April 15, 2015

Dr. Dave Campana, PharmD
,

Dear Dr. Campana:

Your request for information regarding Lemtrada™ (alemtuzumab) injection and the following topic(s) has been forwarded to Medical Information Services by our Genzyme Medical Representative, Anthony Ranno:

- Clinical Trial Summary

Lemtrada is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

Lemtrada is contraindicated in patients who are infected with Human Immunodeficiency Virus (HIV) because Lemtrada causes prolonged reductions of CD4+ lymphocyte counts.

WARNING: AUTOIMMUNITY, INFUSION REACTIONS, AND MALIGNANCIES

See full presribing information for complete boxed warning.

- Lemtrada causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine counts at periodic intervals for 48 months after the last dose of Lemtrada.
- Lemtrada Causes serious and life-threatening infusion reactions. Lemtrada must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for two hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2 hour monitoring period.
- Lemtrada may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams.
- Lemtrada is available only through a restricted distribution program.

This information is supplied as a professional courtesy in response to your inquiry. It is intended to provide pertinent data that will assist you in forming your own conclusions and making your own decisions. Some of the content within this correspondence maybe inconsistent with the approved product labeling (an unapproved use), and no conclusions regarding the safety or efficacy can be made for such uses. This information is not intended to advocate any indication, dosage, administration, patient population or other usage that is not covered in the enclosed package insert.

Clinical Trial Summary

Summary

- Alemtuzumab is a CD52-directed cytolytic monoclonal antibody approved on November 14th, 2014 by the Food and Drug Administration for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.[1]

- Initial investigator-sponsored observational, open-label studies[2,3] provided the following preliminary findings:

  - In relapsing remitting multiple sclerosis (RRMS) patients, alemtuzumab treatment resulted in a reduction of relapse rates and a stabilization of disability.
  - In secondary progressive multiple sclerosis (SPMS) patients, alemtuzumab treatment resulted in a reduction of new MRI lesions but did not stabilize disease progression and accumulation of disability.
  - Adverse events are summarized in the Background section below.

- In a randomized phase 2 study[4,5] with 5 years of follow-up, alemtuzumab-treated RRMS patients compared with interferon beta-1a treated RRMS patients experienced:

  - A 72% reduction in the risk for sustained accumulation of disability (P<0.0001)
  - A 69% reduction in the risk for relapse (P<0.0001)
  - The most notable alemtuzumab-associated adverse events included infusion associated reactions, infections of predominantly mild to moderate severity, and autoimmune disorder development (primarily thyroid in nature)

- Two Phase 3 studies compared treatment with alemtuzumab and interferon beta-1a in treatment-naïve RRMS patients (CARE-MS I)[6] and RRMS patients who relapsed after prior disease modifying therapy (CARE-MS II)[7], each with up to 24 months of follow-up (no placebo arm).

  - In treatment-naïve RRMS patients (CARE-MS I)[7], alemtuzumab-treated patients experienced a 54.9% reduction in the risk for relapse (P<0.0001) compared with interferon beta-1a treated patients, but sustained accumulation of disability rates did not differ between treatment groups (potentially due to an underestimation of interferon beta-1a treatment effects on disability).
  - In RRMS patients who relapsed while on disease modifying therapy (CARE-MS II), alemtuzumab treatment reduced the rate of relapse compared with interferon beta-1a (risk reduction of 49.4%, P<0.0001), and reduced the risk of sustained accumulation of disability compared with interferon beta-1a (risk reduction of 42%, P=0.0084).
  - During the two phase 3 studies, most alemtuzumab-treated patients experienced mild to moderate infusion-associated reactions, infections of mild to moderate severity were more common in alemtuzumab-treated patients (typically upper respiratory tract, urinary tract, or herpetic), and autoimmune disorder development (primarily thyroid in nature) occurred more often in alemtuzumab-treated patients.

Background

Coles et al[2] conducted an open-label clinical study evaluating the efficacy and safety of alemtuzumab treatment in 58 patients with either SPMS or RRMS. Alemtuzumab reduced the annual relapse rate from 2.2 to 0.19 and from 0.7 to 0.001, respectively (P<0.001 for both). Although MRI scans of patients with SPMS showed no new lesion formation, SPMS patients showed sustained accumulation of disability due to uncontrolled disease progression marked by unrelenting cerebral atrophy. In contrast, RRMS patients demonstrated a reduction in disability 6 months after alemtuzumab treatment (mean reduction of 1.2 EDSS points). There was also a significant but smaller mean improvement in disability up to 36 months after alemtuzumab treatment.

In this early investigator-sponsored study, alemtuzumab caused an acute cytokine release syndrome, consisting of pyrexia, headache, malaise, and urticarial rash. Several patients also experienced a transient exacerbation of current or past neurological symptoms associated with this syndrome, which was ameliorated by pre treatment with corticosteroids. Eight infections that probably or possibly were adverse effects of alemtuzumab also occurred. The principal adverse effect of alemtuzumab therapy was the development of Graves' disease. One patient had pre-existing Graves' disease, and 15 new cases were observed after alemtuzumab treatment in the 57 remaining patients (26%). One additional case of autoimmune hypothyroidism was also noted. In addition, one patient in the RRMS group developed Goodpasture's syndrome 10 months after treatment with alemtuzumab and is renal dialysis-dependent.

Based on the foregoing initial study data, alemtuzumab treatment appeared to suppress relapse in SPMS patients but did not prevent the continued progression of disability. This suggests that SPMS might be a consequence of post-inflammatory neurodegeneration and that early intervention might positively influence long term disability.

Hirst et al[3] published their open-label experience with alemtuzumab in 39 patients with aggressive RRMS. Patients received one of 5 alemtuzumab dosages for 5 days, and less than half of the patients received 3 days of re-treatment at 12 to 18 month intervals. Patients were followed for a mean of 1.89 years (range 0.2 to 4.7 years). A significant reduction was seen in the annualized relapse rate between the year prior to treatment and the year following treatment (P<0.001). Patients who had unstable Expanded Disability Status Scores (EDSS) at baseline (n=12) had a mean change in EDSS of 1.5 (-3 to 0.5), and in patients with stable EDSS the mean change was 0.2 (-1.5 to 1.5). Infusion reactions were frequent, and 18% of patients experienced infection. Two patients developed thyroid adverse events, while 2 patients developed anti thyroperoxidase antibodies without clinically detectable thyroid disease. Nine patients developed mild platelet abnormalities (no cases of ITP were reported).

Clinical Data

Phase 2 Study

Genzyme conducted a Phase 2, randomized, rater-blinded study comparing 2 dosages of alemtuzumab with interferon beta-1a (CAMMS223). Three hundred thirty-four (334) patients with early RRMS (not previously treated with MS therapies other than steroids) were randomized in a 1:1:1 ratio at 49 medical centers in the United States and Europe. Patients were treated with alemtuzumab at one of 2 doses (12 mg/day or 24 mg/day, for 5 consecutive days then for 3 days one year later with an option for a third course) or high-dose interferon beta-1a dosed 44 mcg 3-times weekly by subcutaneous injection. Primary outcome measures included sustained accumulation of disability confirmed through 6 months and relapse rate. Secondary outcomes were also evaluated and included the proportion of relapse-free patients at 3 years after initial treatment, changes in lesion burden (as seen on T_2-weighted MRI), and brain volume (as seen on T_1-weighted MRI). MRI scans were reported annually and evaluated by blinded readers. A final 3-year analysis of this study was published in the New England Journal of Medicine in October 2008.[5]

Overall, patients receiving alemtuzumab experienced a 74% reduction in the rate of relapse as compared to patients who received interferon beta-1a ($P<0.001$). Patients in both alemtuzumab treatment arms achieved statistically significant reductions in the risk of sustained disability (increase in EDSS, sustained for at least 6 months) and statistically significant improvements in mean EDSS from baseline. Patients treated with interferon beta-1a had a significant increase in mean EDSS from baseline. Primary and secondary endpoint results are outlined in Table 1.

Table 1 Measures of Multiple Sclerosis Relapse and Disability by Treatment Group[5]

Outcome	Interferon beta-1a (n=111)	Alemtuzumab 12 mg (n=112)	Alemtuzumab 24 mg (n=110)	Alemtuzumab All doses (n=222)
Relapse Rates				
Patients with any event	45	24	17	41
Total no. of events	89	34	25	59
Hazard ratio (95% CI)		0.31 (0.18 to 0.52)	0.21 (0.11 to 0.40)	0.26 (0.16 to 0.41)
P value		<0.001	<0.001	<0.001
Annualized Rate (95% CI)	0.36 (0.29 to 0.44)	0.11 (0.08 to 0.16)	0.08 (0.05 to 0.12)	0.10 (0.07 to 0.12)
Patients without relapse (%) at 36 months	51.6	77.0	83.5	80.2
Disability				
Sustained accumulation for 6 months				
Number of patients with outcome	24 (26.2)	8 (8.5)	10 (9.5)	18 (9.0)
Hazard Ratio (95% CI)	—	0.25 (0.11 to 0.57)	0.33 (0.16 to 0.69)	0.29 (0.16 to 0.54)
Treatment effect, % (95% CI)	—	75 (43 to 89)	67 (31 to 84)	71 (46 to 84)
P value	—	<0.001	0.003	<0.001
Change in mean EDSS score from baseline				
Mean (95% CI)	0.38 (0.13 to 0.63)	–0.32 (–0.55 to to –0.10)	–0.45 (–0.68 to –0.22)	–0.39 (–0.55 to –0.23)
P value	0.003	0.006	<0.001	<0.001

EDSS = Expanded Disability Status Scale

Treatment effect, % (95% CI)	—	59 (31,76)	67 (44,81)	63 (42,77)
P value	—	<0.001	<0.001	<0.001
EDSS = Expanded Disability Status Scale				

All three treatment arms demonstrated reductions in lesion volume (as viewed on T_2-weighted MRI) from baseline to 36 months. The 36 month T_2 lesion volume reduction observed in the alemtuzumab-treatment arm was not statistically significant, and may have been affected by the smaller sample size at month 36 due to study discontinuation and the 26 patients who had missing or deficient MRI scans. However, in the pooled group of alemtuzumab-treated patients there was a greater reduction in T_2 lesion volume than interferon beta-1a in months 0-36 (P=0.005) and at months 0-12 (P=0.01) and months 0-24 (P=0.005).

Alemtuzumab-treated patients (24 mg group) also experienced significantly smaller reductions in brain volume (T_1-weighted MRI) between baseline and month 36 compared to patients treated with interferon beta-1a (secondary endpoint). Since brain atrophy measures can be confounded by early suppression of inflammatory space-occupying lesions, brain volumes were also analyzed starting at month 12. Between months 12 and 36, brain volume increased in the alemtuzumab-treatment arm by 0.9% but decreased in the interferon beta-1a treatment arm by 0.2% (P=0.02). MRI sub-group analyses were conducted to account for various potential confounding factors (ie. study-site location, baseline EDSS score, lesion load on T_2-weighted MRI, cerebral volume on T_1-weighted MRI, sex, race, and age of patients) and the observed alemtuzumab results were sustained after all of the subanalyses. MRI results from this study are outlined in Table 2.

Table 2 MRI Analyses in Treatment-naïve RRMS Patients by Treatment Group (CAMMS223)[5]

Outcome	Interferon beta-1a (n=111)	Alemtuzumab 12 mg (n=112)	Alemtuzumab 24 mg (n=110)	Alemtuzumab Pooled (n=222)
Lesion load on T_2–weighted MRI				
Median change from baseline, *% 0-12 Months*	–12.1	–17.7	–19.2	–18.3
P value	—	0.02	0.03	0.01
Median change from baseline, *% 0-24 Months*	–9.8	–21.2	–20.3	–20.4
P value	—	0.01	0.02	0.005

Outcome	Interferon beta-1a (n=111)	Alemtuzumab 12 mg (n=112)	Alemtuzumab 24 mg (n=110)	Alemtuzumab Pooled (n=222)
Median change from baseline, *% 0-36 Months**	–13.3	–18.2	–13.5	–16.4
P value	—	0.21	0.40	0.24
P value for overall comparison†	—	0.01	0.03	0.005
Brain volume on T_1–weighted MRI				
Median change from baseline, *% 0-36 Months**	–1.8	–0.9	0	–0.5
P value	—	0.16	0.04	0.05
Median change from baseline, *% 12-36 Months*	–0.2	1.2	0.7	0.9
P value	—	0.03	0.04	0.02
P values are for the comparison between alemtuzumab and interferon beta-1a *secondary endpoint †The P value is for a multivariate comparison for all time points calculated wiht the Wei–Lachin test.				

Adverse events occurred in 100% of the patients in the interferon beta-1a arm and in 99.5% of patients in the alemtuzumab arms. Infusion-associated adverse events occurred in almost all of the alemtuzumab-treated patients, most were mild to moderate and 1.4% were serious. Infection-related adverse events were noted in approximately 66% of alemtuzumab-treated patients. Thyroid-related adverse events were reported in approximately 23% of alemtuzumab-treated patients. Ninety-six percent (96%) of the thyroid related events in the alemtuzumab-treated patients were associated with thyroid autoantibodies. Six confirmed cases of ITP occurred in alemtuzumab-treated patients (2.8%); one patient developed ITP and suffered a fatal intracerebral hemorrhage; the other 5 patients responded to medical management for ITP and are in remission. In response to the cases of ITP, Genzyme implemented enhanced education and monitoring for ITP and created a comprehensive risk management plan to help physicians and patients detect ITP early in an attempt to minimize the risk of complications.

CAMMS223 Complete Follow-up

All CAMMS223 patients were encouraged to participate in a 2-year extension study, and out of the original 334 patients, 198 patients participated (alemtuzumab treated: n=151; interferon

beta-1a-treated: n=47).[4] During the extension study, the use of disease-modifying therapies (DMTs) was permitted, and alemtuzumab-treated patients had the option of receiving an additional 3-day alemtuzumab course (12 mg/day) at least 12 months after their last treatment cycle. Efficacy outcomes (same outcomes as the original CAMMS223 study) were analyzed from the baseline of the original trial period through 60 months, and safety follow-up extended beyond 60 months. Alemtuzumab-treated patients experienced a 69% reduction in the rate of relapse through 5 years (annualized relapse rates remained similar to the 3-year results), see Figure 1. Alemtuzumab-treated patients also experienced a 72% reduction in the risk of sustained accumulation of disability through 5 years (71% reduction at 3 years). A slight worsening in mean disability occurred in both treatment groups (alemtuzumab and interferon beta-1a) between month 36 and 60, see Figure 2.

Sensitivity analyses were conducted and censored patients at the time when they received any nonstudy DMT during the first 36 months of the study, and any DMT (including interferon beta-1a) or alemtuzumab retreatment during the extension phase. Risk of sustained accumulation of disability through complete follow-up (nonsensitivity) and after sensitivity analyses were similar, risk reduction of 71% and 68%, respectively. Relapse rates through complete follow-up (nonsensitivity) and after sensitivity analyses were generally similar (risk reduction of 68% and 70%, respectively); but the rate of relapse between month 36 to month 60 without and with the sensitivity analyses were not similar (risk reduction of 49% and 27%, respectively).

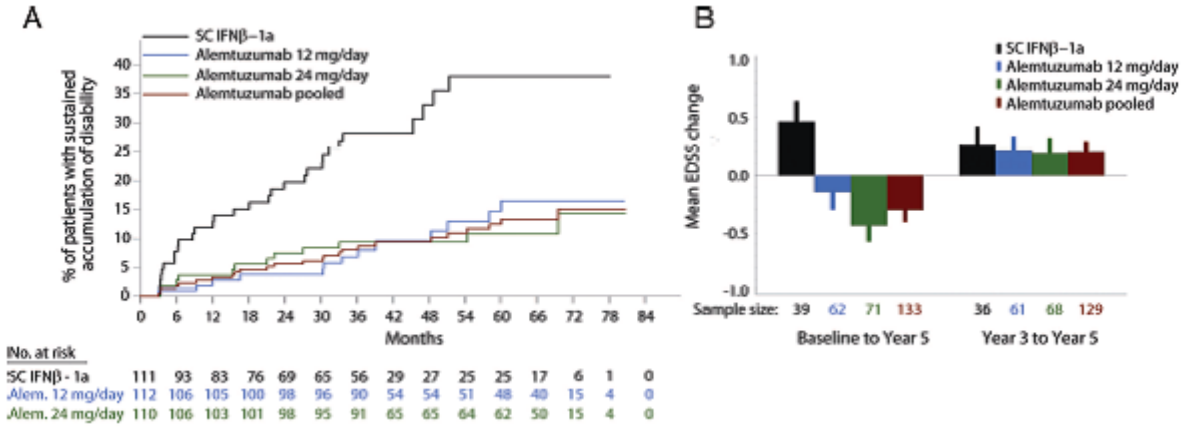
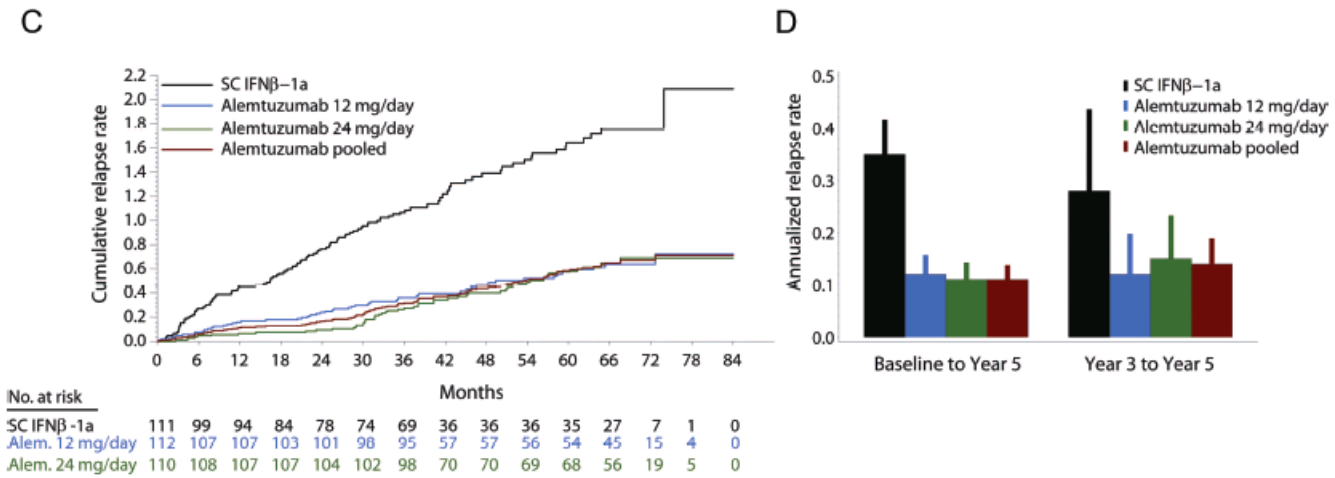


Figure 1 Sustained Accumulation of Disability and Mean EDSS Change through Month 60 and Complete Follow-up, CAMMS223[4]



(C) The cumulative relapse rate from randomization through complete follow-up. (D) The annualized relapse rate from baseline of the original study through year 5 and from year 3 to year 5. Alem. = alemtuzumab; IFNβ-1a = interferon β-1a; SC = subcutaneous

Figure 2 Cumulative and Annualized Relapse Rates through Month 60 and Complete Follow-up, CAMMS223[4]

During the extension study, the safety profile for alemtuzumab-treated patients was similar to that reported during the original study period. The most notable events reported during the extension study were infusion-associated reactions, infections, and secondary autoimmunity (principally thyroid in nature). Infusion-associated reactions during the extension study were qualitatively the same as those reported during the original study period, but there were fewer infusion-associated reports during the extension study (46% versus 99% of alemtuzumab-treated patients during the extension and original study, respectively). Infections in any given year during the extension study ranged between 10 and 27% of patients with the majority of alemtuzumab patients being untreated (only 50 patients received a retreatment alemtuzumab cycle during the extension study). Infections were seen in 72% of patients through complete follow-up and were mostly mild or moderate (96%) in severity; with upper respiratory tract infections reported most frequently. The incidence of secondary autoimmune disease after initial alemtuzumab treatment increased each year to a maximum in year 3 (14%) and then declined during the extension period. Thyroid disease was the most common autoimmune event and was noted in 30% of alemtuzumab-treated patients (onset ranged from 6 to 61 months after the first exposure to alemtuzumab). No additional cases of ITP were reported during the extension period. One case of anti-GBM disease was reported 39 months after the second annual alemtuzumab cycle (12-mg alemtuzumab-treated patient). The patient was successfully treated with plasmapheresis, cyclophosphamide, and corticosteroids.

Phase 3 Studies

CARE-MS I

Genzyme conducted a randomized, rater-blinded, phase 3 trial in treatment-naïve RRMS patients that compared alemtuzumab with interferon beta-1a (CARE-MS I).[6] Patients were enrolled at 101 academic medical centers in 16 countries and had active RRMS with at least 2 relapses in the previous 2 years, at least one relapse in the previous year, EDSS scores of 3.0 or lower, and cranial abnormalities on MRI attributable to multiple sclerosis. Patients were randomly allocated in a 2:1 ratio to receive alemtuzumab (12 mg per day intravenously, 5–day treatment course at baseline and 3–day course at 12 months) or interferon beta-1a (44 mcg subcutaneously three-times per week); 563 patients were randomized and received at least one dose of study drug.

Benefit was assessed by the co-primary endpoints of relapse rate and time to 6 month sustained accumulation of disability. Relapse was defined as new or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination assessed by a masked rater. All potential relapses were confirmed via adjudication by a committee comprising 6 independent and masked neurologists. Sustained accumulation of disability was defined as an increase from baseline of at least 1.0 EDSS point (or at least 1.5 points if the baseline score was 0) confirmed over 6 months. Secondary endpoints were measured over 24 months and included the proportion of relapse-free patients, change in EDSS, percentage change in T_2-hyperintense lesion volume, and change in multiple sclerosis functional composite (MSFC). Analysis of secondary efficacy endpoints used a hierarchical closed testing procedure in which secondary endpoints were sequentially analyzed in the following order: Relapse-free, EDSS change from baseline, % Change MRI T2 lesions volume, MSFC. Each endpoint could only be formally tested if both primary endpoints and the prior secondary endpoints were significant. For descriptive purposes, even if earlier endpoints were not met, estimated treatment effects (including p-values) are presented secondary efficacy endpoints. Safety was assessed with monthly patient questionnaires and monthly labs (complete blood counts, serum creatinine, urinalysis and microscopy – every 3 months in interferon beta-1a treated patients), and thyroid function tests every 3 months. Infusion associated reactions were defined as any adverse event beginning during or within 24 hours after alemtuzumab infusion.

Alemtuzumab reduced the rate of relapse compared with interferon beta-1a (risk reduction of 54.9%), but sustained accumulation of disability rates did not differ between treatment groups, see Figure 3. As noted by the authors, the power calculations for the sustained accumulation of disability endpoint expected at least 20% of interferon beta-1a treated patients to incur additional disability by 2 years and were based upon previous study results (including Genzyme's phase 2 trial). During this trial unexpectedly few interferon beta-1a treated patients (11%) experienced increased disability over 24 months of therapy. More alemtuzumab-treated patients were relapse-free at 2 years when compared with the interferon beta-1a treated patients. Decreases in T_2-hyperintense lesion volume by 24 months and mean EDSS score improvements did not differ between treatment groups. The difference in MSFC change over 24 months was not regarded as significant (based upon the prespecified plan of sequential testing of secondary

endpoints to control for multiple comparisons). For more information on the primary, secondary and tertiary endpoints; please see Table 3.

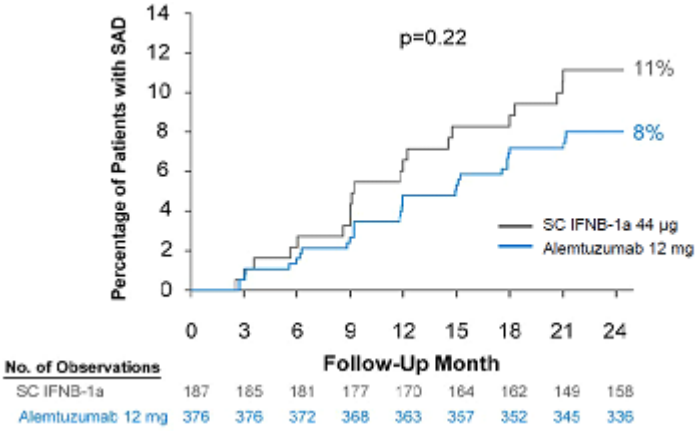


Figure 3 Sustained Accumulation of Disability CARE-MS I

Table 3 Clinical Outcomes in Treatment-naïve RRMS Patients by Treatment Group (CARE-MS I)[6]

	Interferon beta-1a (n=187)	Alemtuzumab (n=376)	p value
Relapse			
Patients with any event	75 (40%)	82 (22%)	
Total number of events	122	119	
Rate ratio (95% CI)	– –	0.45 (0.32 to 0.63)	<0.0001
Yearly rate (95% CI)	0.39 (0.29 to 0.53)	0.18 (0.13 to 0.23)	
Relapse-free patients, % (95% CI*)	58.7% (51.1 to 65.5)	77.6% (72.9 to 81.6)	<0.0001
Disability			
Sustained accumulation confirmed over 6 months			
Patients	20 (11%)	30 (8%)	
Percentage of patients (95% CI)*	11.12% (7.32 to 16.71)	8.00% (5.66 to 11.24)	0.22
Hazard ratio (95% CI)	– –	0.70 (0.40 to 1.23)	

	Interferon beta-1a (n=187)	Alemtuzumab (n=376)	p value
Mean change in EDSS (95% CI)	–0.14 (–0.29 to 0.01)	–0.14 (–0.25 to –0.02)	0.97
Mean change in MSFC†	0.07 (0.45)	0.15 (0.52)	0.01
MRI			
Median volume change in T_2–hyperintense lesions	–6.5% (–20.7 to 2.5)	–9.3% (–19.6 to –0.2)	0.31
Patients with new or enlarging T_2 hyperintense lesions‡	99/172 (58%)	176/363 (48%)	0.04
Patients with gadolinium-enhancing lesions at 24 months‡	34/178 (19%)	26/366 (7%)	<0.0001
Median change in brain parenchymal fraction‡	–1.488% (–2.355 to –0.567)	–0.867% (–1.470 to –0.254)	<0.0001
Diseas-free survival			
Patients clincially disease-free‡	104 (56%)	279 (74%)	
Odds ratio (95% CI)	– –	2.36 (1.62 to 3.43)	<0.0001
Patients MRI and clinically disease-free‡	46/172 (27%)	139/360 (39%)	
Odds ratio (95% CI)	– –	1.75 (1.17 to 2.61)	0.006

Data are n (%), mean (SD), median (IQR), or n/n assessed (%), unless otherwise stated. EDSS = expanded disability status scale, MSFC= multiple sclerosis functional composite. *Kaplan-Meier estimates †As per the prespecified plan for sequential testing of the four secondary endpoints and the non-sigificant findings for changes over 24 months in EDSS adn T_2-hyperintense lesion volume, this difference was not regarded as significant. ‡Prespecified tertiary endpoint.

Adverse events (1 or more event) were reported in 92% of interferon beta-1a treated patients and in 96% of alemtuzumab-treated patients. Adverse events resulting in study discontinuation occurred in 11 (6%) interferon beta-1a treated patients and in 5 (1%) alemtuzumab-treated patients. The most common adverse events with interferon beta-1a were flu-like illness, relapse

of multiple sclerosis, and headache. The most common adverse events with alemtuzumab were infusion-associated reactions (headache, rash, and pyrexia) and relapse of multiple sclerosis.

Overall, 14% of 376 alemtuzumab-treated patients and 8% of 187 interferon beta-1a treated patients reported serious adverse events other than MS relapse. Serious infusion-associated reactions were reported in alemtuzumab-treated patients: 2 patients each (atrial fibrillation, incorrect dose administered, and hypotension) and 1 patient each (bradycardia, sinus bradycardia, sinus tachycardia, tachycardia, nausea, chest discomfort, pyrexia, anaphylactic shock, myalgia, brain stem syndrome, headache, migraine, pleurisy, throat tightness, angioedema, and urticaria). Serious infectious adverse events were reported in alemtuzumab-treated patients: 2 patients each (appendicitis) and 1 patient each (disseminated tuberculosis, herpes zoster, meningitis herpes, postoperative wound infection, tooth infection, uterine infection, and hepatitis A). One patient in the alemtuzumab treatment group died as a result of an automobile accident during the study, and one alemtuzumab-treated patient died of sepsis after the study. For additional safety information, please see Table 4.

Table 4 Adverse Events by Treatment Group (CARE-MS I)[6]

	Interferon beta-1a (n=187)	Alemtuzumab (n=376)
Infusion-associated reactions		
Any event	NA	338 (90%)
Events affecting >10% in alemtuzumab group		
Headache	NA	160 (43%)
Rash	NA	155 (41%)
Pyrexia	NA	125 (33%)
Nausea	NA	51 (14%)
Urticaria	NA	43 (11%)
Flushing	NA	43 (11%)
Chills	NA	38 (10%)

Data are n (%), unless otherwise stated. NA=not applicable. *Herpes simplex includes the perferred terms herpes simples, oral herpes, and genital herpes. †Hyperthyroidism includes the perferred terms hyperthyroidism and Basedow's disease; hypothyroidism includes the preferred terms hypothyroidism and primary hypothyroidism; and thyroiditis includes the preferred terms thyroiditis, autoimmune thyroiditis, and thyroiditis subacute. ‡Events that were not infusion-associated reactions. γIncludes only events with preferred terms multiple sclerosis relaplse, and might not correspond to relapse tally for efficacy endpoints.

	Interferon beta-1a (n=187)	Alemtuzumab (n=376)
Infections		
Any Event	85 (45%)	253 (67%)
Events affecting >10% in any group		
Nasopharyngitis	25 (13%)	74 (20%)
Urinary Tract Infection	8 (4%)	64 (17%)
Herpes viral infections	3 (2%)	62 (16%)
Herpes simplex*	3 (2%)	50 (13%)
Herpes zoster	0	12 (3%)
Herpes virus infection	0	2 (1%)
Meningitis herpes	0	1 (<1%)
Pneumonia herpes viral	0	1 (<1%)
Varicella	0	1 (<1%)
Upper respiratory tract infection	25 (13%)	57 (15%)
Thyroid Disorders		
Any event†	12 (6%)	68 (18%)
Hyperthyroidism	3 (2%)	28 (7%)
Hypothyroidism	4 (2%)	18 (5%)
Goitre	0	6 (2%)
Thyroiditis	0	11 (3%)

Data are n (%), unless otherwise stated. NA=not applicable. *Herpes simplex includes the perferred terms herpes simples, oral herpes, and genital herpes. †Hyperthyroidism includes the perferred terms hyperthyroidism and Basedow's disease; hypothyroidism includes the preferred terms hypothyroidism and primary hypothyroidism; and thyroiditis includes the preferred terms thyroiditis, autoimmune thyroiditis, and thyroiditis subacute. ‡Events that were not infusion-associated reactions. γIncludes only events with preferred terms multiple sclerosis relaplse, and might not correspond to relapse tally for efficacy endpoints.

	Interferon beta-1a (n=187)	Alemtuzumab (n=376)
Thyroid mass	0	1 (<1%)
Thyrotoxic crisis	0	1 (<1%)
Serious adverse event	0	4 (1%)
Basedow's disease	0	2 (1%)
Goitre	0	1 (<1%)
Hyperthyroidism	0	1 (<1%)
Thyrotoxic crisis	0	1 (<1%)
Blood and lymphatic system disorders		
Any event	36 (19%)	66 (18%)
Serious adverse event	0	5 (1%)
Immune thrombocytopenic purpura	0	3 (1%)
Agranulocytosis	0	2 (1%)
Malignant Disease		
Thyroid cancer	0	2 (1%)
Liver toxicity		
Any event	32 (17%)	15 (4%)
Serious adverse events	1 (1%)	0
Administration-site reactions		
Any event	87 (47%)	19 (5%)

Data are n (%), unless otherwise stated. NA=not applicable. *Herpes simplex includes the perferred terms herpes simples, oral herpes, and genital herpes. [†]Hyperthyroidism includes the perferred terms hyperthyroidism and Basedow's disease; hypothyroidism includes the preferred terms hypothyroidism and primary hypothyroidism; and thyroiditis includes the preferred terms thyroiditis, autoimmune thyroiditis, and thyroiditis subacute. [‡]Events that were not infusion-associated reactions. [γ]Includes only events with preferred terms multiple sclerosis relaplse, and might not correspond to relapse tally for efficacy endpoints.

	Interferon beta-1a (n=187)	Alemtuzumab (n=376)
Other events affecting >10% of patients in any group‡		
General condition		
Fatigue	16 (9%)	50 (13%)
Influenza like illness	43 (23%)	11 (3%)
Injection site erythema	46 (25%)	0
Nervous sytem disorders		
Headache	35 (19%)	86 (23%)
Multiple sclerosis relapse[γ]	73 (39%)	80 (21%)
Skin and subcutaneous tissue disorders		
Rash	7 (4%)	44 (12%)

Data are n (%), unless otherwise stated. NA=not applicable. *Herpes simplex includes the perferred terms herpes simples, oral herpes, and genital herpes. [†]Hyperthyroidism includes the perferred terms hyperthyroidism and Basedow's disease; hypothyroidism includes the preferred terms hypothyroidism and primary hypothyroidism; and thyroiditis includes the preferred terms thyroiditis, autoimmune thyroiditis, and thyroiditis subacute. [‡]Events that were not infusion-associated reactions. [γ]Includes only events with preferred terms multiple sclerosis relaplse, and might not correspond to relapse tally for efficacy endpoints.

CARE-MS II

Genzyme conducted a randomized, rater-blinded, comparative (alemtuzumab versus interferon beta-1a), phase 3 trial in RRMS patients with at least one relapse on either interferon beta or glatiramer (CARE-MS II).[7] Patients were enrolled at 194 academic medical centers and clinical practices in 23 countries and had RRMS with at least 2 attacks in the previous 2 years, at least one relapse while on interferon beta or glatiramer after at least 6 months of treatment, EDSS scores of 5.0 or lower, and cranial and spinal MRI lesions fulfilling protocol-defined criteria. Patients were randomly allocated in a 2:2:1 ratio to receive alemtuzumab (either 12 mg or 24 mg per day intravenously, 5 day treatment course at baseline and 3 day course at 12 months) or interferon beta-1a (44 mcg subcutaneously three-times per week); 840 patients were randomized when recruitment closed. Early in the trial randomization into the 24 mg alemtuzmab treatment arm was discontinued, and the 2:1 randomization was maintained between alemtuzumab 12 mg and interferon beta-1a.

Benefit was assessed by the co-primary endpoints of relapse rate and time to 6 month sustained accumulation of disability. Relapse was defined as new or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination assessed by a masked rater. All potential relapses were confirmed via adjudication by a committee comprising 6 independent and masked neurologists. Sustained accumulation of disability was defined as an increase from baseline of at least 1.0 EDSS point (or at least 1.5 points if the baseline score was 0) confirmed over 6 months. Secondary endpoints were measured over 24 months and included the proportion of relapse-free patients, change in EDSS, percentage change in T_2-hyperintense lesion volume, and change in multiple sclerosis functional composite (MSFC). Analysis of secondary efficacy endpoints used a hierarchical closed testing procedure in which secondary endpoints were sequentially analyzed in the following order: Relapse-free, EDSS change from baseline, % Change MRI T2 lesions volume, MSFC. Each endpoint could only be formally tested if both primary endpoints and the prior secondary endpoints were significant. For descriptive purposes, even if earlier endpoints were not met, estimated treatment effects (including p-values) are presented for secondary efficacy endpoints. Safety was assessed with monthly patient questionnaires and monthly labs (complete blood counts, serum creatinine, urinalysis with microscopy – every 3 months in interferon beta-1a treated patients), and thyroid function tests every 3 months. Infusion associated reactions were defined as any adverse event beginning during or within 24 hours after alemtuzumab infusion.

Alemtuzumab reduced the rate of relapse compared with interferon beta-1a (risk reduction of 49.4%), and reduced the risk of sustained accumulation of disability compared with interferon beta-1a (risk reduction of 42%), see Figure 4. The co primary endpoint outcomes were maintained across the previous therapy subgroups and were unaffected by anti-interferon antibodies at baseline or developing during the course of the trial. More alemtuzumab-treated patients were relapse-free at 2 years when compared with the interferon beta-1a treated patients (65.4% versus 46.7%). Mean EDSS scores improved in the alemtuzumab treatment group and declined in the interferon beta-1 a treatment group. Decreases in T_2-hyperintense lesion volume by 24 months did not differ between treatment groups. The difference in MSFC change over 24 months was not regarded as significant in the hierarchical analysis plan. For more information on the primary, secondary and tertiary endpoints; please see Table 5.

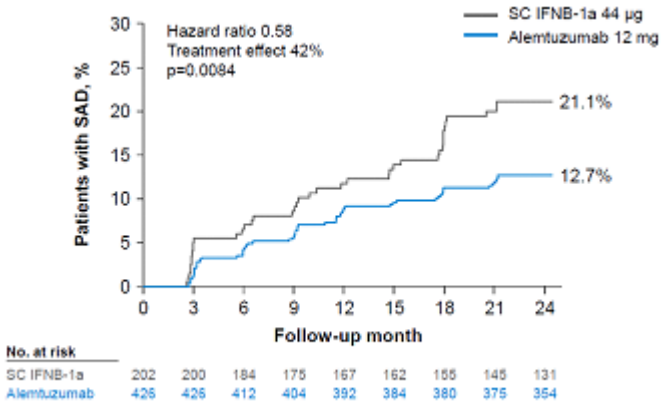


Figure 4 Sustained accumulation of Disability in CARE-MS II

Table 5 Clinical Outcomes in RRMS Patients with Relapse after Disease-Modifying Therapy by Treatment Group (CARE-MS II)[7]

	Interferon beta-1a (n=202)	Alemtuzumab 12 mg (n=426)	p value
Relapse			
Patients with any event	104 (53%*)	147 (35%*)	
Total number of events	201	236	
Rate ratio (95% CI)	– –	0.51 (0.39 to 0.65)	<0.0001
Yearly rate (95% CI)	0.52 (0.41 to 0.66)	0.26 (0.21 to 0.33)	
Relapse-free patients (95% CI)*	46.7% (39.5 to 53.5)	65.4% (60.7 to 69.7)	<0.0001
Disability			
Sustained accumulation confirmed over 6 months			
Patients	40 (20%)	54 (13%)	
Percentage of patients (95% CI)*	21.13% (15.95 to 27.68)	12.71% (9.89 to 16.27)	
Hazard ratio (95% CI)	– –	0.58 (0.38 to 0.87)	0.0084
Change in EDSS score from baseline			

	Interferon beta-1a (n=202)	Alemtuzumab 12 mg (n=426)	p value
Mean change (95% CI)	0.24 (0.07 to 0.41)	–0.17 (–0.29 to –0.05)	<0.0001
Sustained reduction for 6 months			
Patients	18 (9%)	92 (22%)	
Percentage of patients (95% CI)*	12.93% (8.34 to 19.77)	28..82% (24.18 to 34.13)	
Hazard ratio (95% CI)	– –	2.57 (1.57 to 4.20)	0.0002
Change in mean MSFC score from baseline			
Mean (95% CI)	– 0.04 (–0.10 to 0.02)	0.08 (0.04 to 0.12)	0.002†
MRI			
Median change in volume of T_2–hyperintense lesions	–1.23% (–11.13 to 11.39)	–1.27% (–12.70 to 7.78)	0.14
Patients with new or enlarging T_2hyperintense lesions‡	127/187 (68%)	186/403 (46%)	<0.0001
Patients with gadolinium-enhancing lesions at 24 months‡	44/190 (23%)	38/140 (9%)	<0.0001
Median change in brain parenchymal fraction‡	–0.810% (–1.539 to 0.203)	–0.615% (-1.299 to 0.006)	0.01
Disease-free survival			
Patients clincially disease-free‡	83 (41%)	254 (60%)	
Odds ratio (95% CI)	– –	2.14 (1.52 to 3.01)	<0.0001
Patients MRI and clincally disease-free‡	25/184 (14%)	127/396 (32%)	
Odds ratio (95% CI)	– –	3.03 (1.89 to 4.86)	<0.0001

	Interferon beta-1a (n=202)	Alemtuzumab 12 mg (n=426)	p value
Data are n (%), n, median (IQR), or n/n assessed, unless otherwise stated. EDSS=expanded disability status scale. MSFC=multiple sclerosis functional composite. *Kaplan-Meier estimation. ‡Tertiary outcome. †With the hierarchical model, MSFC changes are not significant and are included for descriptive purposes.			

Adverse events (1 or more event) were reported in 95% of interferon beta-1a treated patients and in 98% of alemtuzumab-treated 12 mg patients. Adverse events resulting in study discontinuation occurred in 15 (7%) interferon beta-1a treated patients and in 14 (3%) alemtuzumab-treated 12 mg patients. The most common adverse events with alemtuzumab were mild-to-moderate infusion-associated reactions (most commonly headache, rash, nausea and pyrexia) and relapse of multiple sclerosis.

Overall, 13% of 435 alemtuzumab-treated 12 mg patients and 13% of 202 interferon beta-1a treated patients reported serious adverse events other than MS relapse. Serious infusion-associated reactions were reported in 12 mg alemtuzumab-treated patients: 2 patients each (pyrexia and urticaria) and 1 patient each (chest discomfort, hypothyroidism, nausea, vomiting, chest pain, infusion related reaction, non-cardiac chest pain, status migrainosus, cough, dyspnea, and hemoptysis). Serious infectious adverse events were reported in 12 mg alemtuzumab-treated patients: 4 patients each (herpes zoster) and 3 patients each (gastroenteritis), 2 patients each (appendicitis) and 1 patient each (female infection, herpes zoster, influenza, labyrinthitis, esophageal candidiasis, pasteurella infection, pyelonephritis, tooth infection, upper respiratory tract infection, urinary tract infection). One patient in the 12 mg alemtuzumab treatment group died as a result of an automobile accident during the study, and one 12 mg alemtuzumab-treated patient died because of a brain stem relapse occurring 1 year previously. For additional safety information, please see Table 6.

Table 6 Adverse Events by Treatment Group (CARE-MS II)[7]

	Interferon beta-1a (n=202)	Alemtuzumab 12 mg (n=435)
Infusion-associated reactoins		
Any event	NA	393 (90%)
Events affecting >10% in any group		
Headache	NA	188 (43%)
Rash	NA	168 (39%)
Nausea	NA	72 (17%)

	Interferon beta-1a (n=202)	Alemtuzumab 12 mg (n=435)
Pyrexia	NA	69 (16%)
Urticaria	NA	64 (15%)
Pruritis	NA	50 (11%)
Insomnia	NA	44 (10%)
Fatigue	NA	39 (9%)
Chills	NA	32 (7%)
Chest discomfort	NA	27 (6%)
Dyspnea	NA	27 (6%)
Myalgia	NA	24 (6%)
Infections		
Any event	134 (66%)	334 (77%)
Events affecting >10% in any group		
Nasopharyngitis	48 (24%)	128 (29%)
Urinary tract infection	23 (11%)	93 (21%)
Upper respiratory tract infection	25 (12%)	71 (16%)
Herpes viral infections	8 (4%)	68 (16%)
Herpes simplex*	4 (2%)	42 (10%)
Herpes zoster†	3 (1%)	26 (6%)
Herpes dermatitis	0	1 (<1%)
Varicella	0	1 (<1%)
Herpes virus infection	1 (<1%)	0
Sinusitis	20 (10%)	58 (13%)
Influenza	11 (5%)	41 (9%)
Thyroid disorders		

	Interferon beta-1a (n=202)	Alemtuzumab 12 mg (n=435)
Any event[‡]	10 (5%)	69 (16%)
Hyperthyroidism	1 (<1%)	22 (5%)
Hypothyroidism	3 (1%)	19 (4%)
Thyroiditis	0	7 (2%)
Goiter	1 (<1%)	6 (1%)
Serious adverse event	0	2 (<1%)
Hypothyroidism	0	2 (<1%)
Hyperthyroidism	0	1 (<1%)
Blood and lymphatic system disorders		
Any event	28 (14%)	59 (14%)
Serious adverse events	0	3 (1%)
Autoimmune thrombocytopenia[γ]	0	3 (1%)
Malignant disease		
Basal cell carcinoma	1 (<1%)	1 (<1%)
Thyroid cancer	0	1 (<1%)
Acute myeloid leukemia	1 (<1%)	0
Liver toxicity		
Any event	13 (6%)	19 (4%)
Serious adverse event	5 (2%)	4 (1%)
Administration-site reactions		
Any event	56 (28%)	40 (9%)
Other events affecting >10% of patients in any group**		
General conditions		

	Interferon beta-1a (n=202)	**Alemtuzumab 12 mg (n=435)**
Pyrexia	18 (9%)	95 (22%)
Fatigue	26 (13%)	81 (19%)
Chills	9 (4%)	35 (8%)
Pain	8 (4%)	35 (8%)
Chest discomfort	1 (<1%)	33 (8%)
Influenza-like illness	47 (23%)	31 (7%)
Injection site erythema	28 (14%)	0
Nervous system disorders		
Headache	36 (18%)	230 (53%)
Multiple sclerosis relapse[††]	99 (49%)	143 (33%)
Paresthesia	20 (10%)	50 (11%)
Dizziness	11 (5%)	48 (11%)
Hypoasthesia	16 (8%)	35 (8%)
Skin and subcutaneous tissue disorders		
Rash	11 (5%)	193 (44%)
Urticaria	2 (1%)	75 (17%)
Pruritus	5 (2%)	66 (15%)
Generalized rash	2 (1%)	33 (8%)

	Interferon beta-1a (n=202)	Alemtuzumab 12 mg (n=435)
Data are incidence in patients, n(%), unless otherwise stated. NA=not applicable. *Includes the preffered terms herpes simplex, oral herpes, genital herpes, and herpes simplex opthalmic. †Includes the preferred terms herpes zoster and herpes zoster multidermatomal. ‡Includes investigations; hyperthyroidism included preferred terms hyperthyroidism and Basedow's disease; hypothyroidism included preferred terms hypothyroidism and primary hypothyroidism; thyroiditis included preferred terms thyroiditis, autoimmune thyroiditis, and subacute thyroiditis. γAutoimmune thrombocytopenia includes terms autoimmune thrombocytopenia and idiopathic thrombocytopenia purpura. **Events that were not infusion-associated reactions.††Includes only events with preferred term multiple sclerosis relapse, and might not correspond to relapse tally for efficacy endpoints.		

IMPORTANT SAFETY INFORMATION

WARNING: AUTOIMMUNITY, INFUSION REACTIONS, AND MALIGNANCIES

LEMTRADA causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals for 48 months after the last dose of LEMTRADA.

LEMTRADA causes serious and life threatening infusion reactions. LEMTRADA must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for two hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period.

LEMTRADA may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams.

LEMTRADA is available only through a restricted distribution program.

CONTRAINDICATIONS

LEMTRADA is contraindicated in patients who are infected with Human Immunodeficiency Virus (HIV) because LEMTRADA causes prolonged reductions of CD4+ lymphocyte counts.

LEMTRADA causes cytokine release syndrome resulting in infusion reactions. Serious reactions occurred in 3% of these patients and included anaphylaxis in 2 patients (including anaphylactic shock), angioedema, bronchospasm, hypotension, chest pain, bradycardia, tachycardia (including atrial fibrillation), transient neurologic symptoms, hypertension, headache, pyrexia, and rash. In some patients, infusion reactions were reported more than 24 hours after LEMTRADA infusion.

Immune thrombocytopenia (ITP) occurred in 2% of LEMTRADA-treated patients in clinical studies in MS. One LEMTRADA-treated patient developed ITP that went unrecognized prior to the implementation of monthly monitoring requirements, and died from an intracerebral hemorrhage.

Glomerular nephropathies occurred in 0.3% of LEMTRADA-treated patients in MS clinical trials. There are published and post-marketing cases of MS patients treated with alemtuzumab who developed anti-GBM disease and subsequently developed end stage renal disease requiring renal transplantation.

Autoimmune thyroid disorders occurred in 34% of LEMTRADA-treated patients in clinical studies. Serious thyroid events occurred in 2% of these patients. In patients with an ongoing thyroid disorder, LEMTRADA should be administered only if the potential benefit justifies the potential risks. Obtain thyroid function tests prior to initiation of treatment and every 3 months until 48 months after the last infusion. Thyroid disease poses special risks in women who are pregnant. LEMTRADA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Autoimmune cytopenias occurred in LEMTRADA-treated MS patients in clinical trials. One LEMTRADA-treated patient with autoimmune pancytopenia died from sepsis. Serious infections occurred in 3% of patients treated with LEMTRADA and 1% of patients treated with interferon beta-1a and included: appendicitis, gastroenteritis, pneumonia, herpes zoster, and tooth infection. Consider delaying LEMTRADA administration in patients with active infection until the infection is fully controlled.

Pneumonitis occurred in 6 of 1217 (0.5%) LEMTRADA-treated patients in clinical studies.

LEMTRADA contains the same active ingredient (alemtuzumab) found in CAMPATH®. If LEMTRADA is considered for use in a patient who has previously received CAMPATH, exercise increased vigilance for additive and long-lasting effects on the immune system.

In clinical trials, the most common adverse reactions (incidence ≥10% and > interferon beta-1a) were: rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting.

LEMTRADA is available only through a restricted program called the LEMTRADA REMS Program because of the risks of autoimmunity, infusion reactions, and malignancies.

Only prescribers, patients, pharmacies and healthcare facilities certified and enrolled in the REMS program can prescribe, receive, dispense or administer LEMTRADA. Healthcare facilities must have on-site access to equipment and personnel trained to manage infusion reactions (including anaphylaxis and cardiac and respiratory emergencies).

Thank you for your interest in Genzyme products. If we may be of any further assistance, please contact us by telephone at 1-800-745–4447, option #2 or email us at medinfo@genzyme.com.

Mark Eggleston, PharmD, MBA

Director, Medical Information Services

Enclosure List:

- Lemtrada Med Guide [package insert]. Cambridge, MA: Genzyme; November 2014.
- Lemtrada [package insert]. Cambridge, MA: Genzyme; November 2014.

Reference List:

1. Lemtrada [package insert]. Cambridge, MA: Genzyme; November 2014.

2. Coles AJ, Cox A, Le Page E, et al. The window of therapeutic opportunity in multiple sclerosis evidence from monoclonal antibody therapy. *J Neurol.* 2006; 253 (1):98-108.

3. Hirst CL, Pace A, Pickersgill TP, et al. Campath 1-H treatment in patients with aggressive relapsing remitting multiple sclerosis. *J Neurol.* 2008; 255 (2):231-238.

4. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 Clinical Trial . *Neurology.* 2012; 78 (17):1069-1078.

5. Coles AJ, Compston DA, Selmaj KW, et al. Alemtuzumab vs. inferferon-beta 1-a in early Multiple Sclerosis. *N Engl J Med.* 2008; 359 (17):1786-1801.

6. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet.* 2012; 380 (9856):1819-1828.

7. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet.* 2012; 380 (9856):1829-1839.