	173	173																						
Alem 12 mg/day	376	376	373	375	375	372	372	366	366																						
Trial 324	<p>CAMMS324 Estimated Mean EDSS Mean Score and 95% Confidence Interval at Each Assessment: Full Analysis Set</p> <p>No. of Obs.</p> <table><tr><th>Follow-Up Month</th><th>0</th><th>3</th><th>6</th><th>9</th><th>12</th><th>15</th><th>18</th><th>21</th><th>24</th></tr><tr><td>SC IFNB-1a</td><td>202</td><td>198</td><td>194</td><td>190</td><td>185</td><td>180</td><td>176</td><td>172</td><td>174</td></tr><tr><td>Alem 12 mg/day</td><td>426</td><td>419</td><td>419</td><td>419</td><td>422</td><td>415</td><td>410</td><td>413</td><td>413</td></tr></table>	Follow-Up Month	0	3	6	9	12	15	18	21	24	SC IFNB-1a	202	198	194	190	185	180	176	172	174	Alem 12 mg/day	426	419	419	419	422	415	410	413	413
Follow-Up Month	0	3	6	9	12	15	18	21	24																						
SC IFNB-1a	202	198	194	190	185	180	176	172	174																						
Alem 12 mg/day	426	419	419	419	422	415	410	413	413																						

Note: red line with shadow added by in this review to display baseline EDSS score.

6.6 Analysis of Secondary Endpoints

In the plan for hierarchical analysis communicated by FDA to the sponsor, only those secondary endpoints that were preceded by statistically significant differences in the two primary outcomes and all preceding secondary outcomes were to be considered. This ordering was a means for controlling for multiplicity. The shaded cells in Table 19 met the sponsor's criteria for success in the hierarchical analysis. Prior to the analysis, FDA commented that both relapse rate and SAD outcomes should be positive before any secondary outcomes were analyzed. Therefore, FDA has reservations about considering the proportion relapse free as a positive result of CAMMS323 because the trial failed to show a reduction in SAD events. All three trials failed to show a statistically significant difference in median T₂ lesion volume.

Table 19 Secondary Outcomes -- Shaded Endpoints Meet the Criteria of the Hierarchical Analysis

Secondary Outcomes For 223, 323, and 324 ⁵⁰							
Endpoint	Trial						
	CAMMS223 ^a			CAMMS323 ^a		CAMMS324 ^a	
	Rebif N=111	Alem 12 N=113	Alem 24 N=110	Rebif N=195	Alem 12 N=386	Rebif N=231	Alem 12 N=436
Proportion relapse free, N (%)	111 (100)	112 (99.1)	110 (100)	187 (95.9)	376 (97.4)	202 (87.4)	426 (97.7)
No event	0.50	0.76	0.84	58.69	77.59	46.70	65.38
Hazard ratio		0.37	0.23		0.45		0.53
p-value		0.0001	<0.0001		<0.0001		<0.0001
Change in EDSS*, N(%)	111 (100)	112 (99.1)	110 (100)	187 (95.9)	376 (97.4)	202 (87.4)	426 (97.7)
Mean	0.41	-0.36	-0.45	-0.14	-0.14	0.24	-0.17
p-value		<0.0001	<0.0001		0.4188		<0.0001
Change in T2 volume, n (%)	66 (59.5)	81 (71.7)	88 (80.0)	177 (90.8)	364 (94.3)	190 (82.3)	412 (94.5)
Median %	-10.7	-17.9	-14.6	-6.5	-9.3	-1.23	-1.27
p-value		0.3077	0.3632		0.3080		0.1371
Observed, Yr 2, n (%)	66	81 (71.7)	88 (80.0)	178 (91.3)	366 (94.8)	192 (83.1)	413 (94.7)

⁵⁰ Response to Information Request, Sequence 122, May 13, 2012, Table 3, page 26 of 123. Table reports proportion as percentage in some columns and decimal in others.

Secondary Outcomes For 223, 323, and 324 ⁵⁰							
Endpoint	Trial						
	CAMMS223 ^a			CAMMS323 ^a		CAMMS324 ^a	
	Rebif N=111	Alem 12 N=113	Alem 24 N=110	Rebif N=195	Alem 12 N=386	Rebif N=231	Alem 12 N=436
Median	10.1	7.7	12.4	3.3	3.6	5.87	5.51
Change in MSFC* N (%)	111 (100)	112 (99.1)	110 (100)	187 (95.9)	376 (97.4)	202 (87.4)	426 (97.7)
Estimate	0.32	0.44	0.49	0.05	0.12	-0.04	0.08
p-value		0.2780	0.1335		0.0115		0.0022

6.7 Tertiary and Exploratory Endpoints

The protocols for 223, 323, and 324 listed additional tertiary and exploratory outcome analyses. Hierarchical testing was stopped before reaching the last secondary outcome in all three trials. Therefore, in order to control for multiplicity, the results of the analyses for all the tertiary and exploratory outcomes have questionable relevance for assessing effectiveness. They are included here because they provide some insight into the consistency of the results within and between the three trials. For this review, a table showing only the p-values for the comparisons of alemtuzumab to interferon- β -1a was extracted from a much more detailed six-page table prepared by the sponsor.⁵¹ See Table 20, below.

Table 20 P-values for Tertiary Outcomes Including MRI Outcomes In Prespecified Order

Tertiary Endpoints ⁵² (In order listed in 323 and 324 Protocols) MRI Outcomes p-Values > 0.05	P-Value of Comparison to Placebo			
	223		323	324
	12 mg	24 mg	12 mg	12 mg
Time to first relapse	0.0001	<0.0001	<0.0001	<0.0001
Relapse rate based on relapses treated with steroid therapy	--	--	<0.0001	<0.0001
Time to SAD (3-month criterion)	0.0024	0.0002	0.3266	0.0799
Worsened, stable or improved from baseline – EDSS Yr 2	--	--	0.7357	<0.0001
Time to SRD based on EDSS, N(%)	--	---	0.5192	0.0002

⁵¹ coverletter.pdf, Table 3, pages 26-32.

⁵² Response to Information Request, Sequence 122, May 13, 2012, Table 3, page 27 of 123. Table reports proportion as percentage in some columns and decimal in others.

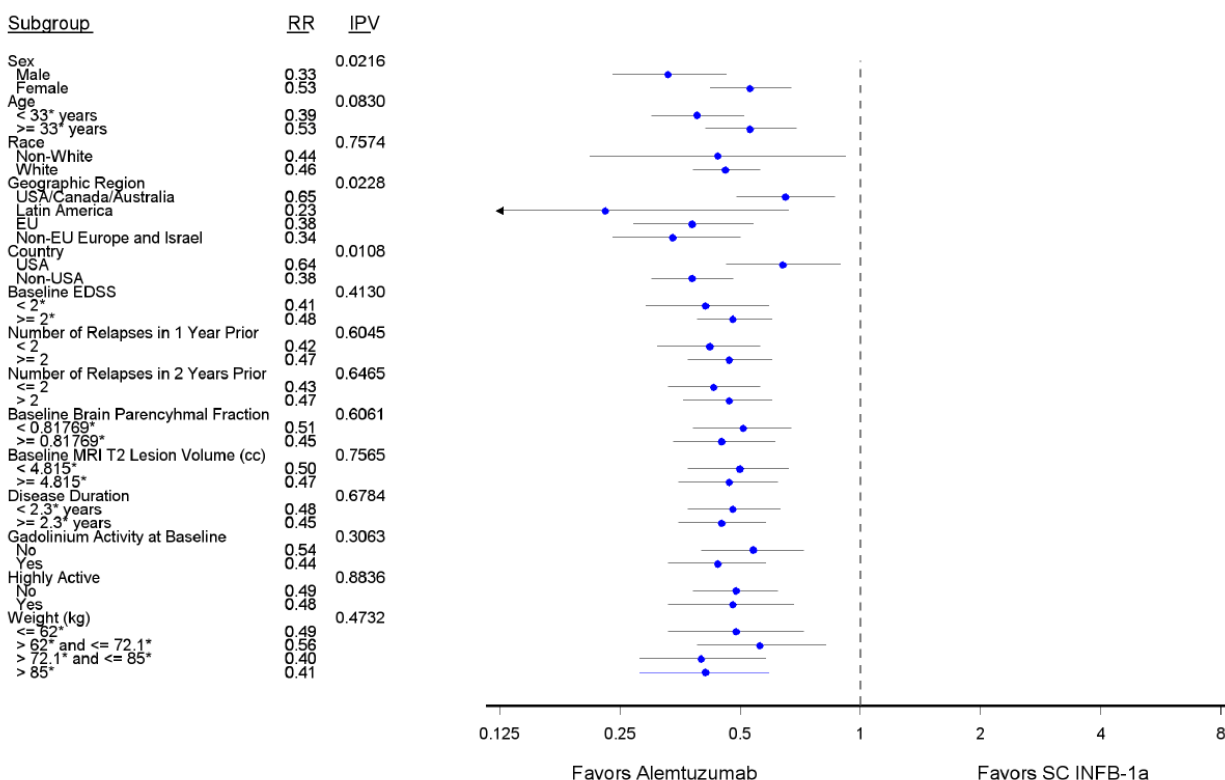
Tertiary Endpoints ⁵² (In order listed in 323 and 324 Protocols) MRI Outcomes p-Values > 0.05	P-Value of Comparison to Placebo			
	223		323	324
	12 mg	24 mg	12 mg	12 mg
Worsened, stable or improved – MSFC, Yr 2	--	--	0.2321	0.0300
Change from baseline in MSFC+ Sloan, Yr 2	--	--	0.0065	0.0097
Worsened, stable or improved – +Sloan (2.5%) Yr2	--	--	0.2832	0.1699
Cumulative New and enlarging T2-hyperintense lesions mean	--	--	0.0288	<0.0001
Percent patients with New and Enlarging T2- hyperintense lesion activity	--	--	0.0352	<0.0001
Patients with New T1-hypointense lesions (Cumulative) mean lesion count t			0.0952	0.0005
Percent patients with New T1-hypointense lesion activity	--	--	0.0545	<0.0001
Patients with Gd-enhancing lesions (Cumulative), Mean lesion count	--	--	0.5278	0.1742
Percent patients with Gd-enhancing lesion activity,	--	--	0.0008	<0.0001
Patients with New Gd-enhancing lesions (Cumulative) Mean lesion count	--	--	0.5155	0.1658
Percent patients with New Gd-enhancing lesion activity	--	--	0.0006	<0.0001
Change from baseline in T1-hypointense lesion volume median	--	--	0.0018	0.1489
Conversion of Gd- enhancing lesions to black holes, Mean	--	--	0.1289	0.0071
Cerebral atrophy (2 ^o outcome in 223) Median % change from M12 to M24	0.1100	0.0337	0.0052	0.1481
Clinical Disease activity Yr 2	--	--	<0.0001	<0.0001
MRI Activity, Composite of Months 12 and 24	--	--	0.0388	<0.0001
Free of MS DiseaseActivity	--	--	0.0064	<0.0001
Quality of Life FAMS FAMS – Mean Change from baseline Yr 2	--	--	0.0463	0.0095
EQ-5D – Mean Change from baseline Yr 2,	--	--	0.6450	0.5445
SF-36- Change from baseline	0.3022	0.0057	0.1795	0.0052
Notes: EDSS = Expanded Disability Status Scale; FAMS = Functional Assessment of MS; Gd = gadolinium; MSFC = Multiple Sclerosis Functional Composite; SAD = sustained accumulation of disability; SRD = sustained reduction of disability -- = endpoint not applicable to study Mean change is used for EDSS. Median change is used MRI-T2 lesion volume and Brain Parenchymal Fraction CAMMS223 values shown are for Month 36 (Yr 3) For CAMMS323 and CAMMS324 values shown are for M24 (Yr 2) with the exception of Cerebral Atrophy. p-value > 0.05				

Reviewer comment: There is no consistent pattern in the tertiary and exploratory outcomes that would support the conclusion that the differences seen in the primary outcomes would have overwhelmed any difference due to placebo effect or observer bias.

6.8 Subpopulations

The point estimate for the relative risk (alemtuzumab to interferon- β -1a) of relapse and sustained disability was less than one for all the pre-specified subgroups. See Figure 3 and Figure 4 below.

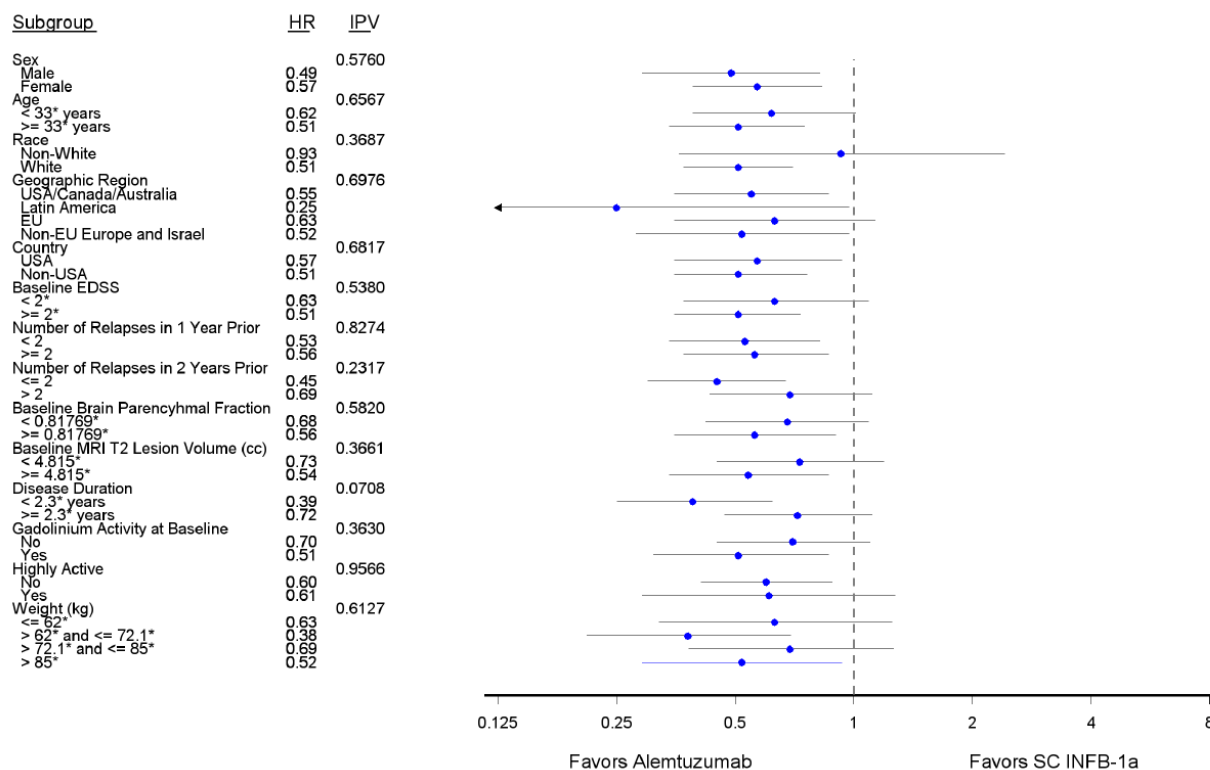
Figure 3 Rate Ratio (RR) of Relapse in Subgroups of CAMMS223, 323, and 324 Subjects⁵³



IPV denotes the p-value from the multiple degree of freedom interaction test of treatment effect homogeneity

⁵³ camms-integrated-summary-clin-efficacy-final.pdf, page 175 of 202

Figure 4 Hazard Ratio (HR) of Sustained Disability in Subgroups of CAMMS223, 323, and 324



IPV denotes the p-value from the multiple degree of freedom interaction test of treatment effect homogeneity.

6.9 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor tested two alemtuzumab dosages, 12mg and 24mg, each given as two courses one year apart, the first course consisting of 5 daily infusions, the second 3 daily infusions. Accompanying treatment included pretreatment with antihistamines at the discretion of the treating physician, pretreatment with IV methylprednisolone and 30 days of acyclovir after treatment. There was no apparent difference in efficacy for the two doses. This may be due to the small sample sizes. The primary comparison of the 12 and 24mg doses would have come from the CAMMS324 trial; however, the sponsor stopped recruitment for the 24mg arm of that trial with only 173 subjects. As requested in the submission, efficacy data for the 24mg dose is treated as corroborative but not substantial evidence of effectiveness for the 12mg dose.

The sponsor's integrated summary of efficacy concluded that there was no evidence of a difference in clinical outcomes between 12mg and 24 mg doses:

"Overall, exploratory efficacy analyses showed that the 12 mg/day dose was generally equivalent to the 24 mg/day dose in clinical outcomes, but had reduced efficacy (or

trends toward reduction) in most MRI based measures. Both of the alemtuzumab dose levels were significantly better than IFNB-1a on the relapse co-primary endpoint and on multiple MRI endpoints.”⁵⁴

6.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

6.11 Antibody formation and effectiveness

6.11.1 Alemtuzumab antibodies

The sponsor reports that 85.2% of the subjects who took either 12 or 24mg doses of alemtuzumab in the 323 and 324 trials tested positive for anti-alemtuzumab antibodies (691 of 811 tested). Of those with antibodies, 92.2% (637 of 691) had inhibitory antibodies. The proportion with antibodies peaked at 1 to 3 months after each of the two treatment cycles. The sponsor found no association between treatment effect and the presence of antibodies. In fact, as shown in Table 21 below, the point estimate of the relapse rate was lower in alemtuzumab subjects with antibodies to alemtuzumab.

Table 21 Relapse Rate and Alemtuzumab Antibodies for 323 and 324⁵⁵

Relapse Rate in 323 and 324 alemtuzumab-treated subjects with and without antibodies to alemtuzumab.			
	No Antibodies at any time	Antibodies	Inhibitory Antibodies
Subjects	119	683	629
Subjects with Relapse	42	187	175
ARR	0.32	0.20	0.24

⁵⁴ camms-integrated-summary-clin-efficacy-final.pdf, page 72 of 206

⁵⁵ adapted from ise-appendix-8-8.pdf, Table 1.2.2.2, page 43 of 192

6.11.2 Interferon antibodies.

Testing for neutralizing antibodies to interferon- β -1a in the 324 trial demonstrated that approximately 16% of subjects entered the trial with neutralizing antibodies to interferon- β -1a. At two years, those with antibodies had a higher event rate. The opposite was true for those with positive antibodies at 24 months. See Table 22.

Table 22 Interferon Neutralizing Antibodies and Clinical Outcomes in CAMMS324 Trial

324 Trial Interferon Neutralizing Antibodies at Baseline and 24 Months with Treatment Effects Compared to Alemtuzumab 12mg at 24 Months ⁵⁶							
Time of Antibody Test		Outcome at 24 Months					
Treatment Group	Antibodies	Subjects		Events		Treatment Effect	
		N (% of 202)	With Events N (%)	n	Rate	RR	p-Value
Baseline Neutralizing Antibody Status							
SC 1FNB - 1a	Positive	34 (16.8%)	20 (58.8%)	42	0.70	0.40	<.0001
SC 1FNB - 1a	Negative	159 (78.7%)	78 (49.1%)	147	0.50	0.55	<.0001
Alemtuzumab 12 mg		426 (100.0)	147 (34.5%)	236	0.28		
24-Month Neutralizing Antibody Status							
SC 1FNB - 1a	Positive	23 (11.4%)	12 (52.2%)	22	0.50	0.56	0.021
SC 1FNB - 1a	Negative	155 (76.7%)	83 (53.5%)	166	0.57	0.48	<.0001
Alemtuzumab 12 mg		426 (100.0)	147 (34.5%)	236	0.28		
There were 202 interferon-β-1a subjects in the Full Analysis set for the 324 trial, 426 alemtuzumab subjects. 193 of 231 (84%) randomized subjects were tested at baseline for the presence of interferon neutralizing antibodies. 178 (77%) were tested at 24 months. The 24-month event rates were higher in those subjects who tested positive for interferon antibodies at Baseline.							

6.12 Compliance with Criteria for Well-controlled Trials in CFR §314.126(b)

As outlined in Table 23, below, FDA regulations (CFR §314.126(b)) define the criteria for determining whether trials were adequate and well-controlled. The protocols for 323 and 324 did not have the ability to distinguish any effects on the subjective clinical outcomes due to alemtuzumab from placebo effects and observer bias. Some bias from the EDSS rater may have been reduced by blinding the raters. However, rater blinding would not have reduced bias introduced by unblinded trial participants and treating

⁵⁶ adapted from camms32400507-body.pdf, Table 14.2.1.2.13, page 1166-7 of 8541

physicians. The protocols lacked procedures to increase the objectivity of the clinical outcomes by minimizing the opportunity for observer bias and placebo effects to modify the clinical outcomes. In fact, some features of the protocols increased the opportunity for bias and placebo effect to influence the clinical outcomes (see Table 24). Drop-out rates that differ by treatment assignment demonstrate that bias was present. Inconsistencies between the MRI and clinical results in both 323 and 324 as well as differences in the SAD outcome between 323 and 324 suggest that a significant portion of the differences in clinical outcomes could be due to biased reporting and placebo effects that were not well-controlled.

Table 23 Extent to which trials 323 and 324 meet criteria for well-controlled trials

Characteristics of Adequate and Well-Controlled Trials from CFR §314.126(B) Found in CAMMS323 and CAMMS324 Trials	
Characteristic of adequate and well-controlled studies from CFR §314.126(B).	Do CAMMS323 and 324 Trials have the characteristic?
(1) There is a clear statement of the objectives of the investigation. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.	Yes.
(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether the treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized: (a) Placebo control; (b) No treatment concurrent control; (c) Dose-response control; (d) Active Control; (e) Historical Control	No. The 323 and 324 trials do not completely satisfy this criteria. A population of similar subjects treated with Rebif provided an adequate active-control population for comparison. However, the protocols introduced bias by requiring different procedures and ancillary treatments for the treatment and active-control groups. Also, the sponsor changed the sample size and stopped a treatment arm after randomization began in the CAMMS324 trial.
(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.	Yes. However, for the 324 trial, Rebif may be no more effective than placebo for treating subjects who have previously failed Rebif or other interferon treatment. Hence equivalence to Rebif as an active comparator may be little different than equivalence to placebo.
(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug. The protocol for the study and the report of its results should describe how subjects were assigned to groups. Ordinarily, in a concurrently controlled study, assignment is by randomization, with or without stratification.	No. The 2:1 and 4:1 randomization ratio selected patients and clinical investigators who had high expectations for treatment with alemtuzumab. Because early drop-out differed in the Rebif and alemtuzumab groups, the treatment group assignment for the full analysis (FA) population was biased. The unblinded design likely increased the extent to which this bias in expectations could have a significant effect on clinical outcomes like relapse rate and EDSS which were dependent entirely on reports from unblinded trial subjects and unblinded treating physicians or a subject's effort and self-report

<p>Characteristics of Adequate and Well-Controlled Trials from CFR §314.126(B)</p> <p>Found in CAMMS323 and CAMMS324 Trials</p>	
	during the EDSS examination.
(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.	No. The protocol blinded EDSS raters, but rater bias is only one source of bias. The unblinding of subjects and treating physicians did nothing to control bias on the part of subjects and site-investigators, primary sources of data used to determine the two key clinical outcomes. The protocols contained features that increased this bias (see Table 24). For example, raters determined the baseline EDSS score used to determine SAD events and confirm relapses after randomization when subjects could know their treatment assignment. In addition, the consent form promised that treatment with the study drug would be discontinued if a subject experienced worsening. It would seem reasonable to expect subjects who preferred to stay on alemtuzumab would have minimized reports of relapses and made more effort during EDSS testing. In order to move on to better treatment, subjects who knew they were receiving Rebif may have been eager to report symptoms and made less effort to attain low EDSS scores.
(6) The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.	No. The protocols described recommendations for the processes to determine relapse events and EDSS scores but had no requirements or documentation that the recommendations were followed at the sites. For instance, a key event in determining relapses was notification, presumably by telephone, from a patient that a relapse was suspected. The sites were not required to keep a log of such notifications.
(7) There is an analysis of the results of the study adequate to assess the effects of the drug. The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed.	No. The analysis followed a pre-specified plan but was not able to determine that part of difference between the groups due to the placebo effect, drop-out, differences in the two treatment arms other than the study drug, and biased reporting from the trial subjects and treating physicians. Use of the FA population for a mITT analysis in the 324 trial failed to account for the differences across treatment groups.

Table 24 Features of 323 and 324 trials that increased opportunity for observer bias

Table of 323 and 324 Protocol features that may have increased biased reporting and unbalance drop-out	
Protocol procedure that decreased ability to distinguish drug effect from placebo effect or biased observation.	Type of bias possibly introduced by protocol procedure
Baseline EDSS scores were determined after randomization when patients could know their treatment assignment.	Baseline EDSS scores are biased with direct effects on the SAD primary clinical outcome.

Table of 323 and 324 Protocol features that may have increased biased reporting and unbalance drop-out	
Protocol procedure that decreased ability to distinguish drug effect from placebo effect or biased observation.	Type of bias possibly introduced by protocol procedure
Consent forms state that “if your disease becomes worse during treatment, you will be told and the study treatment will be stopped and alternative medical care will be discussed with you.” ⁵⁷	Added bias to the placebo effect and increased reporting bias.
For relapse evaluation visits, the unblinded treating neurologist performs a physical examination, obtains vital signs, takes a history of recent symptoms, and fills out the clinical event report form that is reviewed by the Relapse Adjudication Panel. ⁵⁸	Introduces treating physician bias into process for determination of relapse events. This bias is not removed by the RAP process.
Unbalanced 4:1 and 2:1 randomization (A:I) selects subjects and physicians who have a predisposition to think that alemtuzumab treatment is effective	Augments differences in placebo effect between trial arms and increases likelihood of biased reporting.
Publication of the positive results of the 223 trial before recruitment began for the two phase 3 trials.	Augments biased reporting from subjects and treating physicians. Adds to biased (i.e. informed) dropout from trial.
Preventive treatment of only alemtuzumab subjects with acyclovir to prevent herpes outbreaks. Acyclovir has been tested as a potential treatment for MS.	Complicates attribution of cause for any apparent treatment effects.
The selection of an active comparator that required frequent self-injections and is poorly tolerated by patients is likely to add bias to reporting.	Lack of equally difficult double dummy control in alemtuzumab group may have increased subjects’ preference for alemtuzumab over Rebif.
Clinical event report process depended heavily on the unblinded patient to initiate reports of relapse events and on the unblinded treating physician to describe the clinical presentation of possible relapse events.	Patient and treating physician preferences and biases could directly alter reporting of primary clinical outcomes.
Protocol allowed unblinded clinical coordinator or treating physician to determine whether a clinical event was “obviously” not a relapse.	Unblinded site investigators could introduce bias in determination relapse rate.
Only Rebif subjects were scheduled for clinical evaluations by treating physicians at the 1 and 13 month visits.	Relapse rate reporting bias may have been increased by the increased contact with Rebif subjects.

6.13 The significance of the extremely low relapse rates

Both the 323 and 324 results showed some of the lowest relapse rates ever reported for any approved treatment for MS. Extremely large treatment effects could overwhelm any influence by placebo or reporting bias.

In the key 324 trial there were two groups of patients. One group took alemtuzumab once per year in five- and three-day courses of intravenous infusions in a clinical

⁵⁷ camms32400507-16-1-3.pdf, consent forms, page 112/113.

⁵⁸ camms32400507-16-1-1.pdf, protocol

setting. This group received a drug that the patients in both treatment arms would view as more likely to be effective because of the widely known results of an open label phase 2 trial and because they have already continued to have relapses on the active comparator drug. Furthermore, the consent form suggests that they will have to stop taking the preferred drug if they provide evidence that their disease is worsening.

The other group were required to inject themselves three times weekly with Rebif, a drug that could cause disfiguring skin changes at the injection site and flu-like symptoms in as many as 60% of the subjects. They also took yearly courses of methylprednisolone infusion corresponding to the infusions given the alemtuzumab group. This group also knew that the Rebif had failed to work for them before and that if they report worsening of their condition they may be able to stop taking the Rebif and switch to another treatment.

In the 323 and 324 trials, any placebo effect may have been magnified by the unblinding of the patients and treating physicians. Patients who know they are on the preferred drug will be more likely to have a positive placebo effect. Patients who know they are on the drug that is poorly tolerated and has failed before are more likely to have a negative placebo effect.

The trial does not provide any evidence to suggest the extent to which the differences between the relapse rates are due to placebo effects and reporting bias from the unblinded participants in the trial. If the combined effects of placebo and bias changed the relapse outcomes in 10 to 15% of the trial subjects, then the differences attributed to alemtuzumab in the 324 trial would not have been statistically significant. See Table 25.

Table 25 Sensitivity of relapse rate p-value to different degrees of bias in outcome reporting for 324 trial

Table of p-Values for Percent with No Relapses with Various Under- and Over-Reporting Rates 324 Trial FA Population Relapse ⁵⁹								
Pts. with no relapse Alemtuzumab/Rebif p-Value		Rebif Patients Over-Reporting Relapses (Negative Placebo Rate)						
		0%	2%	4%	6%	8%	10%	12%
Alemtuzumab Under-Reporting Relapses (Positive Placebo Rate)	0%	147\104 <.0001	147\102 .0001	147\100 .0003	147\98 .0008	147\96 .0018	147\94 .0038	147\92 .0078
	2%	153\104 .0002	153\102 .0005	153\100 .0012	153\98 .0026	153\96 .0055	153\94 .0109	153\92 .0208
	4%	158\104 .0006	158\102 .0014	158\100 .0031	158\98 .0065	158\96 .0128	158\94 .0241	158\92 .0432
	6%	164\104 .0021	164\102 .0045	164\100 .0090	164\98 .0174	164\96 .0319	164\94 .0558	164\92 .0932

⁵⁹ Values in table verified by FDA statistical reviewer.

Table of p-Values for Percent with No Relapses with Various Under- and Over-Reporting Rates 324 Trial FA Population Relapse ⁵⁹							
Pts. with no relapse Alemtuzumab/Rebif p-Value	Rebif Patients Over-Reporting Relapses (Negative Placebo Rate)						
	0%	2%	4%	6%	8%	10%	12%
8%	169\104 .0053	169\102 .0105	169\100 .0200	169\98 .0363	169\96 .0627	169\94 .1034	169\92 .1630
10%	175\104 .0142	175\102 .0264	175\100 .0468	175\98 .0791	175\96 .1277	175\94 .1973	175\92 .2904
12%	180\104 .0300	180\102 .0524	180\100 .0877	180\98 .1400	180\96 .2138	180\94 .3122	180\92 .4369
14%	186\104 .0662	186\102 .1084	186\100 .1696	186\98 .2537	186\96 .3633	186\94 .4987	186\92 .6573
16%	192\104 .1325	192\102 .2032	192\100 .2980	192\98 .4187	192\96 .5642	192\94 .7307	192\92 .9112

Table 25 calculates the χ^2 p-value for a comparison of the number of subjects with no relapses in the alemtuzumab subjects in the 324 trial to the subjects treated with interferon- β -1a. For instance, if 10% of the subjects treated with alemtuzumab who did not report any relapses (10% of 279 = 28 patients) did actually have a relapse, and if 6% of the subjects treated with interferon- β -1a (6% of 105 = 6 patients) over-reported their relapse events, then the p-value for a difference would be 0.0791. See Table 26, below for the source of the data in Table 25.

Table 26 Subjects Relapse Free in 223, 323, and 324 Trials

Subjects with One or More Relapse in 223, 323, and 324 Trials ⁶⁰						
	CAMMS223		CAMMS323		CAMMS324	
	Alem 12 mg	SC IFNB-1a	Alem 12 mg	SC IFNB-1a	Alem 12 mg	SC IFNB-1a
Subjects Randomized	113	111	386	195	436	231
Subjects in FA Population	107	107	376	187	426	202
Subjects with Relapse	26	47	82	75	147	105
FA Subject with No Relapses	81	60	294	112	279	97
Percent with Relapse	23.01%	42.34%	21.24%	38.46%	33.72%	45.45%
Percent without Relapse	76.99%	57.66%	78.76%	61.54%	66.28%	54.55%

6.14 Consistency of the outcomes between and within the 323 and 324 trials.

The increase in time to SAD event demonstrated in the 324 trial was not confirmed in the 323 trial. In both 323 and 324, the T2 lesion volume MRI outcome pre-specified in the hierarchical analysis failed to show a statistically significant difference between

⁶⁰ Integrated Summary of Efficacy, Tables 2-1, 3-7, and 3-8. Pages 59, 94, and 98 of 202

groups that was consistent with the highly significant difference reported for relapse rates. The MRI T2 lesion volume outcome confirms doubts raised in the statistical review about whether there was any drug effect on the time to SAD in the 324 trial. The multiple exploratory MRI outcomes were not consistently positive (see Table 20).

6.15 Efficacy Summary

The two pivotal trials are not well controlled despite rater blinding and a relapse adjudication panel. The two pivotal trials demonstrate remarkable reductions in relapse rate for the alemtuzumab groups, but there is no evidence that placebo effects and observer bias did not explain a significant proportion of these reductions. There was no evidence of a reduction in SAD rate in the 323 trial to support the statistically significant reduction found in the alemtuzumab group of the 324 trial. Furthermore, because of bias introduced by the determination of the baseline EDSS after randomization in the 324 trial, the FDA the statistical reviewer determined that there was no increase in the time to SAD that can be attributed to treatment with alemtuzumab. The review of safety determined that there were significant concerns about the occurrence of serious malignancies, infections, and autoimmune disorders.

These findings are consistent with the concerns expressed in an editorial accompanying the publication of the results of the 323 and 324 trials in the Lancet:⁶¹

“The real magnitude of the effect is difficult to assess. The only rater-blinded design might have been a source of bias in assessments of clinical outcomes, especially in the context of the high expectations created with the phase 2 study [223]. The absence of an effect on progression of impairment in CARE-MS I [323] could be partly attributable to the unexpectedly low progression in the interferon group, but it also suggests that in this early multiple sclerosis population we still do not have valid criteria to select those patients who need more aggressive treatment to prevent progression of disability.”

With inadequate evidence to suggest that alemtuzumab prevents progression of disability and with potentially biased evidence for a reduction in relapse rates, there is doubt that the risks of alemtuzumab outweigh any benefits.

⁶¹ Till Sprenger, Ludwig Kappos. Lancet. Vol 380. November 24, 2012. pp. 1795-6

7. Review of Safety

Safety Summary

See the safety review performed by Evelyn Mentari, M.D., Division of Neurological Products.

8. Post-Marketing Information

None for the MS indication.

9. Appendices

9.1 Complete List of Selection Criteria for CAMMS323 Trial

Inclusion Criteria

1. Signed informed consent form (ICF)
2. Age 18 to 50 years old (inclusive) as of the date the ICF is signed
3. Diagnosis of MS per update of McDonald criteria [see Appendix 9.2 below], and cranial MRI scan demonstrating white matter lesions attributable to MS within 5 years of Screening
4. Onset of MS symptoms (as determined by a neurologist, either at present or retrospectively) within 5 years of the date the ICF is signed
5. EDSS score 0.0 to 3.0 (inclusive) at Screening
6. ≥ 2 MS attacks (first episode or relapse) occurring in the 24 months prior to the date the ICF is signed, with ≥ 1 attack in the 12 months prior to the date the ICF is signed, with objective neurological signs confirmed by a physician, nurse practitioner, or other Genzyme-approved health-care provider. The objective signs may be identified retrospectively.

Exclusion Criteria

1. Current participation in another clinical study
2. Received prior therapy for MS other than corticosteroids, e.g., alemtuzumab, interferons, IV immunoglobulin, glatiramer acetate, natalizumab, and mitoxantrone
3. Exposure to azathioprine, cladribine, cyclophosphamide, cyclosporine-A, methotrexate, or any other immunosuppressive agent other than systemic corticosteroid treatment
4. Received treatment with a monoclonal antibody for any reason
5. Previous treatment with any investigational medication, i.e. drug has not been approved at any dose or for any indication (Prior treatment with herbal medications or nutritional supplements is permitted)
6. Has any progressive form of MS
7. History of malignancy (except basal skin cell carcinoma)
8. Any disability acquired from trauma or another illness that, in the opinion of the Investigator, could interfere with evaluation of disability due to MS
9. Previous hypersensitivity reaction to any immunoglobulin product
10. Known allergy or intolerance to interferon beta, human albumin, or mannitol
11. Intolerance of pulsed corticosteroids, especially a history of steroid psychosis

12. Inability to self-administer SC injections or receive SC injections from caregiver
13. Inability to undergo MRI with gadolinium administration
14. CD4+ cell count (absolute CD3+CD4+) < lower limit of normal (LLN) at Screening
15. CD8+ cell count (absolute CD3+CD8+) <LLN at Screening
16. B-cell count (absolute CD19+) <LLN at Screening
17. Absolute neutrophil count <LLN at Screening
18. Known bleeding disorder (e.g., dysfibrinogenemia, factor IX deficiency, hemophilia, Von Willebrand's disease, disseminated intravascular coagulation (DIC), fibrinogen deficiency, or clotting factor deficiency)
19. Seropositivity for human immunodeficiency virus (HIV)
20. Significant autoimmune disease including but not limited to immune cytopenias, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease, severe psoriasis
21. Presence of anti-thyroid stimulating hormone (TSH) receptor (TSHR) antibodies (i.e., above the LLN)
22. Active infection, e.g., deep-tissue infection, that the Investigator considers sufficiently serious to preclude study participation
23. In the Investigator's opinion, is at high risk for infection (eg, indwelling catheter, dysphagia with aspiration, decubitus ulcer, history of prior aspiration pneumonia or recurrent urinary tract infection)
24. Latent tuberculosis unless effective anti-tuberculosis therapy has been completed, or active tuberculosis. More specific guidance on tuberculosis testing and patient eligibility is provided in the Study Operations Manual (SOM).
25. Infection with hepatitis C virus
26. Past or present hepatitis B infection (positive hepatitis B serology)
27. Childbearing potential with a positive serum pregnancy test, pregnant, or lactating
28. Unwilling to agree to use a reliable and acceptable contraceptive method throughout the study period (fertile patients only). Reliable and effective contraceptive method(s) include: intrauterine device (IUD), hormonal-based contraception, surgical sterilization, abstinence, or double-barrier contraception (condom and occlusive cap [diaphragm or cervical cap with spermicide]).
29. Major psychiatric disorder that is not adequately controlled by treatment
30. Epileptic seizures that are not adequately controlled by treatment

31. Major systemic disease or other illness that would, in the opinion of the Investigator, compromise patient safety or interfere with the interpretation of study results, e.g., current peptic ulcer disease or other conditions that may predispose to hemorrhage
32. Medical, psychiatric, cognitive, or other conditions that, in the Investigator's opinion, compromise the patient's ability to understand the patient information, to give informed consent, to comply with the trial protocol, or to complete the study
33. Confirmed platelet count < LLN of the evaluating laboratory at Screening or documented at <100,000/ μ L within the past year on a sample without platelet clumping
34. Prior history of invasive fungal infections
35. Cervical high risk human papillomavirus (HPV) positivity or abnormal cervical cytology other than abnormal squamous cells of undetermined significance (ASCUS)
36. Seropositive for Trypanosoma cruzi or the Human T-lymphotropic virus type I or type II (HTLV I/II) (testing required in endemic regions only). Guidance on region-specific testing recommendations and patient eligibility is provided in the SOM.
37. Any other illness or infection (latent or active) that, in the Investigator's opinion, could be exacerbated by either study medication
38. Any hepatic or renal function value grade 2 or higher at Screening, with the exception of hyperbilirubinemia due to Gilbert's syndrome. See Table below, drawn from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE), published 09 August 2006.

Hepatic	
Bilirubin	>1.5 \times ULN
SGOT/AST	>2.5 \times ULN
SGPT/ALT	>2.5 \times ULN
Alkaline phosphatase	>2.5 \times ULN
Renal	
Creatinine	>1.5 \times ULN

9.2 The McDonald Criteria from the CAMMS323 protocol

McDonald Diagnostic Criteria for MS¹

Clinical (Attacks)	Number of Anatomical Sites Clinically Affected	Additional Requirements to Make Diagnosis
2 or more	2 or more	<ul style="list-style-type: none"> None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
2 or more	1	<ul style="list-style-type: none"> Dissemination in <u>space</u> by MRI^{3,4} or positive CSF and 2 or more MRI lesions consistent with MS or further clinical attack involving different site
1	2 or more	<ul style="list-style-type: none"> Dissemination in <u>time</u> by MRI or second clinical attack
1 (mono-symptomatic)	1	<ul style="list-style-type: none"> Dissemination in <u>space</u> by MRI^{3,4} or positive CSF and 2 or more MRI lesions consistent with MS <p>AND</p> <ul style="list-style-type: none"> Dissemination in <u>time</u> by MRI or second clinical attack
0 (progression from onset) ²	1	<ul style="list-style-type: none"> Positive CSF <p>AND</p> <ul style="list-style-type: none"> Dissemination in <u>space</u> by MRI evidence of 9 or more T2 brain lesions or 2 or more cord lesions or 4-8 brain and 1 cord lesion or positive VEP with 4-8 MRI lesions or positive VEP with less than 4 brain lesions plus 1 cord lesion <p>AND</p> <ul style="list-style-type: none"> Dissemination in <u>time</u> by MRI or continued progression for 1 year

¹ McDonald et al. Recommended Diagnostic Criteria for MS. Ann Neurol 2001;50:121-127.

² Thompson et al. Diagnostic criteria for primary progressive MS: A position paper. Ann Neurol 2000;47:831-835.

³ Barkhof et al. Comparison of MR imaging criteria at first presentation to predict conversion to clinically definite MS. Brain 1997;120:2059-2069.

⁴ Tintoré et al. Isolated demyelinating syndromes: comparison of different imaging criteria to predict conversion to clinically definite MS. Am J Radiology 2000;21:702-706.

9.3 Tertiary Outcome Measures for 323 and 324 Trials

The following seventeen tertiary outcome measures are listed in the trial protocol:

- Time to first relapse
- Proportion of patients with no MS disease activity (i.e., MRI, relapse, SAD)
- Time to SAD, sustained over a 3-month period
- Acquisition of disability as measured by change from Baseline in MSFC and MSFC components plus Sloan Charts

- The proportion of patients who have worsened, remained stable, or improved as indicated by change from Baseline in MSFC scores
- The proportion of patients who have worsened, remained stable, or improved as indicated by change from Baseline in EDSS scores
- The proportion of patients who have worsened, remained stable, or improved as indicated by change from Baseline in MSFC scores plus Sloan Charts
- Time to sustained reduction in disability (SRD) based on EDSS scores
- Percent change from Baseline in MRI findings:
 - o MRI-T1-measured cerebral volume
 - o MRI-T1-hypointense lesion volume
 - o Unconventional MRI sequences (performed at selected study centers) e.g., magnetization transfer ratio (MTR), magnetic resonance spectroscopy (MRS), and/or diffusion weighted imaging (DWI)
- Number of new gadolinium-enhancing lesions on MRI-T1
- Number of new or enlarging hyperintense lesions measured by T2-weighted MRI
- Relapse rate based on relapses requiring corticosteroid therapy
- Change from Baseline in HRQoL measures, including:
 - o Functional Assessment of MS (FAMS)
 - o EuroQol in 5 dimensions (EQ-5D)
 - o Medical Outcomes Study 36-Item Short-Form Survey (SF-36)
- Comparison of healthcare resource utilization using the HRUQ

9.4 Advisory Committee Meeting

The meeting is scheduled for November 13, 2012.

9.5 EDSS Scale Components

Table 27 EDSS Components for All Visits for 324 Subject 1066

Trial CAMMS324 EDSS Components for Screened and Randomized Subjects				
	XNTEST (Neurostatus Item)	XNLOC	XNSCAT	Records [§]
1	*Able to lift only one leg at a time	Left	Pyramidal-Limb Strength	3028
2	*Able to lift only one leg at a time	Right	Pyramidal-Limb Strength	3025
3	*Able To Walk Without Rest Or Aid		Ambulation	8000
4	*Constant assistance walk 100 meters		Ambulation	311
5	*Cutaneous Reflexes	Left	Pyramidal-Reflexes	5417
6	*Cutaneous Reflexes	Right	Pyramidal-Reflexes	5417
7	*Disc Pallor	Left	Vision (Optic) Functions	5714
8	*Disc Pallor	Right	Vision (Optic) Functions	5713
9	*Fatigue		Cerebral Functions	6610

Trial CAMMS324 EDSS Components for Screened and Randomized Subjects				
	XNTEST (Neurostatus Item)	XNLOC	XNSCAT	Records [§]
10	*Hopping On Foot	Left	Pyramidal-Limb Strength	4740
11	*Hopping On Foot	Right	Pyramidal-Limb Strength	4740
12	*Lhermitte		Sensory Functions	5462
13	*Palmomental Reflex	Left	Pyramidal-Reflexes	3368
14	*Palmomental Reflex	Right	Pyramidal-Reflexes	3368
15	*Paraesthesiae LE	Left	Sensory Functions	5159
16	*Paraesthesiae LE	Right	Sensory Functions	5157
17	*Paraesthesiae Trunk	Left	Sensory Functions	5143
18	*Paraesthesiae Trunk	Right	Sensory Functions	5141
19	*Paraesthesiae UE	Left	Sensory Functions	5167
20	*Paraesthesiae UE	Right	Sensory Functions	5165
21	*Position Test LE, Sinking	Left	Pyramidal-Limb Strength	4954
22	*Position Test LE, Sinking	Right	Pyramidal-Limb Strength	4954
23	*Position Test UE, downward drift	Left	Pyramidal-Limb Strength	5421
24	*Position Test UE, downward drift	Right	Pyramidal-Limb Strength	5421
25	*Position Test UE, Pronation	Left	Pyramidal-Limb Strength	5517
26	*Position Test UE, Pronation	Right	Pyramidal-Limb Strength	5516
27	*Sexual Dysfunction		Bladder/Bowel Functions	3951
28	*Walking On Heels	Left	Pyramidal-Limb Strength	5357
29	*Walking On Heels	Right	Pyramidal-Limb Strength	5359
30	*Walking On Toes	Left	Pyramidal-Limb Strength	5365
31	*Walking On Toes	Right	Pyramidal-Limb Strength	5367
32	Actual Distance Up To 500 Meters		Ambulation	7297
33	Ankle	Left	Pyramidal-Reflexes	8440
34	Ankle	Right	Pyramidal-Reflexes	8439
35	Arm	Left	Pyramidal-Spasticity	8417
36	Arm	Right	Pyramidal-Spasticity	8418
37	Biceps	Left	Pyramidal-Limb Strength	8439
38	Biceps	Left	Pyramidal-Reflexes	8439
39	Biceps	Right	Pyramidal-Limb Strength	8441
40	Biceps	Right	Pyramidal-Reflexes	8439
41	Bowel Dysfunction		Bladder/Bowel Functions	8437
42	Bowel/Bladder (Converted FS Score)		EDSS	8447
43	Bowel/Bladder FSS		Bladder/Bowel Functions	8445
44	Brachioradialis	Left	Pyramidal-Reflexes	8441
45	Brachioradialis	Right	Pyramidal-Reflexes	8439
46	Brainstem Function		EDSS	8447
47	Brainstem Functions FSS		Brainstem Functions	8446
48	Catheterisation		Bladder/Bowel Functions	8405
49	Cerebellar Function		EDSS	8436
50	Cerebellar Functions FSS		Cerebellar Functions	8433
51	Cerebral Function		EDSS	8447
52	Cerebral Functions FSS		Cerebral Functions	8443
53	Decrease In Mentation		Cerebral Functions	8433
54	Deltoids	Left	Pyramidal-Limb Strength	8440
55	Deltoids	Right	Pyramidal-Limb Strength	8444
56	Depression		Cerebral Functions	8439
57	Dorsiflexion (feet/toes)	Left	Pyramidal-Limb Strength	8425
58	Dorsiflexion (feet/toes)	Right	Pyramidal-Limb Strength	8424
59	Dysarthria		Brainstem Functions	8444
60	Dysphagia		Brainstem Functions	8445

Trial CAMMS324 EDSS Components for Screened and Randomized Subjects				
	XNTEST (Neurostatus Item)	XNLOC	XNSCAT	Records [§]
61	EDSS Step		EDSS	8442
62	Eom Impairment		Brainstem Functions	8446
63	Euphoria		Cerebral Functions	8429
64	Facial Weakness		Brainstem Functions	8444
65	Gait	Left	Pyramidal-Spasticity	8398
66	Gait	Right	Pyramidal-Spasticity	8396
67	Gait Ataxia		Cerebellar Functions	8419
68	Head Tremor		Cerebellar Functions	8443
69	Hearing Loss		Brainstem Functions	8445
70	Hesitancy/Retention		Bladder/Bowel Functions	8442
71	Hip Flexors	Left	Pyramidal-Limb Strength	8432
72	Hip Flexors	Right	Pyramidal-Limb Strength	8432
73	Knee	Left	Pyramidal-Reflexes	8439
74	Knee	Right	Pyramidal-Reflexes	8439
75	Knee Extensors	Left	Pyramidal-Limb Strength	8443
76	Knee Extensors	Right	Pyramidal-Limb Strength	8442
77	Knee Flexors	Left	Pyramidal-Limb Strength	8444
78	Knee Flexors	Right	Pyramidal-Limb Strength	8443
79	Leg	Left	Pyramidal-Spasticity	8419
80	Leg	Right	Pyramidal-Spasticity	8416
81	Nystagmus		Brainstem Functions	8446
82	Other cranial nerve functions		Brainstem Functions	8234
83	Other, E.G. Rebound		Cerebellar Functions	7704
84	Plantar flexion (feet/toes)	Left	Pyramidal-Limb Strength	8440
85	Plantar flexion (feet/toes)	Right	Pyramidal-Limb Strength	8439
86	Plantar Response	Left	Pyramidal-Reflexes	8375
87	Plantar Response	Right	Pyramidal-Reflexes	8377
88	Position Sense LE	Left	Sensory Functions	8434
89	Position Sense LE	Right	Sensory Functions	8434
90	Position Sense UE	Left	Sensory Functions	8441
91	Position Sense UE	Right	Sensory Functions	8442
92	Pyramidal Function		EDSS	8445
93	Pyramidal Functions FSS		Pyramidal-Spasticity	8444
94	Rapid Alternate Move LE	Left	Cerebellar Functions	8402
95	Rapid Alternate Move LE	Right	Cerebellar Functions	8400
96	Rapid Alternate Move UE	Left	Cerebellar Functions	8437
97	Rapid Alternate Move UE	Right	Cerebellar Functions	8438
98	Reported Range Without Aid - Meters		Ambulation	7584
99	Reported Range Without Aid - Minute		Ambulation	7172
100	Romberg Test		Cerebellar Functions	8405
101	Scotoma	Left	Vision (Optic) Functions	8406
102	Scotoma	Right	Vision (Optic) Functions	8403
103	Sensory Function		EDSS	8444
104	Sensory Functions FSS		Sensory Functions	8442
105	Superficial Sensation LE	Left	Sensory Functions	8437
106	Superficial Sensation LE	Right	Sensory Functions	8436
107	Superficial Sensation Trunk	Left	Sensory Functions	7976
108	Superficial Sensation Trunk	Right	Sensory Functions	7977
109	Superficial Sensation, UE	Left	Sensory Functions	8442
110	Superficial Sensation, UE	Right	Sensory Functions	8443
111	Tandem Walking		Cerebellar Functions	8422

Trial CAMMS324 EDSS Components for Screened and Randomized Subjects				
	XNTEST (Neurostatus Item)	XNLOC	XNSCAT	Records [§]
112	Tremor/Dysmetria LE	Left	Cerebellar Functions	8425
113	Tremor/Dysmetria LE	Right	Cerebellar Functions	8421
114	Tremor/Dysmetria UE	Left	Cerebellar Functions	8439
115	Tremor/Dysmetria UE	Right	Cerebellar Functions	8438
116	Triceps	Left	Pyramidal-Limb Strength	8439
117	Triceps	Left	Pyramidal-Reflexes	8441
118	Triceps	Right	Pyramidal-Limb Strength	8440
119	Triceps	Right	Pyramidal-Reflexes	8442
120	Trigeminal Damage		Brainstem Functions	8446
121	Truncal Ataxia		Cerebellar Functions	8431
122	Urgency/Incontinence		Bladder/Bowel Functions	8442
123	Vibration Sense LE	Left	Sensory Functions	8440
124	Vibration Sense LE	Right	Sensory Functions	8440
125	Vibration Sense UE	Left	Sensory Functions	8439
126	Vibration Sense UE	Right	Sensory Functions	8440
127	Visual (Converted FS Score)		EDSS	8430
128	Visual Acuity (Corrected)	Left	Vision (Optic) Functions	8331
129	Visual Acuity (Corrected)	Right	Vision (Optic) Functions	8323
130	Visual Fields	Left	Vision (Optic) Functions	8417
131	Visual Fields	Right	Vision (Optic) Functions	8413
132	Visual FSS		Vision (Optic) Functions	8428
133	Wrist/Finger Extensors	Left	Pyramidal-Limb Strength	8439
134	Wrist/Finger Extensors	Right	Pyramidal-Limb Strength	8442
135	Wrist/Finger Flexors	Left	Pyramidal-Limb Strength	8439
136	Wrist/Finger Flexors	Right	Pyramidal-Limb Strength	8441
Total number of records in XN.xpt File for CAMMS324 Trial				1033696
§ From 975 subjects, 840 randomized.				



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: BLA 103,948
Supplement #: 5139
Drug Name: Aletuzumab
Indication(s): Multiple Sclerosis
Applicant: Genzyme
Date(s): Submission: November 27, 2012
Review Priority: Standard Review
Biometrics Division: Neurology
Statistical Reviewer: Sharon Yan, Ph.D.
Concurring Reviewers: Kun Jin, Ph.D., Team Leader
Jim Hung, Ph.D., Director
Medical Division: Neurology
Clinical Team: John Marler, M.D., Clinical Reviewer
Evelyn Mentari, M.D., Safety Reviewer
Billy Dunn, M.D., Team Leader
Eric Bastings, Acting Division Director
Project Manager: Hamet Toure, Pharm.D., MPH

Keywords:

Baseline imbalance, open label, relative risk, sensitivity analysis

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1 EXECUTIVE SUMMARY

Two pivotal studies, Studies 323 and 324, are submitted by Genzyme to support the claim that aletuzumab is effective for the treatment of patients with relapsing forms of multiple sclerosis (MS) to slow or reverse the accumulation of physical disability and reduce the frequency of clinical exacerbation.

Both studies are randomized, active-controlled and rater-blinded in design with identical co-primary endpoints: annualized relapse rate (ARR) and sustained accumulation of disability (SAD). The protocols of the two pivotal studies were initially submitted in May 2007 under the SPA request. Despite FDA's strong recommendation of double-blind, double-dummy design, Genzyme initiated the two studies as originally designed without FDA's agreement for SPA.

Statistically significant treatment difference was shown in annualized relapse rate in both pivotal studies 323 and 324. Study 324 also showed significant treatment difference in sustained accumulation of disability (SAD), while Study 323 failed to demonstrate the efficacy on SAD.

The question is how much of the difference is due to the study drugs. The bias in patients' preference toward aletuzumab over the active control of IFNB-1a is evident as shown in the unbalanced dropout rates between the treatment groups (Table 12).

It is troublesome to see that so many patients were not assessed for baseline and were not treated until weeks after the randomization. Such delaying not only allowed patients to drop out before receiving any treatment and assessments when assigned treatment was undesired but also effectively invalidated the baseline scores. When screening EDSS score was used as baseline, the SAD events went down by more than 10% in all IFNB-1a groups and went up by more than 10% in all aletuzumab groups in the two studies, resulted a p-value of 0.2010 for treatment difference (Table 15). The results suggest that possible unblinding might not be limited to patients.

The reviewer concludes that for the primary endpoint of SAD, efficacy is not validly established based on 1) validity of EDSS baseline scores; 2) selection bias in the full analysis set; and 3) inconsistency in results between the two studies and among the regions (Table 21 and Table 22).

Results in relapse rate are relatively consistent. However, patients' bias in preference of aletuzumab, possible over reporting of relapses in IFNB-1a group and under reporting in aletuzumab groups, and questions in interpreting the results in Study 324 have made accurate estimate of relapse rate impossible.

The reviewer concludes that adequate and well controlled studies need to be conducted to establish the efficacy of aletuzumab for treatment of patients with multiple sclerosis.

2 INTRODUCTION

2.1 Overview

Lemtrada® (alemtuzumab) is proposed for the treatment of patients with relapsing forms of Multiple Sclerosis (MS) to slow or reverse the accumulation of physical disability and reduce the frequency of clinical exacerbations.

Alemtuzumab was approved in the United States in May 2001 under Biologics License Application (BLA) 103948 for the treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL) and is known by the proprietary name Campath® for this indication. Development of alemtuzumab for use in MS was conducted under IND 10,717. Four clinical studies, including one phase-2 study, 2 pivotal phase-3 studies, and a long-term extension study, comprised Genzyme's development program in MS. The two pivotal phase-3 studies are included in this review.

The two pivotal phase 3 studies 323 and 324 were active-controlled, randomized, rater-blinded studies comparing the safety and efficacy of alemtuzumab to SC IFNB-1a (Rebif®) in patients with relapsing forms of MS. Study CAMMS323 enrolled treatment-naïve patients and study CAMMS324 enrolled patients who had at least 1 relapse during prior treatment (for ≥ 6 months) with interferon beta or glatiramer acetate.

Patients received annual cycles of alemtuzumab or 3-times weekly IFNB-1a. Alemtuzumab was administered via daily IV infusions for 5 consecutive days at Month 0 (Cycle 1) and for 3 consecutive days at Month 12 (Cycle 2). IFNB-1a was administered via 3-times weekly SC injections at a dose of 44 µg (the highest approved dose) after an initial dose titration over 4 weeks.

The two Phase-3 studies had the same primary efficacy endpoints: relapse rate and time to 6-month sustained accumulation of disability. Patients were followed for efficacy for 2 years after initiation of treatment. The following table presents a summary of the studies included in this review.

Table 1 List of all studies included in analysis

	Phase and Design	Treatment Period	Comparator	# of Subjects per Arm	Study Population
CAMMS323 Pivotal Trial	Phase 3, randomized, rater-blind, 2-arm, active-controlled	2 years	IFNB-1a	Aletuzumab 12 mg: 386 IFNB-1a: 195	Aletuzumab naïve patients
CAMMS324 Pivotal Trial	Phase 3, randomized, rater-blind, 3-arm, active-controlled	2 years	IFNB-1a	Aletuzumab 12 mg: 436 Aletuzumab 24 mg: 173 IFNB-1a: 231	Patients who failed prior MS therapy

2.2 Data Sources

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Genzyme originally submitted this sBLA for MS on June 8, 2012, following which the Division issued a refuse-to-file letter on August 7, 2012 due to serious issues in safety, clinical and efficacy data. Resubmission of the BLA was submitted on November 27, 2012 and was filed.

The reviewer's analysis of the primary endpoints is based on original data transcribed from case report form by the sponsor.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Two pivotal phase 3 studies, Protocols 323 and 32400507 (referred as 324 thereafter), are included in this review. The objectives of the two studies were to compare the safety and efficacy of 2 annual cycles of intravenous (IV) alemtuzumab to 3-times weekly SC interferon beta-1a (IFNB-1a, Rebif) in patients with RRMS who have recent MS disease activity as demonstrated by clinical relapses.

The 2 studies were designed similarly with the exception of patient population in disease condition and prior treatment: both are phase 3, randomized, rater-blinded and active-controlled with identical primary endpoints. Study 323 enrolled treatment-naïve patients and study 324 enrolled patients who had at least 1 relapse during prior treatment (for ≥ 6 months) with interferon beta or glatiramer acetate.

In Study 323, a total of 525 patients were planned and 581 patients were actually randomized in a 2:1 ratio to receive 2 annual cycles of 12 mg/day alemtuzumab or 3-times weekly IFNB-1a. Patients were enrolled in 97 study sites worldwide.

Under the original protocol of Study 324, approximately 1200 patients were to be randomized in a 2:2:1 ratio to receive 2 annual cycles of alemtuzumab 12 mg/day or 24 mg/day, or 3-times weekly IFNB-1a. Beginning with Amendment 2, after data from the phase 2 trial 223 became available, alemtuzumab 24 mg/day group was closed to newly enrolling patients. All patients enrolled after approval of Amendment 2 were randomized in a 2:1 ratio to receive alemtuzumab

12 mg/day or IFNB-1a. The sample size for both alemtuzumab 12 mg and IFNB-1a was reduced. The duration of the study was changed from 2 years after the randomization of the last patient to 2 years from the initial treatment. A total of 840 patients were randomized in 181 study sites worldwide.

For both studies, patients assigned to alemtuzumab were to receive 5 daily IV infusions during cycle 1 at Month 0, and 3 daily IV infusions during cycle 2 at Month 12. Patients assigned to IFNB-1a were to receive injections of 44 µg, 3 times a week from Month 0 through Month 24, after initial dose titration over 4 weeks. The dose of IFNB-1a could be adjusted to a lower dose if the 44 µg dose was not well tolerated.

The main inclusion criteria for the two studies were patients who were 18 to 50 years in age, diagnosed of MS based on updated McDonald criteria, had cranial MRI scan demonstrating white matter lesions attributing to MS within 5 years of screening, had EDSS score of 0.0 to 3.0 for study 323 and EDSS score 0.0 to 5.0 for study 324 (inclusive), and had ≥ 2 MS attacks occurring in the prior 24 months and ≥ 1 MS attack in the prior 12 months.

Treatment Blinding

The two pivotal studies were designed as rater-blinded. Key efficacy assessments, including the EDSS, the multiple sclerosis functional score (MSFC), and Sloan charts were performed by blinded raters. Analysis of the relapse co-primary endpoint and all other relapse-related endpoints was based on relapse determinations made by an independent, blinded Relapse Adjudication Panel (RAP). All cranial MRIs were evaluated by one or more neuroradiologists at an independent central facility with no access to patients' treatment assignment.

Per the protocol, for each patient at the Month 12 and Month 24 (or early discontinuation) visit, there was an "assessment of blinding for blinded neurologists and MSFC assessors." All assessors were asked to complete a source worksheet specifying whether they were blinded to the patient's treatment status (a yes/no question) every time they conducted a blinded assessment.

In the event that a blinded rater indicated that they were aware of a patient's treatment assignment, a different blinded evaluator was to perform all subsequent assessments for the patient for whom the blind had been broken.

The initial protocols permitted EDSS assessments to be performed by the unblinded treating physician under circumstances where the blinded rater was not available to evaluate a patient who presented with a suspected relapse. Under Amendment 5 and after FDA continued concern of unblinded assessments over multiple correspondences, relapse EDSS assessments by unblinded personnel were no longer permitted.

3.2.1.2 Study Endpoints

The two pivotal studies 323 and 324 had identical primary efficacy endpoints: relapse rate and time to sustained accumulation of disability (SAD).

Clinical Relapses

In the event of a suspected relapse, patients were required to contact their center within 48 hours, and visit the center within 7 days of symptom onset. At the center, the trained, blinded rater was to perform an examination, with no reference to previous scores.

The analysis of the relapse endpoint was based on relapse determinations made by an independent, blinded Relapse Adjudication Panel (RAP). Six independent neurologists with expertise in multiple sclerosis (MS) clinical research made up the RAP. An independent Contract Research Organization (CRO), Applied Clinical Intelligence (ACI), assembled the RAP.

Each potential relapse was reviewed by 2 RAP members. The RAP members worked and entered their evaluations independently, on cases randomly assigned to them by ACI. RAP members could not reference case adjudication details from other RAP members.

ACI consolidated individual RAP member assessments. If the 2 reviewers provided a conflicting assessment, a third RAP member reviewed the case such that a majority vote could be obtained. In such cases, the third RAP reviewer was not aware of review details as provided by the other RAP members, nor were they aware that their review was solicited to resolve a split vote. The majority vote of up to 3 RAP members served as the final determination as to whether an event met criteria for an on-study protocol defined relapse.

Sustained Accumulation of Disability (SAD)

Disability was evaluated based on EDSS scores, assessed every 3 months. The scale ranges from 0.0 (normal neurological examination) to 10.0 (death due to MS) in half-point increments. A patient was considered to have reached SAD, sustained over a 6-month period, when the following conditions had been met:

- For patients with a baseline EDSS score of 0, their EDSS score must increase by at least 1.5 points and remain at least 1.5 points above baseline during the next 2 scheduled assessments (i.e., 6 consecutive months).
- For patients with a baseline EDSS score of greater than or equal to 1, their EDSS score must increase by at least 1 point and remain at least 1 point above baseline during the next 2 scheduled assessments (i.e., 6 consecutive months).

The onset date of SAD was to be the date of the first EDSS assessment that began the 6 consecutive month period of SAD. Patients who did not reach the SAD endpoint were to be censored at their last visit.

Any unscheduled EDSS assessments (except for early study discontinuations) were not to be included in the determination of SAD.

Other Efficacy Variables

Secondary efficacy endpoints are rank ordered as follows:

1. Proportion of patients who are relapse free at Year 2;
2. Change from baseline in EDSS;
3. Percent change in MRI T2-lesion volume at Year 2.
4. Acquisition of disability as measured by change from baseline in MSFC;

Cranial MRIs were performed at baseline and at Months 12 and 24. Imaging was performed at local site and data were read at central facility by blinded neuroradiologists.

The MSFC is a composite measure of Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT), and Paced Auditory Serial Addition Test (PASAT). Each of the component score is standardized to a Z score using the overall (across all treatment groups) mean and standard deviation for the given component at baseline (i.e., $Z_{9HPT} = [Raw\ Score_{9HPT} - MEAN_{9HPT}] / SD_{9HPT}$). A Z-score for the overall MSFC can be calculated as the average of the Z-scores from the three individual components. Increases in MSFC Z-scores are indicative of improvement.

The MSFC was administered by trained, blinded assessors at Baseline and every 6 months thereafter until Month 24/early discontinuation.

3.2.2 Statistical Methodologies

The two studies had similar design and shared the same Statistical Analysis Plan with some added notes for Protocol 324. Under Amendment 2 of Protocol 324 and all subsequent amendments, all efficacy analyses for Study 324 were restricted to 12 mg alemtuzumab and IFNB-1a arms. Efficacy of alemtuzumab 24 mg was for exploratory purpose only.

The efficacy analyses were to use Full Analysis Set consisted of all patients who were randomized to treatment and had received any amount of study drug.

3.2.2.1 Analyses of the Primary Endpoints

The analyses of the 2 primary endpoints were to be adjusted for multiple comparisons via the Hochberg method. The study was to be considered to have met its primary efficacy objective if a statistically significant difference between alemtuzumab and IFNB-1a was observed in relapse rate and/or time to SAD with the p-values corresponding to the analysis of the primary endpoints satisfy at least 1 of the following conditions:

The maximum of the 2 p-values is ≤ 0.05

The minimum of the 2 p-values is ≤ 0.025

The study drug is to be considered effective on both SAD and relapse rate if the maximum of the p-values is ≤ 0.05 . If one of the p-values is > 0.05 , then only if the other p-value is ≤ 0.025 the study drug would be considered effective for the endpoint corresponding to the p-value of ≤ 0.025 .

Analysis of Relapse Rate

The relapse rate was to be compared between the treatment groups via recurrent event methods. The definition of relapse and the counting process data representation for the analysis are presented here.

According to an international consensus definition, symptoms of relapse must be preceded by 30 days of clinical stability. Therefore, another clinical event within 30 days after onset of a relapse was not to be counted as a separate relapse, and a patient was not to be considered at risk for relapse during the 30-day window following the onset of a relapse event.

The data for each patient was to be represented as a sequence of observations with a definitive beginning and end time points. For each patient, the first period was to begin on the day of initial treatment. The period was to end on the last day on study for patients who had no relapses. For patient who had any number of relapses, the end of the first period was to be the onset day of the first relapse. Each of the following periods was to begin exactly 30 days after the onset of the prior relapse and to end on the onset day of the next relapse or the last day on study for patients who did not have another relapse.

Example: Patient 1 experienced a relapse that started 20 days before first study treatment and he/she was censored without any further relapses at Day 150. Patient 2 had relapses at Day 100, 210 and 415 and was censored at Day 730. The counting process representation for Patients 1 and 2 would be the following:

	Relapse-Risk Period		Censoring
	Start day	Stop day	
Patient 1	10	150	0
Patient 2	0	100	1
	130	210	1
	240	415	1
	445	730	0

Censoring=0: no relapse occurred; censoring=1: relapse occurred

The comparison of the relapse rate was to be conducted on all patients follow-up data using the proportional means model. The proportional means model is a semi-parametric model that allows for the relapse rate to change over time but assumes that the relapse rate ratio between the treatment groups is constant over time. Covariates for the proportional means model were treatment group and geographic region and robust variance estimation was used.

As the annualized relapse rate (ARR) cannot easily be estimated with the proportional means model, the ARR was to be estimated using a negative binomial model with robust variance estimation. The observed number of relapses was the dependent variable, the log of follow-up time in days from date of first study treatment for each patient was the offset variable, and treatment group and geographic region were the model covariates.

Analysis of Time to Sustained Disability (SAD)

The treatment comparison of the SAD was to be analyzed using a Cox proportional hazards (PH) regression model. Covariates for the PH model included treatment group and geographic region.

Sensitivity Analysis

Various sensitivity analyses were planned to assess factors that could potentially affect the primary analyses of the primary endpoints. The influence of alternative MS treatments, unblinded EDSS raters, baseline covariates and alternative ways to analyze the data were to be explored.

3.2.2.2 Analysis of Secondary Endpoints

Hypothesis testing for the secondary efficacy analyses was performed using a closed testing procedure with the rank order given in 3.2.1.2.

The hypothesis testing proceeded from highest rank to lowest rank, and if statistical significance ($p \leq 0.05$) was not achieved at an endpoint, then endpoints of lower rank were not to be considered statistically significant.

The proportion of patients who were relapse free at Year 2 was to be estimated using the Kaplan-Meier (KM) method and compared using Cox PH regression with robust variance estimation.

The analysis of the change from baseline in EDSS was to be based on the Wei-Lachin test, a nonparametric test of repeated measures data. Patients who discontinued early were to have subsequent EDSS assessments imputed using last observation carried forward (LOCF).

The percent change in T2-hyperintense lesion volume from baseline to Year 2 was to be analyzed through ranked ANCOVA with adjustment for the baseline lesion volume and geographic region.

Change from Baseline in MSFC was to be analyzed in the same manner as change from baseline in EDSS.

In general, patients who discontinued from the study early had subsequent observations imputed using the last observation carried forward (LOCF) approach.

3.2.3 Study Results of Protocol 323

3.2.3.1 Patient Disposition, Demographic and Baseline Characteristics

Disposition of Patients

A total of 581 patients were randomized in a 1:2 ratio to receive IFNB-1a (195 patients) or aletuzumab (386 patients) at 97 investigational sites. Of these, 131 patients were randomized at 36 US sites.

A total of 18 patients (8 in IFNB-1a and 10 in aletuzumab) discontinued study prior to receiving treatment. Nearly all treated patients completed the 2-year. The median time of follow-up for both IFNB-1a- and aletuzumab-treated patients was 24.0 months.

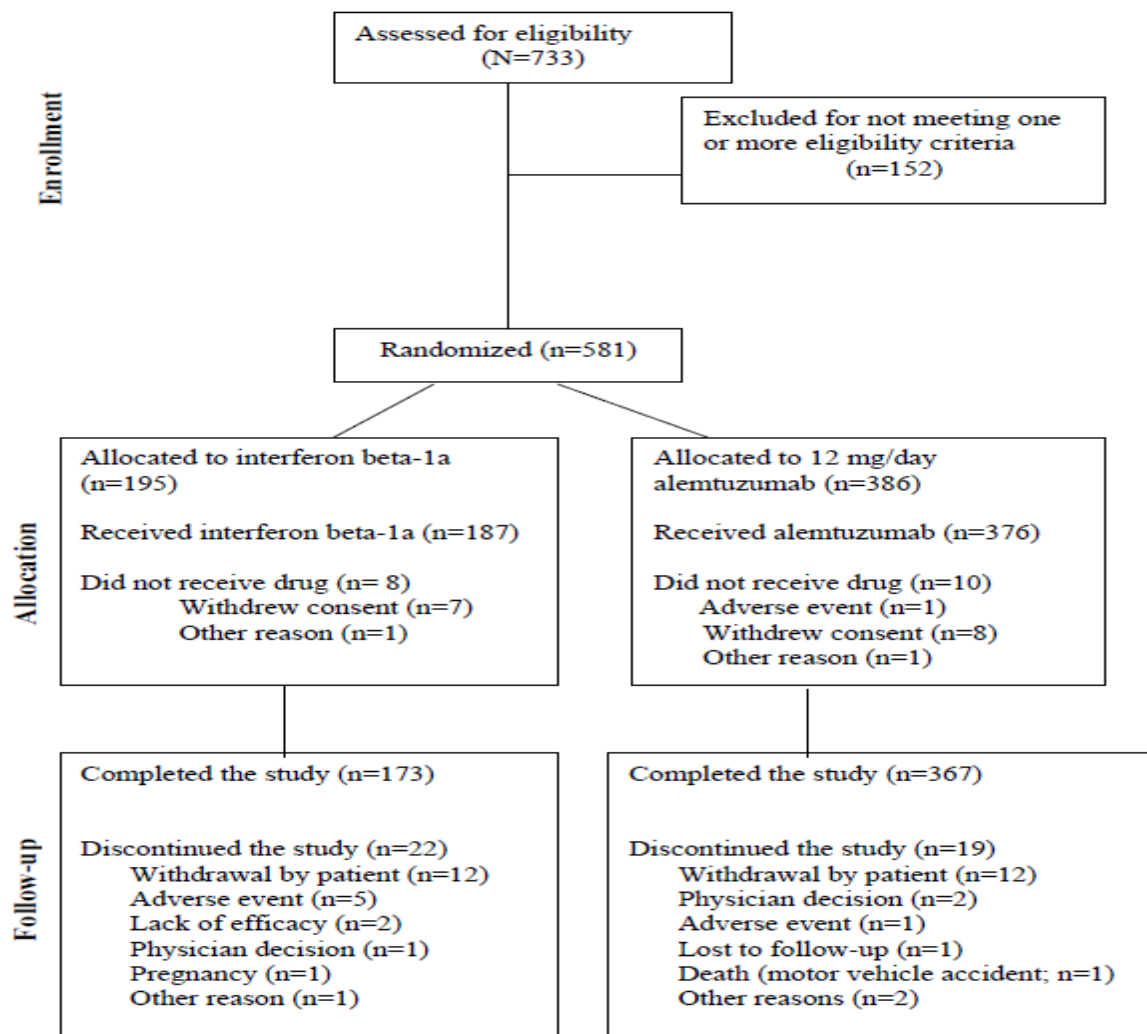


Figure 1 Patient Disposition - Protocol 323 (Source: Figure 9.1 of Study Report)

Demographic and Baseline Disease Characteristics

The mean age of the patients in this study was 33 years, approximately 2/3 (64.8%) of the patients were female, and the majority (94.5%) were white. Demographic characteristics were balanced across the treatment groups, and were similar across the regions that participated in the study, and in the randomized set.

At baseline, the mean EDSS score was 2, the mean number of years since onset of MS symptoms was 2.1, the mean number of relapses in the 2 years prior to study entry was 2.5, and approximately one-half of both treatment groups had gadolinium enhancing lesions on MRI with a mean number of approximately 2.3. All MS disease-related baseline characteristics were balanced across the treatment groups.

Table 2 Baseline Disease Characteristics (Source: Table 9.3-9.4 of Study Report)

Parameter	IFNB-1a (N=187)	Aletuzumab 12 mg/day (N=376)
EDSS Score, n (%)		
0	9 (4.8)	15 (4.0)
1.0-3.0	175 (93.6)	353 (93.9)
3.5-4.0	3 (1.6)	8 (2.1)
Mean (SD)	2.0 (0.79)	2.0 (0.81)
Median	2.0	2.0
Min, Max	0.0, 3.5	0.1, 4.0
Years Since Initial Episode		
Mean (SD)	2.0 (1.32)	2.1 (1.36)
Median	1.5	1.7
Min, Max	0.2, 5.0	0.1, 5.2
Number of Episodes in Prior Year		
Mean (SD)	1.8 (0.83)	1.8 (0.81)
Median	2.0	2.0
Min, Max	0.0, 5.0	0.0, 5.0
Number of Episodes Prior 2 Years		
Mean (SD)	2.5 (0.76)	2.5 (0.85)
Median	2.0	2.0
Min, Max	1.0, 6.0	1.0, 7.0
Gd-Enhancing Lesion Count		
N	183	371
Mean (SD)	2.22 (4.92)	2.33 (5.10)
Median	1.0	0.0
Min, max	0.0, 36.0	0.0, 32.0
Patients with Lesions , n (%)	94 (51.4%)	171 (46.1)

3.2.3.2 Efficacy Results Reported by the Sponsor

A total of 18 randomized patients who discontinued study prior to receiving study drug were excluded from the Fall Analysis (FA) data set for efficacy analysis. The FA consisted of 563 patients with 187 patients in the IFNB-1a group and 376 patients in the Aletuzumab group.

Annualized Relapse Rate (ARR) – Primary Endpoint

The sponsor reported that alemtuzumab significantly reduced the relapse rate through 2 years by 55% compared with IFNB-1a ($p < 0.0001$) (Table 3; Figure 2). The estimated ARR through 2 years was 0.18 for alemtuzumab versus 0.39 for IFNB-1a.

Table 3 Relapse Rate and Treatment Effect Summary (Source: Table 10-2 of Study Report)

Statistic	SC IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Patients with event, n	75	82
Total number of events, n	122	119
Annualized rate (95% CI)	0.39 (0.29, 0.53)	0.18 (0.13, 0.23)
Rate ratio (95% CI)		0.45 (0.32, 0.63)
Risk reduction		54.88
p-value		<0.0001

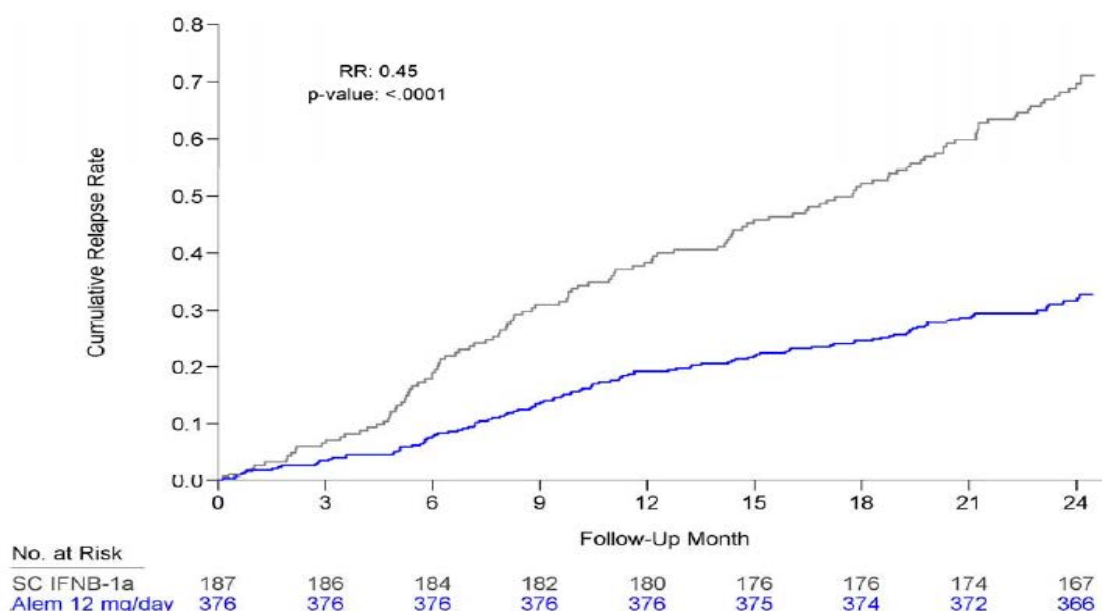


Figure 2 Cumulative Plot of Relapse Rate (Source: Figure 10-1 of Study Report)

Sensitivity analyses were conducted to assess the influence of alternative MS treatments, unblinded EDSS raters, and other factors that could potentially affect the primary relapse analysis. The results of these analyses are illustrated in Figure 3, which contains the estimated rate ratio comparing alemtuzumab to IFNB-1a for each of the sensitivity analyses. These rate ratios are very close to the estimated rate ratio from the primary relapse analysis.

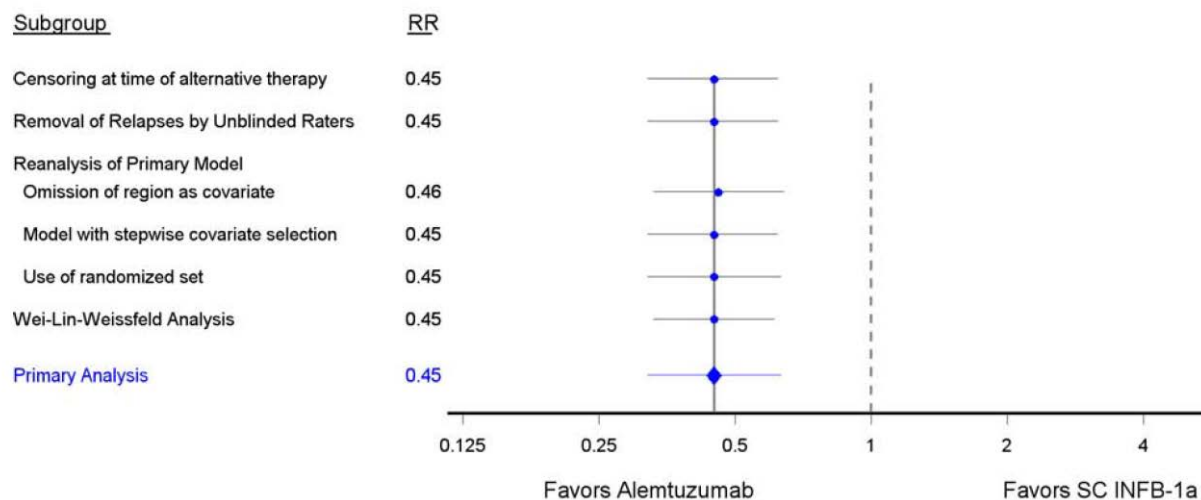


Figure 3 Summary of Relapse Rate Ratio Sensitivity Analyses (Source: Figure 10-3 of Study Report)

Time to Sustained Accumulation of Disability (SAD) – Primary Endpoint

There was no significant difference between the treatment groups in the risk of SAD ($p=0.2173$; Table 4; Figure 4). The percentage of patients experiencing SAD at 2 years was 11.1% in the IFNB-1a group and 8.0% in the alemtuzumab group.

Table 4 SAD Event and Treatment Effect Summary (Source: Table 10-3 of Study Report)

Statistic	SC IFNB-1a (N=187)	Alemtuzumab 12 mg/day (N=376)
Patients with event, n	20	30
KM estimate of event (95% CI)	11.12 (7.32, 16.71)	8.00 (5.66, 11.24)
KM estimate of no event (95% CI)	88.88 (83.29, 92.68)	92.00 (88.76, 94.34)
Hazard ratio (95% CI)		0.70 (0.40, 1.23)
Risk reduction		30
p-value		0.2173

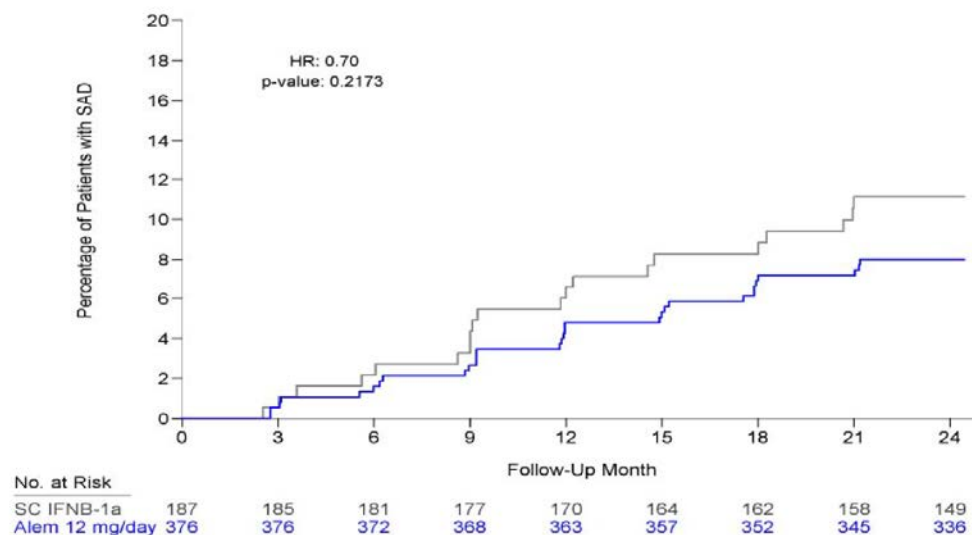


Figure 4 Cumulative Plot of Time to Sustained Accumulation of Disability (Source: Figure 10-6 of Study Report)

Sensitivity analyses were conducted to assess the influence of unblinded EDSS raters, patient use of alternative MS therapy, and other factors on the primary time to SAD results. As shown in Figure 5, none of the factors assessed altered the estimate of the treatment effect for time to SAD.

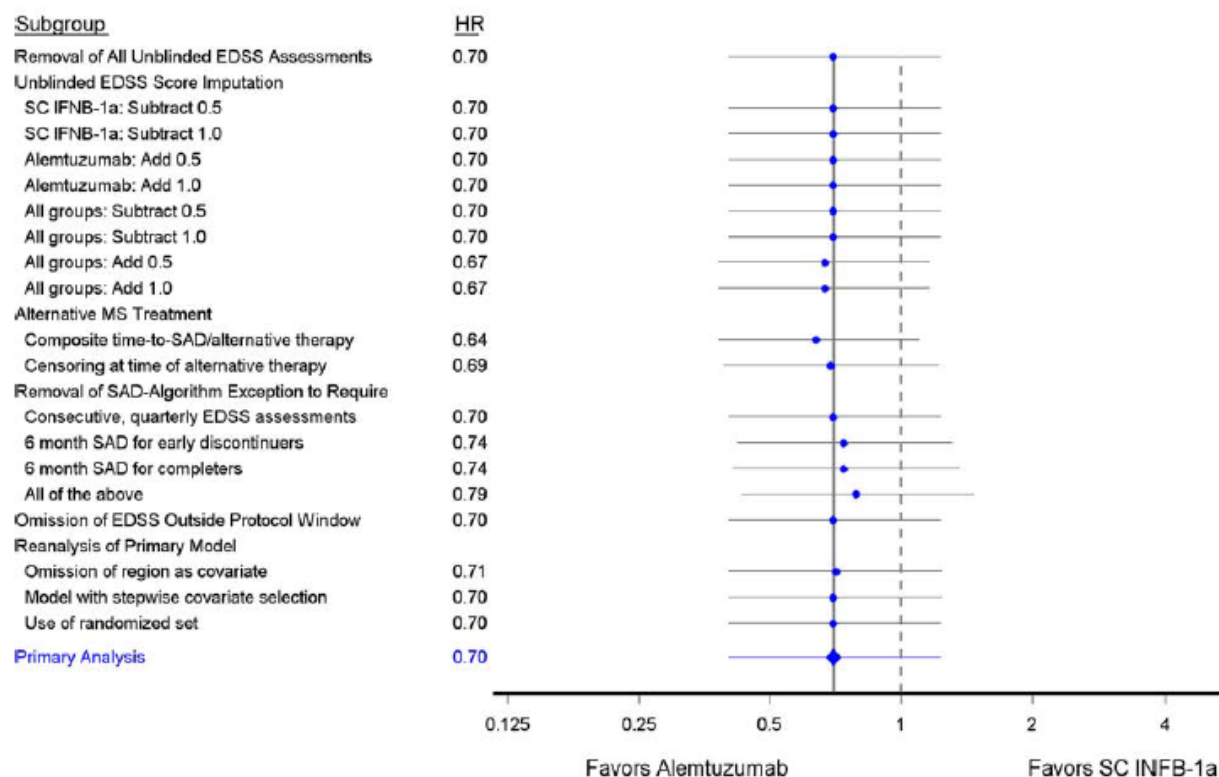


Figure 5 Summary of Sustained Accumulation of Disability (SAD) Sensitivity Analyses (Source: Figure 10-7 of Study Report)

Proportion of Patients who are Relapse Free (a secondary endpoint)

At Year 2, 78% of alemtuzumab versus 59% of IFNB-1a treated patients remained relapse free, which represents a 55% reduction in the risk of relapse over 2 years ($p < 0.0001$; Figure 6).

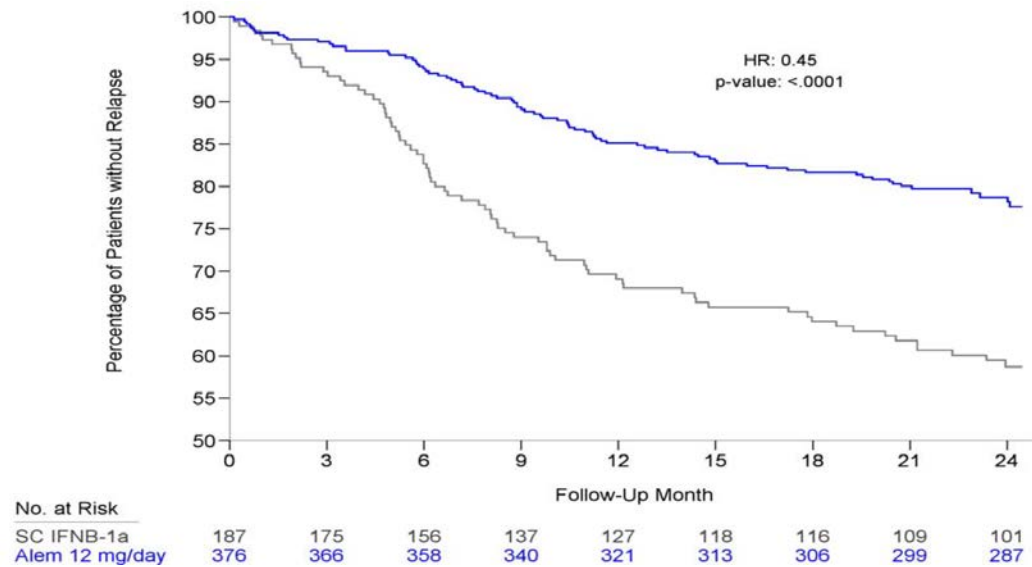


Figure 6 Kaplan-Meier Plot of Time to First Relapse (Source: Figure 10-5 of Study Report)

Change from Baseline in EDSS Scores (a secondary endpoint)

Both alemtuzumab and IFNB-1a-treated patients experienced a mean reduction in EDSS scores over the 2-year study period (Table 5; Figure 7). The difference between the groups was not statistically significant ($p=0.4188$; multivariate nonparametric test).

Table 5 Change from Baseline at Year 2 in EDSS Score (Source: Table 10-4 of Study Report)

Measurement	SC IFNB-1a (N = 187)	Alemtuzumab 12 mg/day (N = 376)
Overall comparison ^a p-value		0.4188
Change from baseline ^b (95% CI) p-value	-0.14 (-0.29, 0.01) 0.0672	-0.14 (-0.25, -0.02) 0.0173
Difference ^b Mean (95% CI) p-value		0 (-0.16, 0.17) 0.9653

Source: Table 14.2.2.2, Table 14.2.2.2.1

a. Wei-Lachin (multivariate, non-parametric test)

b. Using mixed model for repeated measures

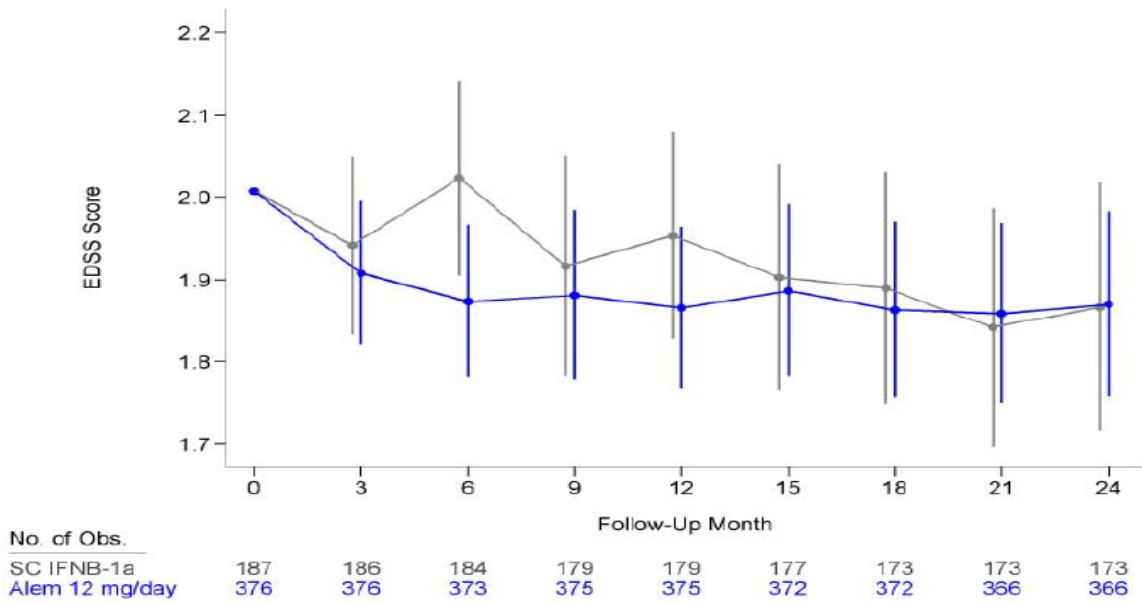


Figure 7 EDSS Mean Change from Baseline Through 2 Years (Source: Figure 10-9 of Study Report)

Change in MRI T2-Hyperintense Lesion Volume (a secondary endpoint)

Patients in both the alemtuzumab and IFNB-1a treatment groups showed substantial reductions in T2-hyperintense lesion volume from baseline to Year 2 (median percent reductions of -9.3 and -6.5, respectively). However, there was no significant difference between alemtuzumab and IFNB-1a ($p=0.3080$; Figure 8).

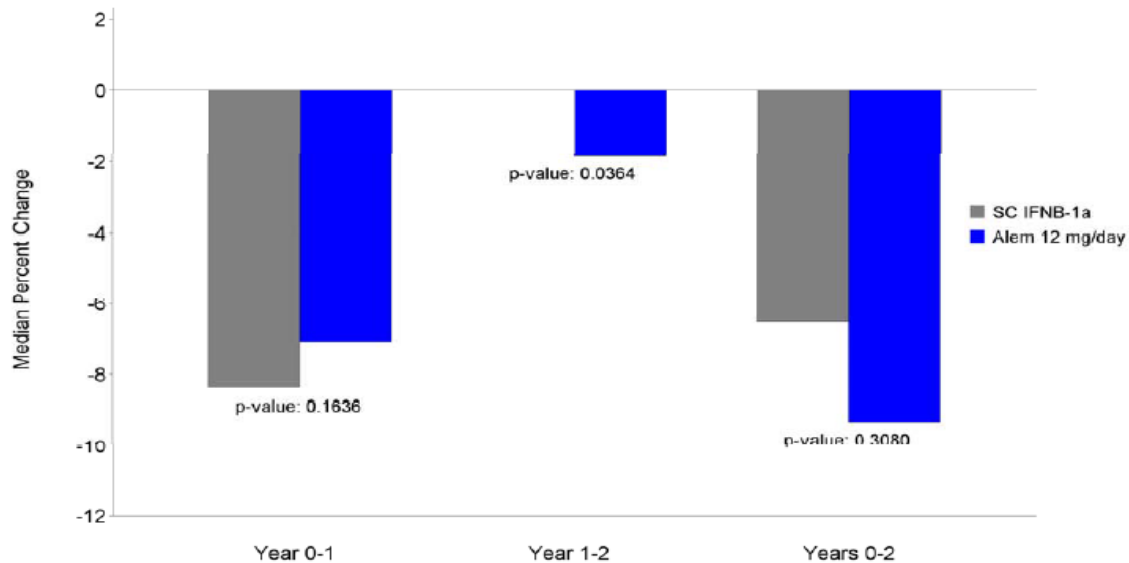


Figure 8 Median Percent Change in T2-Hyperintense Lesion Volume: Full Analysis (Source: Figure 10-12 of Study Report)

Change from Baseline in MSFC (a secondary endpoint)

Both groups of alemtuzumab and IFNB-1a had increased MSFC scores over the treatment period. The treatment difference was statistically significant with a p-value of 0.0115. Table 6 presents the results.

Table 6 Change from Baseline at Year 2 in MSFC Z-Score (Source: Table 10-5 of Study Report)

Measurement	SC IFNB-1a (N = 187)	Alemtuzumab 12 mg/day (N = 376)
Overall ^a p-value		0.0115
Change from baseline ^b (95% CI) p-value	0.05 (-0.02, 0.13) 0.1596	0.12 (0.06, 0.18) < 0.0001
Difference ^b Mean (95% CI) p-value		0.07 (-0.01, 0.15) 0.0735

Source: Table 14.2.2.3, Table 14.2.2.3.1, Table 14.2.2.3.2

a. Wei-Lachin (multivariate, non-parametric test)

b. Using mixed model for repeated measures

The sponsor reported that alemtuzumab showed significantly greater improvements from baseline to year 2 than IFNB-1a patients on 2 of the 3 MSFC components: the 9-hole peg test and the 25-foot walk test.

3.2.4 Study Results of Protocol 324

3.2.4.1 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 840 patients were randomized at 181 investigational Sites worldwide, including 382 patients in 79 US sites.

Initially, patients were randomized in a 2:2:1 ratio to receive alemtuzumab 12 mg/day, alemtuzumab 24 mg/day, or IFNB-1a, respectively. Beginning with Amendment 2, the alemtuzumab 24 mg/day group was closed to newly enrolled patients and all subsequently enrolled patients were randomized in a 2:1 ratio to receive alemtuzumab 12 mg/day or IFNB-1a.

Overall disposition is presented in Figure 9. The highest number of discontinuations from the study occurred in the IFNB-1a group, predominantly for the reason of “withdrew consent”, mostly prior to treatment.

The incidence of patient discontinuation prior to treatment was 10 patients (2.3%) in the alemtuzumab 12 mg/day group compared with 29 patients (12.6%) in the IFNB-1a group, and 3 patients (1.7%) in the alemtuzumab 24 mg/day group.

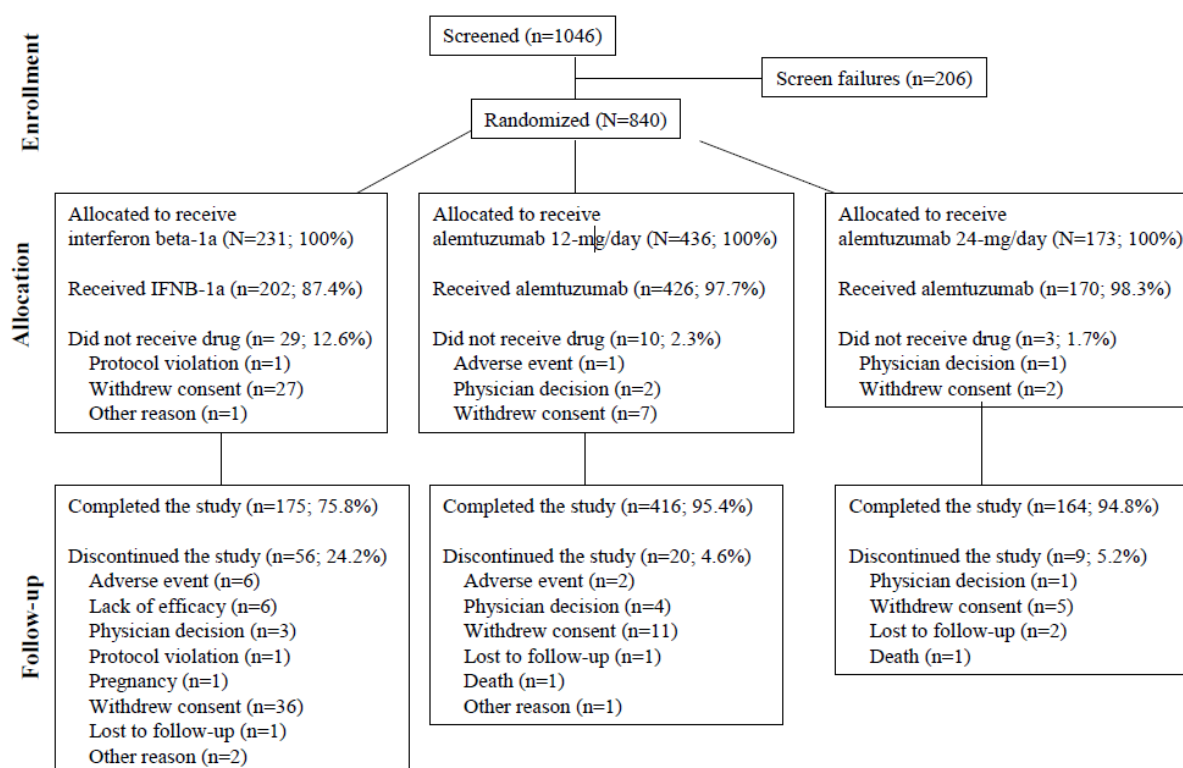


Figure 9 Patient Disposition - Randomized Set (Source: Figure 9-1 of Study Report)

Demographic and Baseline Disease Characteristics

In the FA set, the mean age of the patients in this study was 35.1 years, approximately two-thirds (66.7%) of the patients were female, and the majority (89.5%) were White. Demographic characteristics in the FA set were balanced across the treatment groups, and were similar across the regions that participated in the study.

At baseline, the mean EDSS score was 2.7. The mean number of years since onset of MS symptoms was 4.5. The mean number of relapses in the 2 years prior to study entry was 2.7, and almost half of the patients in the alemtuzumab 12 mg/day and IFNB-1a groups had Gd-enhancing lesions on MRI (Table 7). Furthermore, all MS disease-related baseline characteristics were balanced across the treatment groups. The sponsor reported that baseline disease characteristics of patients who discontinued the study prior to treatment were similar to those patients in the FA set.

Table 7 Baseline Disease Characteristics (Source: Table 9.3-9.4 of Clinical Report)

Parameter	IFNB-1a (N=202)	Aletuzumab 12 mg/day (N=426)	Aletuzumab 24 mg/day (N=170)
EDSS Score, n (%)			
0	5 (2.5)	16 (3.8)	4 (2.3)
1.0-3.0	126 (62.4)	264 (62.0)	112 (65.9)
3.5-5.0	69 (34.1)	140 (32.8)	52 (30.6)
> 5.0	2 (1.0)	6 (1.4)	2 (1.12)
Mean (SD)	2.7 (1.21)	2.7 (1.26)	2.7 (1.17)
Median	2.5	2.5	2.5
Min, Max	0.0, 6.0	0.0, 6.5	0.0, 6.0
Years Since Initial Episode			
Mean (SD)	4.7 (2.86)	4.5 (2.68)	4.3 (2.77)
Median	4.1	3.8	3.7
Min, Max	0.4, 10.1	0.2, 14.4	0.2 (16.9)
Number of Episodes in Prior Year			
Mean (SD)	1.5 (0.75)	1.7 (0.86)	1.6 (0.86)
Median	1.0	1.0	1.0
Min, Max	0.0, 4.0	0.0, 5.0	0.0, 6.0
Number of Episodes Prior 2 Years			
Mean (SD)	2.6 (0.97)	2.8 (1.20)	2.5 (1.02)
Median	2.0	2.0	2.0
Min, Max	1.0, 6.0	1.0, 9.0	1.0, 7.0
Gd-Enhancing Lesion Count			
N	199	420	165
Mean (SD)	2.10 (4.95)	2.28 (6.02)	2.88 (8.47)
Median	0.0	0.0	0.0
Min, max	0, 41	0, 72	0, 90
Patients with Lesions, n (%)	87 (43.7)	178 (42.4)	74 (44.8)

In addition, the sponsor reported that the median duration of time (number of months) patients had been taking prior MS medications was similar across all treatment groups (28 months for alemtuzumab 12 mg/day, 29 for IFNB-1a, and 33 for alemtuzumab 24 mg/day), as was the proportion of patients who had taken 1, 2, 3, or ≥ 4 prior MS medications.

3.2.4.2 Efficacy Results Reported by the Sponsor

Efficacy analyses were restricted to IFNB-1a and aletuzumab 12 mg group as enrollment of aletuzumab 24 mg was stopped after Amendment 2.

A total of 39 randomized patients (10 to the IFNB-1a group and 29 to the aletuzumab 12 mg group) who discontinued prior to receiving study drug were excluded from the Fall Analysis (FA) data set for efficacy analysis. The FA consisted of 628 patients with 202 patients in the IFNB-1a group and 426 patients in the Aletuzumab 12 mg group.

Annualized Relapse Rate – Primary Endpoint

The sponsor reported that Alemtuzumab significantly reduced the relapse rate through 2 years by 49% compared with IFNB-1a ($p < 0.0001$). The ARR through 2 years was 0.26 for alemtuzumab-treated patients versus 0.52 for IFNB-1a-treated patients. Results are presented in Table 8.

Table 8 Annualized Relapse Rate, Relapse Rate Ratio, and Risk Reduction (Source: Table 10-2 of Study Report)

Time Period / Statistic	SC IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Relapse Rate through 2 Years (Co-primary Efficacy Endpoint)		
Patients with any event (number of events)	104 (201)	147 (236)
Annualized rate (95% CI)	0.52 (0.41, 0.66)	0.26 (0.21, 0.33)
Rate ratio (95% CI)		0.51 (0.39, 0.65)
Risk reduction		49.40
p-value		<0.0001

SC = subcutaneous; CI = confidence interval

Note: ARR is estimated through negative binomial regression with robust variance estimation and covariate adjustment for geographic region.

Note: Rate ratio and p-value are from proportional means regression with robust variance estimation and covariate adjustment for geographic region.

Cumulative Relapse Rate by Nelson Aalen plot is presented in Figure 10.

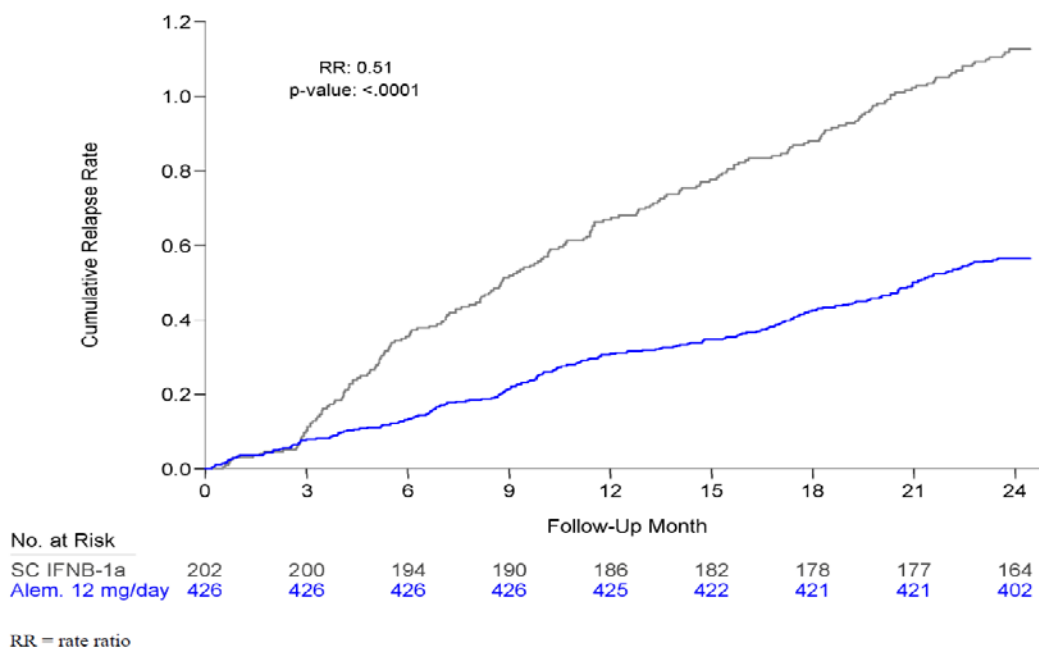


Figure 10 Nelson-Aalen Plot of the Cumulative Relapse Rate (Source: Figure 10-1 of Study Report)

Sensitivity analyses were conducted to assess the influence of unblinded EDSS raters, dropouts prior to treatment, use of alternative MS treatments, exclusion from the PP set, and other factors that could potentially affect the primary relapse analysis. The results of these analyses are illustrated in Figure 11, which contains the rate ratio comparing alemtuzumab with IFNB-1a for each of the sensitivity analyses. These rate ratios are very close to the rate ratio from the primary relapse analysis.

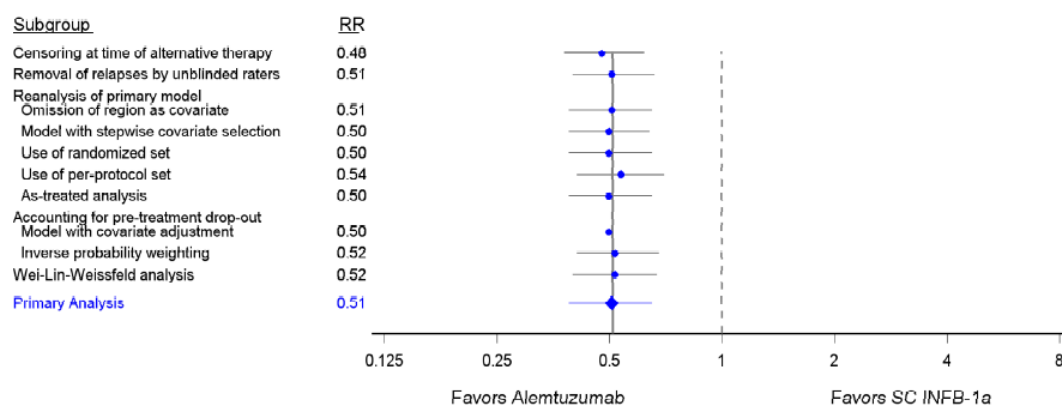


Figure 11 Summary of Relapse Rate Ratio Sensitivity Analyses (Source: Figure 10-3 of Study Report)

Time to Sustained Accumulation of Disability (SAD) – Primary Endpoint

The sponsor reported that alemtuzumab significantly reduced the risk of SAD through 2 years by 42% compared with IFNB-1a ($p=0.0084$). The percentage of patients experiencing SAD at 2 years was 12.7% in the alemtuzumab group and 21.1% in the IFNB-1a group. Results are presented in Table 9 and Figure 12.

Table 9 Sustained Accumulation of Disability (Source: Table 10-3 of Study Report)

Statistic	SC IFNB-1a (N=202)	Alemtuzumab 12 mg/day (N=426)
Patients with event, n	40	54
KM estimate of event (95% CI)	21.13 (15.95, 27.68)	12.71 (9.89, 16.27)
KM estimate of no event (95% CI)	78.87 (72.32, 84.05)	87.29 (83.73, 90.11)
Hazard ratio (95% CI)		0.58 (0.38, 0.87)
Risk reduction		42
p-value		0.0084

KM = Kaplan-Meier

Note: Hazard ratio (HR) and p-value are from proportional hazards regression with robust variance estimation and covariate adjustment for geographic region.

Note: Risk reduction is summarized for hazard ratios less than 1 only.

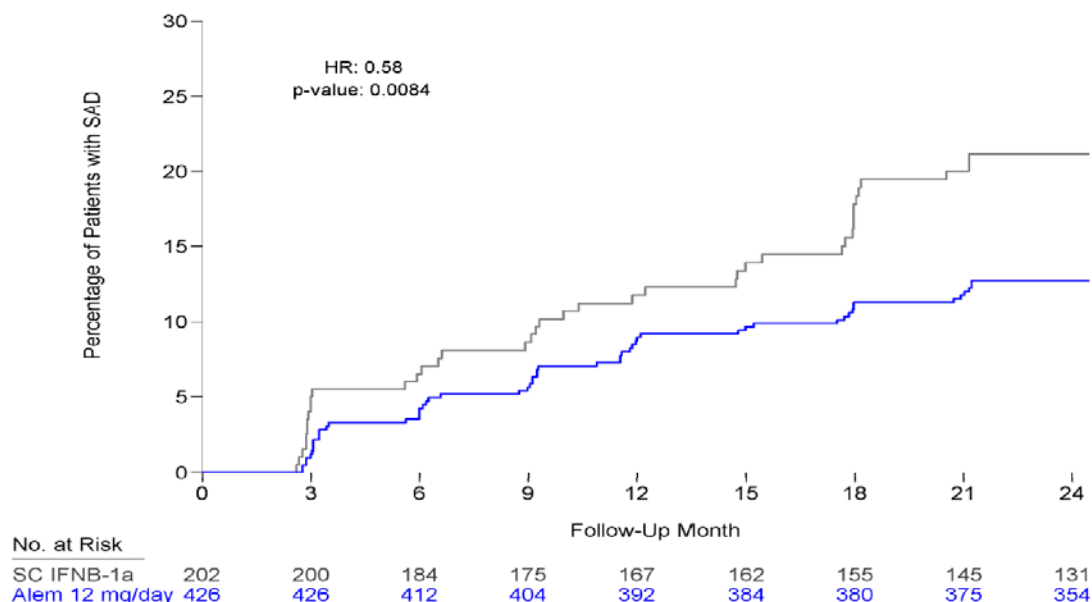


Figure 12 Cumulative Plot of Time to Sustained Accumulation of Disability (Source: Figure 10-6 of Study Report)

The sponsor performed planned sensitivity analyses to assess the influence of unblinded EDSS raters, dropouts prior to and following treatment, use of alternative MS therapy, exclusion from the PP set, and other factors on the primary time to SAD results. The hazard ratio with each of the sensitivity analyses are shown in Figure 13. The analysis with the composite endpoint of SAD and early study discontinuation showed a larger alemtuzumab treatment effect due to the higher number of discontinuations in the IFNB-1a group.

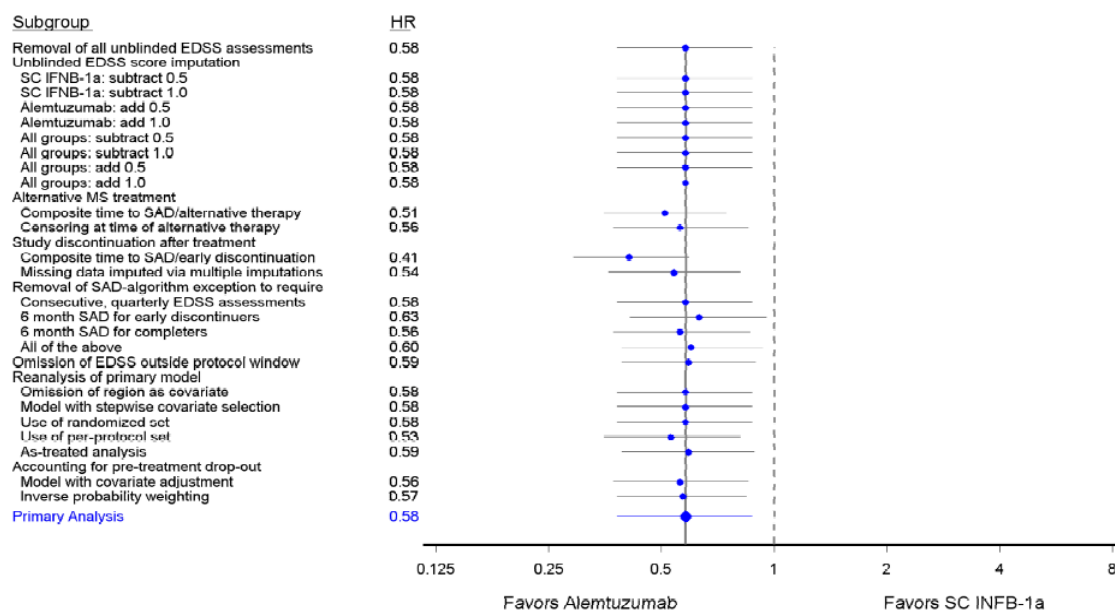


Figure 13 Summary of Sustained Accumulation of Disability Sensitivity Analyses (Source: Figure 10-7 of Study Report)

Proportion of Patients who are Relapse Free (a secondary endpoint)

At Year 2, 65.4% of patients receiving alemtuzumab remained relapse-free compared with 46.7% of IFNB-1a-treated patients, which represents a 47% reduction in the risk of relapse over 2 years ($p < 0.0001$). The Kaplan Meier plot of time to first relapse is presented in Figure 14.

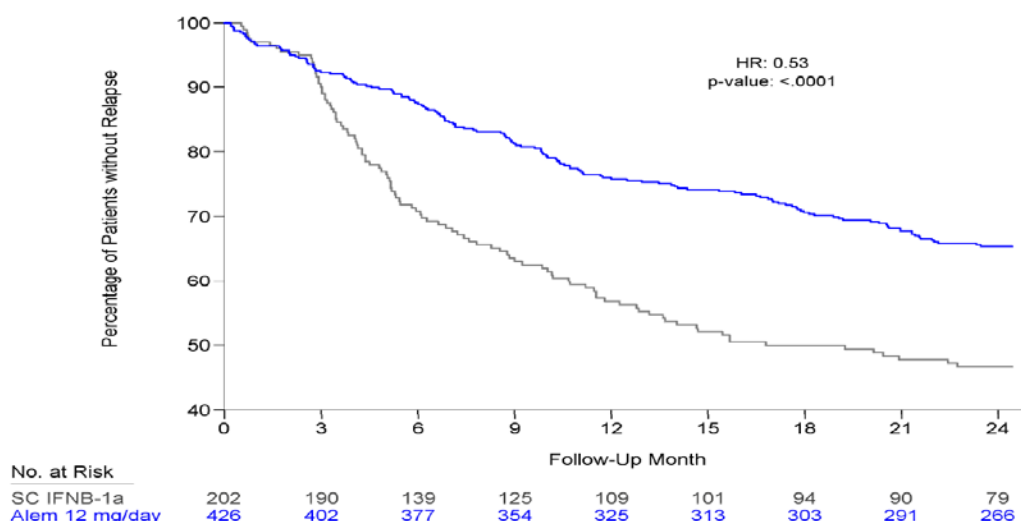


Figure 14 Kaplan-Meier Plot of Time to First Relapse (Source: Figure 10-5 of Study Report)

Change from Baseline in EDSS Scores (a secondary endpoint)

Alemtuzumab-treated patients had significantly lower EDSS scores after treatment compared with IFNB-1a-treated patients ($p < 0.0001$). The sponsor reported that alemtuzumab-treated patients experienced significant improvement from baseline in mean EDSS score, whereas IFNB-1a-treated patients experienced a significant worsening (Table 10; Figure 15).

Table 10 Change from Baseline in EDSS (Source: Table 10-4 of Study Report)

Measurement	SC IFNB-1a (N = 202)	Alemtuzumab 12 mg/day (N = 426)
Overall comparison ^a p-value		<0.0001
Change from baseline ^b (95% CI) p-value	0.24 (0.07, 0.41) 0.0064	-0.17 (-0.29, -0.05) 0.0044
Difference ^b Mean (95% CI) p-value		-0.41 (-0.61, -0.22) <0.0001

CI = confidence interval

^a Wei-Lachin (multivariate, non-parametric test). Empirical p-value is based on 10,000 permutations of the treatment codes.

^b Using mixed model for repeated measures. Changes from baseline and group differences at each time period are estimated using an unstructured covariance model with a time by treatment interaction and covariate adjustment for geographic region and baseline EDSS score.

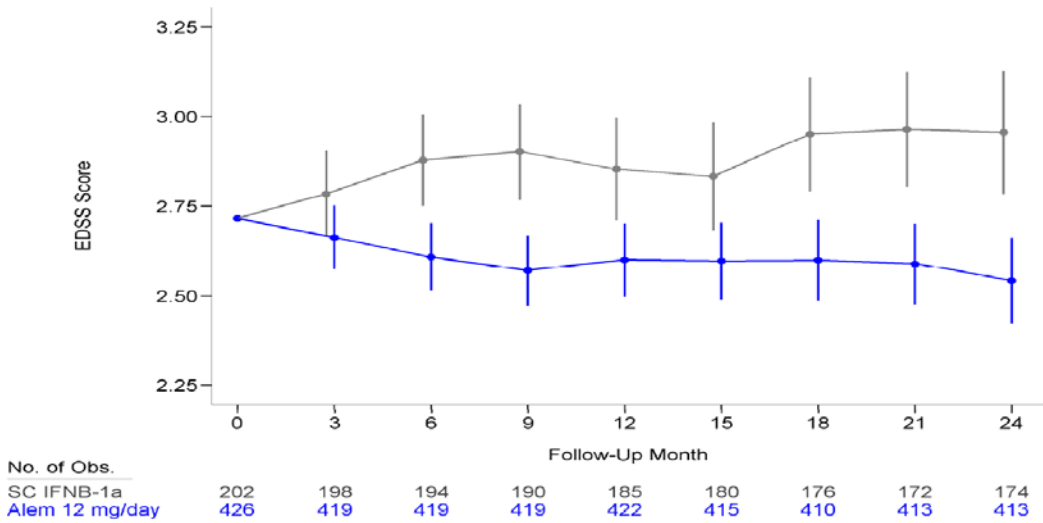


Figure 15 Change from Baseline in EDSS scores (Source: Figure 10-9 of Study Report)

Change in MRI T2-Hyperintense Lesion Volume (a secondary endpoint)

There was no significant difference between alemtuzumab and IFNB-1a in the percent change in T2-hyperintense lesion volume from baseline to Year 2 ($p = 0.1371$; Figure 16). Both treatment groups showed a median percent reduction in T2-hyperintense lesion volume from baseline to Year 2.

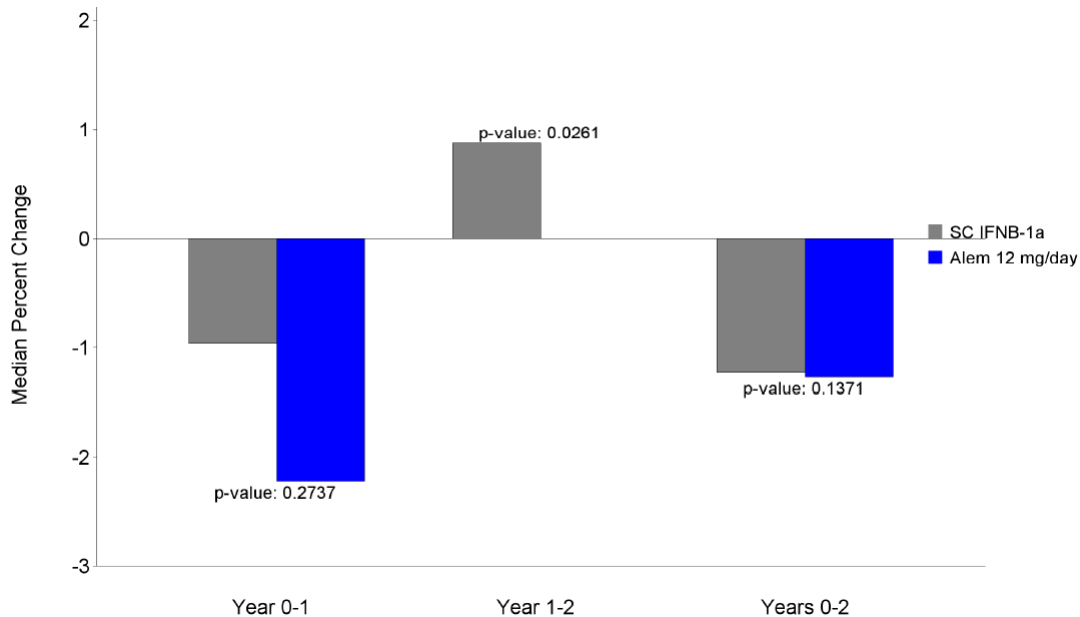


Figure 16 Median percent change in T2-hyperintense lesion volume (Source: Figure 10-13 of Study Report)

Change from Baseline in MSFC (a secondary endpoint)

At the end of the 2-year treatment, the mean MSFC Z score was slightly increase in the aletuzumab group and slightly decreased in the IFNB-1a group. The treatment difference is statistically significant with a p-value of 0.0022). Table 11 presents the results from analysis of MDFC Z-Score.

Table 11 Change from Baseline at Year 2 in MSFC Z-Score (Source: Table 10-5 of Study Report)

Measurement	SC IFNB-1a (N = 202)	Alemtuzumab 12 mg/day (N = 426)
Overall ^a p-value		0.0022
Change from baseline ^b (95% CI) p-value	-0.04 (-0.10, 0.02) 0.2139	0.08 (0.04, 0.12) 0.0003
Difference ^b Mean (95% CI) p-value		0.12 (0.05, 0.19) 0.0009

CI = confidence interval; SC = subcutaneous

^a Wei-Lachin (multivariate, non-parametric test). Empirical p-value is based on 10,000 permutations of the treatment codes.

^b Using mixed model for repeated measures. Changes from baseline and group differences at each time period are estimated using an unstructured covariance model with a time by treatment interaction and covariate adjustment for geographic region and baseline MSFC Z-score.

The sponsor reported that aletuzumab showed significantly greater improvements from baseline to year 2 than IFNB-1a patients on 2 of the 3 MSFC components: the 9-hole peg test and the 25-foot walk test.

3.2.5 Reviewer's Analysis

All efficacy results presented in the previous section have been independently replicated and confirmed. The reviewer will discuss in this section some serious issues, mainly the issue of possible bias caused by the unblinded nature of the study design.

Patient Withdrawal

A significant number of patients in both studies discontinued before or after initial treatment. A majority of the discontinuation was withdrawal by patients. The withdrawal of patients appears to be treatment related. The discontinuation rate in the IFNB-1a group is much higher than in aletuzumab group, particularly in Study 324. The following table presents a summary patient discontinuation before or after initial treatment.

Table 12 Summary of Patients Discontinuation before and after Initial Treatment

	SC IFNB-1a			Aletuzumab 12 mg/day		
	Before Trt	After Trt	Total	Before Trt	After Trt	Total
Study 323	Randomized: N=195			Randomized: N=386		
N discontinued % discontinued	8 (4.10%)	14 (7.18%)	22 (11.28%)	10 (2.59%)	9 (2.33%)	19 (4.92%)
Study 324	Randomized: N=231			Randomized: N=436		
N discontinued % discontinued	29 (12.55%)	27 (11.69%)	56 (24.24%)	10 (2.29%)	10 (2.29%)	20 (4.59%)

There is a distinctive difference in discontinuation rates between the two studies. The discontinuation rates in aletuzumab-treated patients are similar in the two studies, both before and after the initial treatment, while the discontinuation rate is much higher in Study 324 than in Study 323 for the SC IFNB-1a treated patients. This is likely due to the difference in patient population: Study 323 enrolled naïve patients, and Study 324 enrolled patients who had failed previous MS treatment. The majority of patients in Study 324 were previously treated with IFNB-1a for duration of 36 months on average.

There are two implications from the unbalanced discontinuation rate. First, the higher dropout rate in IFNB-1a group, particularly in Study 324 indicates that selection bias might have been introduced in the process, and the Full Analysis set may no longer represent a randomized population. The bias could be in two ways: 1) patients drop out due to undesired treatment assignment; 2) patients continue in the study in order to qualify for receiving aletuzumab in the extension study. Second, the data suggest that patients had knowledge of their treatment assignment before receiving their initial treatment. This implies that baseline measures, assessed at initial treatment for many patients, could be invalid (discussed in more detail below).

Discrepancy in EDSS Scores Between Screening Visit and Baseline Visit

The high rate of withdrawal in the Rebif group before the initial treatment in Study 324 indicates that withdrawal might have been influenced by preference of the treatment assignment. Approximately half of the patients had EDSS assessment at randomization visit that were actually performed after randomization.

After contacting Genzyme during the review process, it was confirmed by Genzyme that the earliest time point that patients could be made aware of treatment assignment was after the site completed randomization process. Therefore, bias might have been introduced in EDSS assessed after randomization, and EDSS score at screening visit may be a valid measure to serve as a baseline measure. The following table presents the mean EDSS scores at screening visit and at randomization visit. Patients in aletuzumab 24 mg group in Study 324 are also included.

Table 13 Difference in EDSS Scores between Screening Visit and Randomization Visit

Mean EDSS scores	IFNB-1a	Aletuzumab 12 mg	Aletuzumab 24 mg
Study 323			
N	187	376	N/A
Randomization Visit	1.97	2.02	
Screening Visit	2.02	2.08	
Difference	-0.05	-0.05	
Study 324			
N	202	596	170
Randomization Visit	2.72	2.72	2.73
Screening Visit	2.82	2.76	2.75
Difference	-0.11	-0.03	-0.02

Note that baseline EDSS score is critical for the determination of primary endpoint of SAD. A large decrease in EDSS score from screening to randomization should raise concern because it could make patients easier to meet the criteria for SAD, particularly when such large decrease occurs in patients whose baseline EDSS were assessed after randomization visit (Table 14).

Table 14 Summary of Baseline EDSS Scores for Patients Assessed at At or After Randomization

EDSS Mean Scores	IFNB-1a	Aletuzumab 12 mg	Aletuzumab 24 mg
	At / After Randomization	At / After Randomization	At / After Randomization
Study 323			
N	84 / 103	166 / 210	N/A
Screening	2.08 / 1.98	2.14 / 2.03	
Randomization	2.02 / 1.94	2.03 / 2.02	
Difference	-0.06 / -0.04	-0.10 / -0.01	
Study 324			
N	102 / 100	203 / 223	92 / 78
Screening	2.75 / 2.90	2.63 / 2.85	2.68 / 2.83
Randomization	2.69 / 2.75	2.63 / 2.80	2.68 / 2.78
Difference	-0.06 / -0.16	-0.01 / -0.05	0.01 / -0.06

In order to examine the impact of discrepancy in the EDSS scores, modified criteria for determination of SAD were applied. Instead of using the EDSS score at randomization visit, patients' on-treatment EDSS scores were compared to EDSS scores at screening visit. A patient would meet this modified criteria for SAD if his/her on-treatment EDSS scores increased by 1 point for screening EDSS score of > 0 and increase by 1.5 point for screening EDSS score of 0 in 3 consecutive visits.

After applying the modified criteria using screening EDSS score as the baseline, the total number of SAD events IFNB-1a group was reduced by 15% from 20 to 17 in Study 323 and was reduced by 12.5% from 40 to 35 in Study 324. In contrast, the total number of SAD events in aletuzumab groups was increased by 13.33%, 11.11%, and 23.08% in the aletuzumab 12 mg in Study 323, aletuzumab 12 mg in Study 324, and Aletuzumab 24 mg in Study 324, respectively (Table 15). Under the modified criteria, no treatment difference was observed in Study 323. In Study 324, the p-value of the treatment difference between aletuzumab 12 mg and IFNB-1a became 0.2010,

which is no longer statistically significant and substantially larger than 0.0084 obtained under original criteria.

Table 15 Summary of SAD Events under Modified Criteria Using Screening EDSS as Baseline

Change in number of SAD	IFNB-1a	Aletuzumab 12 mg	Aletuzumab 24 mg
Study 323			
N	187	376	N/A
N (%) SAD - Modified	17 (9.09%)	34 (9.04%)	
N (%) SAD – Original	20 (10.70%)	30 (7.98%)	
Difference	-3 (15.00%)	4 (13.33%)	
Study 324			
N	202	426	170
N (%) SAD – Modified	35 (17.33%)	60 (14.09%)	32 (18.82%)
p-value compared to IFNB-1a		0.2010	
N (%) SAD – Original	40 (19.80%)	54 (12.68%)	26 (15.29%)
p-value compared to IFNB-1a		0.0084	
Difference	-5 (12.5%)	6 (11.11%)	6 (23.08%)

Note that all groups had higher mean screening EDSS scores (Table 14) as the basis in the modified criteria for SAD. While the lower number of SAD events in IFNB-1a group could be explained by higher screening EDSS score, how would one explain the higher SAD event numbers in all aletuzumab groups when modified criteria were applied?

Such change in SAD events under screening baseline appears to be treatment related, consistent across all groups in both studies and could not be explained by randomness. Although we believe bias from patients has played a considerable role in the studies, the change in SAD events could simply not be explained by the effect from patients.

Regional Difference in SAD

Although the difference in EDSS scores between screening and randomization caused great concern, the absence of such difference in the Non-EU region is equally concerned. The region consisted of countries Croatia, Russia, Serbia, and Ukraine with an additional country Israel in Study 324. It stands out that in that region, about 90% of the subjects had no difference in EDSS scores between screening and randomization visits. The region had lowest rate of SAD.

Table 16 Percentage of Patients with Same EDSS Scores at Screening and Randomization in Non-EU Region versus Other Regions

	Non-EU and Israel	Other Regions	Overall
Study 323			
N	262	301	563
% without difference	87.02%	54.82%	69.80%
N (%) had SAD	17 (6.49%)	33 (10.96%)	50 (8.88%)
Study 324			
N	162	636	798
% without difference	90.12%	50.79%	58.77%
N (%) had SAD	16 (9.88%)	104 (16.35%)	120 (15.04%)

In Study 324, less than 5% of the subjects in Russia had different EDSS score between screening and randomization, and only 4 subjects (6%) had SAD compared to an overall SAD rate of 15%. Ukraine, with 25 subjects in Study 324, had no subjects with different EDSS scores and no subjects had SAD. In fact, 16 of the 25 subjects in Ukraine had no change in EDSS scores in all scheduled visits during the entire study from screening to month 24. Despite that, the SAD rate in this region is higher in aletuzumab 12 mg group than in the IFNB-1a group (see 4.1 for more details). As reported by the sponsor and confirmed by the reviewer, demographic and baseline characteristics of subjects in this region are similar to subjects in other regions.

Table 17 Percentage of Patients with Same EDSS Scores at Screening and Randomization in Non-EU Region

	Russia	Ukraine	Croatia	Serbia	Israel
Study 323					
N	89	53	70	50	N/A
% without difference	83.15%	88.68%	85.71%	94.00%	
N (%) of SAD	3 (3.37%)	3 (5.66%)	6 (8.57%)	5 (10.00%)	
Study 324					
N	66	25	38	19	14
% without difference	95.45%	100%	86.84%	78.95%	71.43%
N (%) of SAD	4 (6.06%)	0 (0%)	8 (21.05%)	2 (10.53%)	2 (14.29%)

It is difficult to know which outcome should be more concerned: the one with wide spread of difference in EDSS or the one lack of it. The difference between screening and randomization in EDSS should not vary that much from region to region.

Relapse Reporting

Analysis of relapse was based on relapse determinations made by an independent, blinded RAP. Cases adjudicated are much higher in the IFNB-1a group (.79 per patient) compared to aletuzumab 12 mg group (.40 per patient), and the confirmed rates are similar between the 2 groups. The higher number of adjudicated cases in IFNB-1a group could be due to higher relapse rate or it could be that IFNB-1a-treated patients were more likely to report a relapse. On the other hand, the higher relapse rate in the IFNB-1a group compared to aletuzumab group could be due to more reported relapses, since a stable 82% of the reported cases were confirmed.

Table 18 Summary of Relapse Cases Adjudicated and Confirmed

	Study 323		Study 324	
	IFNB-1a N=187	Aletuzumab 376	IFNB-1a 202	Aletuzumab 426
Cases adjudicated, n	147	149	250	296
Cases per patient	0.79	0.40	1.24	0.69
RAP-confirmed relapses, n (%)	125 (85.0%)	121 (81.2%)	207 (82.2%)	242 (81.8%)

It is worth noting that suspected relapses reported by patients might have been dismissed and symptoms deemed not to be relapse related at the time of patients' reporting. The phone records for reporting of suspected relapses were not available, and clinicians who determined whether the symptoms were relapse related were not blinded to the treatment. Therefore, the number of suspected relapses could be under reported in the aletuzumab group.

Final Discussion and Conclusion

Although various sensitivity analyses were planned and performed, none of them addressed issue of potential bias due to the unblinded nature of the design.

Perhaps the most objective measure not subjected to bias is the MRI T2 hyperintense lesion volume, a secondary efficacy endpoint. Neither study showed evidence of efficacy in this measure.

The big question is the source of bias. Patients were unblinded. It is not a surprise that patients carried their bias into the study. But there is no reason to allow patients to acquire knowledge of their treatment assignment before the initial treatment and baseline assessment. When the validity of the baseline is in question, the validity of the study is in question.

It appears that the bias may not be limited to the patient's side. The discrepancy in EDSS scores between screening visit and randomization visit that led to opposite directions in change of SAD event numbers cannot be explained by bias from patients.

In summary, the two pivotal studies rendered more questions than answers. No sound statistical analysis can solve the problems from inadequately designed and poorly executed studies.

3.3 Evaluation of Safety

Please refer to Evaluation of Safety by Dr. Evelyn Mentari.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 19 and Table 20 present the results from analysis of the primary endpoints by gender and age group, respectively. There are no consistent findings of difference in gender and age with regard to relapse rate or SAD events.

Table 19 Summary of Relapse Rate and SAD Events by Gender

	IFNB-1a		Aletuzumab 12 mg	
	Male	Female	Male	Female
Study 323				
N	65	122	133	243
Patients with relapse, n (%)	30 (46.2%)	45 (36.9%)	22 (16.5%)	60 (24.7%)
ARR (nominal p-value)	0.51	0.33	0.12 (p<.0001)	0.20 (p=0.0151)
Patients with SAD, n (%)	6 (9.2%)	14 (11.5%)	8 (6.0%)	22 (9.1%)
HR ¹ (nominal p-value)			0.59 (p=.3135)	0.74 (p=.3895)
Study 324				
N	71	131	145	281
Patients with relapse, n (%)	37 (52.1%)	67 (51.1%)	39 (26.9%)	108 (38.4%)
ARR (nominal p-value)	0.38	0.58 (p=.0001)	0.16	0.32 (p<.0001)
Patients with SAD, n (%)	13 (18.3%)	27 (20.6%)	19 (13.1%)	35 (12.5%)
HR ¹ (nominal p-value)			0.67 (p=.2558)	0.54 (p=.0154)

1. Hazard ratio

Note that in Study 324, even though the percentage of relapse is slightly higher in males than in females in the IFNB-1a group (52.1% versus 51.1%), the estimated ARR, from a model adjusted by region, is much lower in the males than in the females, indicating large difference among the regions with possible interaction with gender.

Age group was divided in consistency with the sponsor, who used median age of the overall patient population. In Study 323, patients in age group 1 were younger than 32 years old and patients in age group 2 were at least 32 years old. In Study 324, the age group was divided as younger than 34 and at least 34 years old.

Table 20 Summary of Relapse Rate and SAD Events by Age Group

	IFNB-1a		Aletuzumab 12 mg	
	Group 1	Group 2	Group 1	Group 2
Study 323				
N	89	98	183	193
Patients with relapse, n (%)	37 (41.6%)	38 (38.8%)	35 (19.1%)	47 (24.4%)
ARR (nominal p-value)	0.46	0.31	0.14 (p<.0001)	0.20 (p=.0575)
Patients with SAD, n (%)	6 (6.7%)	14 (14.3%)	11 (6.0%)	19 (9.8%)
HR ¹ (nominal p-value)			0.85 (p=.7565)	0.63 (p=.1877)
Study 324				
N	79	123	207	219
Patients with relapse, n (%)	47 (59.5%)	57 (46.3%)	68 (32.9%)	79 (36.1%)
ARR (nominal p-value)	0.63	0.43 (p<.0001)	0.29	0.23 (p=.0006)
Patients with SAD, n (%)	10 (12.7%)	30 (24.4%)	24 (11.6%)	30 (13.7%)
HR ¹ (nominal p-value)			0.90 (p=.7777)	0.48 (p=.0048)

Large discrepancies are observed in SAD results across regions. Excluding Latin America region, which has too few patients to draw reliable conclusions, a higher hazard ratio in aletuzumab group is observed in EU region in Study 323 and in Non-EU Europe/Israel region in Study 324.

Table 21 Summary of Relapse Rate and SAD Events by Region – Study 323

Study 323	EU	Latin America	Non-EU	USA/CAN/AUS
IFNB-1a				
N	40	4	89	54
Patients with Relapse, n (%)	20 (50.0)	1 (25.0)	32 (36.0)	22 (40.7)
ARR	0.52	0.49	0.25	0.36
Patients with SAD, n (%)	4 (10.0)	0	9 (10.1)	7 (13.0)
Aletuzumab				
N	81	11	173	111
Patients with Relapse, n (%)	20 (24.7)	4 (36.4)	28 (16.2)	30 (27.0)
ARR	0.18	0.23	0.11	0.21
Nominal p-value)	.001	.429	.003	.067
Patients with SAD, n (%)	12 (14.8)	2 (18.2)	8 (4.6)	8 (7.2)
Hazard Ratio of SAD	1.42		0.44	0.50
Nominal p-value	.543	<.001	.086	.183

Table 22 Summary of Relapse Rate and SAD Events by Region – Study 324

Study 324	EU	Latin America	Non-EU/Israel	USA/CAN/AUS
IFNB-1a				
N	44	13	43	102
Patients with Relapse, n (%)	28 (63.6)	7 (53.8)	23 (53.5)	46 (45.1)
ARR	0.67	0.62	0.65	0.44
Patients with SAD, n (%)	12 (27.3)	5 (38.5)	4 (9.3)	19 (18.6)
Aletuzumab				
N	91	26	93	216
Patients with Relapse, n (%)	34 (37.4)	2 (7.7)	33 (35.5)	78 (36.1)
ARR	0.28	0.11	0.28	0.30
Nominal p-value)	<.001	.018	.001	.040
Patients with SAD, n (%)	12 (13.2)	1 (3.9)	12 (12.9)	29 (13.4)
Hazard Ratio of SAD	0.44	0.08	1.34	0.64
Nominal p-value	.046	.022	.608	.131

4.2 Other Special/Subgroup Populations

No analyses of other subgroups have risen to the importance to be presented.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The two pivotal studies were designed as rater-blinded. Despite the Division's strong recommendation for a double-blinded double-dummy design for the two pivotal studies, Genzyme initiated two trials after a no-agreement letter for the requested SPA was issued by the Division. Despite the efforts from the Division as well as Genzyme in implementing measures to

protect blindness after the trials started, the bias shown in the data has far exceeded what was expected.

The issues arisen from the two studies are beyond the scope of statistics and cannot be solved by any statistical methods. It is not about the appropriateness of statistical methods or inflation of α , and p-values from analyses, large or small, are irrelevant. The only way to solve the issues raised in this review is to conduct fresh new studies that are adequately designed and well controlled.

5.2 Collective Evidence

The two studies provided more questions than answers. On the surface, one would see consistent efficacy results across a full range of sensitivity analyses only to find out that behind the surface is a big puzzle with many missing pieces that no one can solve and no statistical methods are useful.

Collectively, the two studies rendered more evidence of ineffectiveness than effectiveness of alemtuzumab on disability. Among patients who had changed EDSS scores from screening to randomization, SAD events took a reversal direction when screening EDSS scores were used to serve baseline. Among patients in the Non-EU Europe region who had no or little change in EDSS scores, alemtuzumab-treated patients had more SAD events than IFNB-1a-treated patients.

It may be arguable that alemtuzumab could be effective in reducing the relapse rate. However, with various biases hampering the actual facts, questions about the validity of baseline EDSS scores and conduct of the studies, accurate estimate of relapse rate is impossible to obtain.

Perhaps the secondary endpoint of T2-hyperintensive lesion volume, the most and only objective measure that is immune to bias, can offer the most convincing conclusion. In both studies, alemtuzumab failed to show evidence of effectiveness in this MRI measure.

5.3 Conclusions and Recommendations

The reviewer concludes that adequately designed and well controlled blinded studies need to be conducted in order to establish the possible efficacy for alemtuzumab.