# Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial

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## Summary

**Background** The anti-CD52 monoclonal antibody alemtuzumab reduces disease activity in previously untreated patients with relapsing-remitting multiple sclerosis. We aimed to assess efficacy and safety of alemtuzumab compared with interferon beta 1a in patients who have relapsed despite first-line treatment.

**Methods** In our 2 year, rater-masked, randomised controlled phase 3 trial, we enrolled adults aged 18–55 years with relapsing-remitting multiple sclerosis and at least one relapse on interferon beta or glatiramer. Eligible participants were randomly allocated in a 1:2:2 ratio by an interactive voice response system, stratified by site, to receive subcutaneous interferon beta 1a 44 μg, intravenous alemtuzumab 12 mg per day, or intravenous alemtuzumab 24 mg per day. Interferon beta 1a was given three-times per week and alemtuzumab was given once per day for 5 days at baseline and for 3 days at 12 months. The 24 mg per day group was discontinued to aid recruitment, but data are included for safety assessments. Coprimary endpoints were relapse rate and time to 6 month sustained accumulation of disability, comparing alemtuzumab 12 mg and interferon beta 1a in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00548405.

**Findings** 202 (87%) of 231 patients randomly allocated interferon beta 1a and 426 (98%) of 436 patients randomly allocated alemtuzumab 12 mg were included in the primary analyses. 104 (51%) patients in the interferon beta 1a group relapsed (201 events) compared with 147 (35%) patients in the alemtuzumab group (236 events; rate ratio 0·51 [95% CI 0·39–0·65]; p<0·0001), corresponding to a 49·4% improvement with alemtuzumab. 94 (47%) patients in the interferon beta 1a group were relapse-free at 2 years compared with 278 (65%) patients in the alemtuzumab group (p<0·0001). 40 (20%) patients in the interferon beta 1a group had sustained accumulation of disability compared with 54 (13%) in the alemtuzumab group (hazard ratio 0·58 [95% CI 0·38–0·87]; p=0·008), corresponding to a 42% improvement in the alemtuzumab group. For 435 patients allocated alemtuzumab 12 mg, 393 (90%) had infusion-associated reactions, 334 (77%) had infections (compared with 134 [66%] of 202 patients in the interferon beta 1a group) that were mostly mild-moderate with none fatal, 69 (16%) had thyroid disorders, and three (1%) had immune thrombocytopenia.

**Interpretation** For patients with first-line treatment-refractory relapsing-remitting multiple sclerosis, alemtuzumab could be used to reduce relapse rates and sustained accumulation of disability. Suitable risk management strategies allow for early identification of alemtuzumab's main adverse effect of secondary autoimmunity.

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## Introduction

What constitutes best management for patients with multiple sclerosis who have clinical or radiological disease activity despite receipt of a first-line disease-modifying therapy is unknown. Although ongoing disease activity does not necessarily mean absence of therapeutic effect, such patients are at increased risk of accumulation of fixed disability, even in the short-term.[1–3] Nonetheless, these patients are frequently advised to continue the same treatment, or switch to another first-line therapy, sometimes because decisions to escalate to second-line drugs require a higher threshold of activity than one relapse on treatment. In this context, few published studies exist that rigorously assess the clinical benefit and risk of escalation to a treatment that is potentially more effective.

Alemtuzumab, a humanised monoclonal antibody targeting CD52, causes depletion and repopulation of B lymphocytes and T lymphocytes, leading to long-lasting changes in adaptive immunity.[4–6] Open-label studies showed efficacy in patients with relapsing-remitting multiple sclerosis, for individuals who had not previously been treated and for patients with active disease after therapy, with secondary autoimmunity the main safety concern.[7–11] These findings in previously untreated relapsing-remitting multiple sclerosis were then substantiated in the randomised rater-masked phase 2[12] and subsequent phase 3 Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS I) trials.[13] In our second phase 3 trial (CARE-MS II), we compared alemtuzumab with

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interferon beta 1a in patients who had recently relapsed while taking a standard disease-modifying therapy.

## Methods

### Study design and patients

In this randomised, rater-masked, phase 3 trial, we enrolled patients from 194 academic medical centres and clinical practices in 23 countries between Oct 20, 2007, and Sept 18, 2009. Eligible patients were aged 18–55 years, with the following clinical characteristics: relapsing-remitting multiple sclerosis fulfilling the 2005 McDonald diagnostic criteria;[14] disease duration of 10 years or less; at least two attacks in the previous 2 years with at least one in the previous year; at least one relapse while on interferon beta or glatiramer after at least 6 months of treatment; expanded disability status scale (EDSS)[15] scores of 5·0 or less; and cranial and spinal MRI lesions fulfilling protocol-defined criteria. Exclusion criteria included progressive forms of multiple sclerosis, previous cytotoxic drug use or investigational therapy, treatment within the previous 6 months with natalizumab, methotrexate, azathioprine or ciclosporin, and a history of clinically significant autoimmunity other than multiple sclerosis. An independent committee reviewed issues relating to safety. The study was done in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Patients provided written informed consent.

### Randomisation and masking

We randomly allocated patients with an interactive voice response system in a 2:2:1 scheme to receive alemtuzumab

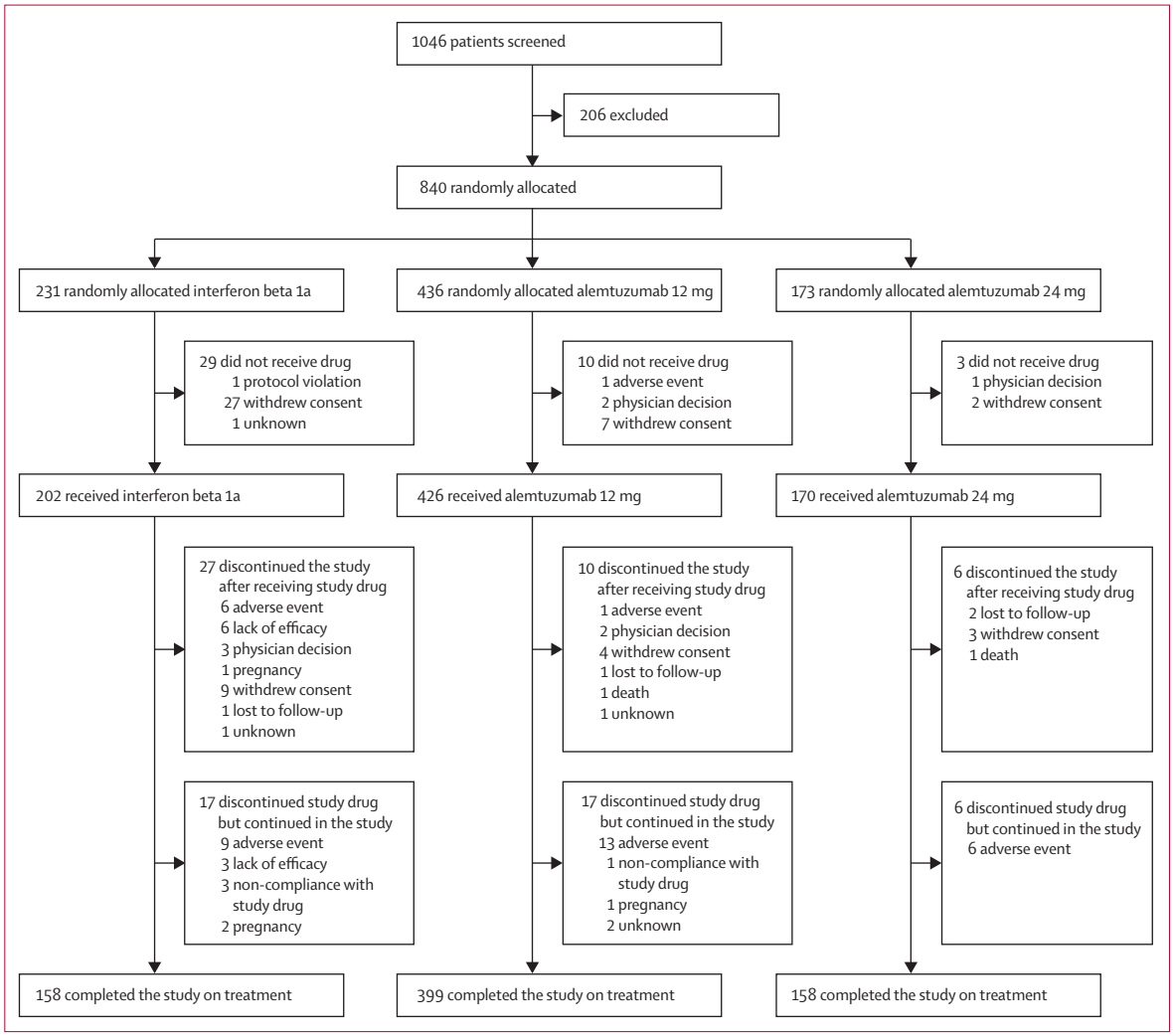



***Figure 1:*** **Trial profile**
Nine patients originally randomly allocated to alemtuzumab 24 mg per day received the 12 mg per day dose. These patients are listed under 24 mg as per their randomisation but are included in the 12 mg group for the safety analyses. Two of these patients dropped out of the study after receiving study drug (one death and one withdrawal by patient).

12 mg per day, alemtuzumab 24 mg per day, or interferon beta 1a. Randomisation was stratified by site. Alemtuzumab was infused intravenously on 5 consecutive days at month 0 and 3 consecutive days at month 12.[9,12] Interferon beta 1a (44 µg) was administered subcutaneously 3 times per week after dose titration. A protocol amendment in December, 2008, discontinued randomisation in the alemtuzumab 24 mg group to accelerate recruitment to the other two study groups. The decision to close recruitment into the alemtuzumab 24 mg arm was made by the Neurology Steering Committee and Genzyme management without review of safety or efficacy data from this study. The 2:1 randomisation allocation was maintained between alemtuzumab 12 mg and interferon beta 1a. Under this amendment, patients in the alemtuzumab group also received aciclovir 200 mg twice daily during alemtuzumab infusion and for 28 days after alemtuzumab infusion as prophylaxis against herpes simplex virus infections, which were noted midway through the CARE-MS trials to be of increased frequency after alemtuzumab. This decision was made by the Data Monitoring committee, who was not involved in the decision to close recruitment in the alemtuzumab 24 mg arm.

Because both study drugs had adverse effects that precluded double-blinding, and interferon beta 1a proprietary syringes could not effectively be duplicated for placebo, clinical data integrity was secured by stringent rater-masking and independent adjudication of relapses. Raters, who were masked to treatment-group assignment, did the EDSS assessments every 3 months and when a relapse was suspected, and the multiple sclerosis functional composite (MSFC)[16] once every 6 months. Raters completed a questionnaire assessing quality of the masking at each EDSS assessment. In the absence of a masked rater, unmasked raters could submit EDSS assessments.

## Procedures

To reduce incidence of adverse events related to infusion, all patients in the alemtuzumab groups received intravenous methylprednisolone of 1 g per day on 3 consecutive days at month 0 and month 12 (antihistamines and antipyretics were also allowed). To control for steroid prophylaxis, patients in the interferon beta 1a group received the same methylprednisolone regime.

We assessed benefit in terms of the coprimary endpoints of relapse rate and time to 6 month sustained accumulation of disability. We defined relapse as new or worsening neurological symptoms attributable to multiple sclerosis, lasting at least 48 h, without pyrexia, after at least 30 days of clinical stability with an objective change on neurological examination. Whether or not a suspected relapse met the protocol definition was decided by the six independent neurologists who made up the relapse adjudication panel, based on their masked review of all the data collected by the site, including whether there was an objective change corresponding to present relapse symptoms (one point on two functional system scales or two points on one functional system scale or increase in EDSS score). Sustained accumulation of disability was defined as an increase from baseline of at least one EDSS point (or ≥1·5 points if the baseline EDSS

| | Interferon beta 1a (n=202) | Alemtuzumab 12 mg (n=426) | Alemtuzumab 24 mg (n=170) |
|---|---|---|---|
| Age, years | 35·8 (8·77) | 34·8 (8·36) | 35·1 (8·40) |
| Sex, female | 131 (65%) | 281 (66%) | 120 (71%) |
| Race, white | 187 (93%) | 385 (90%) | 142 (84%) |
| EDSS score | | | |
| Mean | 2·7 (1·21) | 2·7 (1·26) | 2·7 (1·17) |
| Median | 2·5 (0·0–6·0) | 2·5 (0·0–6·5) | 2·5 (0·0–6·0) |
| EDSS score subgroup | | | |
| 0 | 5 (2%) | 16 (4%) | 4 (2%) |
| 1–1·5 | 44 (22%) | 89 (21%) | 31 (18%) |
| 2·0 | 34 (17%) | 63 (15%) | 29 (17%) |
| 2·5–3·0 | 48 (24%) | 112 (26%) | 52 (31%) |
| 3·5–4·0 | 50 (25%) | 98 (23%) | 38 (22%) |
| 4·5–5·0 | 19 (9%) | 42 (10%) | 14 (8%) |
| 5·5–6·5* | 2 (1%) | 6 (1%) | 2 (1%) |
| Time since first clinical event, years | | | |
| Mean | 4·7 (2·86) | 4·5 (2·68) | 4·3 (2·77) |
| Median | 4·1 (0·4–10·1) | 3·8 (0·2–14·4) | 3·7 (0·2–16·9) |
| Relapses in previous year | | | |
| 0* | 5 (2%) | 6 (1%) | 3 (2%) |
| 1 | 107 (53%) | 211 (50%) | 84 (49%) |
| 2 | 68 (34%) | 151 (35%) | 64 (38%) |
| ≥3 | 22 (11%) | 58 (14%) | 19 (11%) |
| Mean | 1·5 (0·75) | 1·7 (0·86) | 1·6 (0·86) |
| Median | 1·0 (0·0–4·0) | 1·0 (0·0–5·0) | 1·0 (0·0–6·0) |
| Number of gadolinium-enhancing lesions (T1-weighted images) | | | |
| Mean | 2·10 (4·95) | 2·28 (6·02) | 2·88 (8·47) |
| Median | 0·0 (0·0–41·0) | 0·0 (0·0–72·0) | 0·0 (0·0–90·0) |
| Patients with baseline lesions | 87/199 (44%) | 178/420 (42%) | 74/165 (45%) |
| T2-hyperintense lesion volume, $cm^3$ | | | |
| Mean | 9·04 (10·42) | 9·94 (12·25) | 9·47 (9·66) |
| Median | 5·6 (0·0–70·3) | 6·0 (0·0–77·6) | 6·2 (0·1–52·2) |
| Brain parenchymal fraction | | | |
| Mean | 0·817 (0·022) | 0·813 (0·023) | 0·816 (0·024) |
| Median | 0·817 (0·738–0·862) | 0·816 (0·730–0·863) | 0·816 (0·729–0·866) |
| Duration of previous multiple sclerosis drug use, months | | | |
| Mean | 36 (23·7) | 35 (25·0) | 37 (23·9) |
| Median | 29 (6–115) | 28 (4–131) | 33 (6–121) |
| Number of previous multiple sclerosis drugs | | | |
| 1 | 151 (75%) | 299 (70%) | 120 (71%) |
| 2 | 41 (20%) | 92 (22%) | 39 (23%) |
| 3 | 9 (4%) | 24 (6%) | 11 (6%) |
| ≥4 | 1 (<1%) | 11 (3%) | 0 |
| Mean | 1 (0·6) | 1 (0·7) | 1 (0·6) |
| Median | 1 (1–4) | 1 (1–4) | 1 (1–3) |

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| | Interferon beta 1a (n=202) | Alemtuzumab 12 mg (n=426) | Alemtuzumab 24 mg (n=170) |
|---|---|---|---|
| (Continued from previous page) | | | |
| Generic name of previous multiple sclerosis drug | | | |
| Interferon beta-1a | 108 (53%) | 232 (54%) | 102 (60%) |
| Intramuscular interferon beta-1a | 46 (23%) | 120 (28%) | 52 (31%) |
| Subcutaneous interferon beta-1a (22 µg or 44 µg) | 73 (36%) | 146 (34%) | 58 (34%) |
| Interferon beta-1b | 63 (31%) | 154 (36%) | 55 (32%) |
| Glatiramer | 69 (34%) | 146 (34%) | 59 (35%) |
| Natalizumab | 7 (3%) | 15 (4%) | 5 (3%) |
| Immunoglobulin | 1 (<1%) | 11 (3%) | 2 (1%) |
| Azathioprine | 5 (2%) | 6 (1%) | 0 |

Data are mean (SD), n (%), median (range), or n/n assessed (%). Baseline characteristics did not differ significantly between groups. EDSS=expanded disability status scale. Patients were enrolled in the study based on data collected at the screening visit, which occurred before the baseline visit. *Patients with EDSS scores higher than the inclusion level criteria or without relapses in the previous year at the baseline visit had met the criteria at the screening visit.

*Table 1:* **Baseline characteristics**

score was 0) confirmed over 6 months. We defined sustained reduction in disability as a decrease from baseline by at least one EDSS point confirmed over 6 months for patients with baseline EDSS scores of at least 2·0. We tested MSFC three times before baseline to reduce practice effects.[17] Standardised annual cranial MRI scans were analysed by imaging specialists from NeuroRx (Montreal, Canada; lesion analyses) and the Cleveland Clinic MS MRI Analysis Center (OH, USA; normalised brain volume), who were masked to treatment-group assignment. Freedom from clinical disease activity was defined as the absence both of relapses and sustained accumulation of disability. Freedom from disease activity also required the absence both of gadolinium-enhancing lesions on T1-weighted MRI and new or enlarging T2-hyperintense lesions.

To assess safety, we undertook monthly questionnaire follow-up of patients, and did complete blood counts, serum creatinine, and urinalysis with microscopy monthly (every 3 months in patients in the interferon beta 1a group), and thyroid function tests every 3 months. Patients and investigators were given instructional materials about the safety monitoring programme; describing and illustrating the signs and symptoms of potential complications of alemtuzumab therapy (particularly idiopathic thrombocytopenic purpura, anti-glomerular basement membrane disease, and thyroid dysfunction); and guiding appropriate follow-up for suspected cases. The standardised questionnaire asked about symptoms that might signal onset of idiopathic thrombocytopenic purpura or a renal disorder, and which should prompt a medical evaluation. We defined reactions associated with the infusion as any adverse event with onset during or within 24 h after alemtuzumab infusion. We assessed circulating lymphocyte subsets every 3 months in all patients and 1 month after every course of alemtuzumab. We screened for anti-alemtuzumab antibodies with ELISA (Meso Scale Discovery, Gaithersburg, MD, USA) before and at 1 month, 3 months and 12 months after each dosing, and confirmed positive tests with a cell-binding assay. Positive tests were confirmed by competitive binding assay and inhibition of alemtuzumab binding to CD52-expressing CHO cells in a flow cytometric assay. We measured interferon beta 1a-neutralising antibodies at baseline and at 24 months with a cytopathic effect inhibition assay (BioMonitor, Copenhagen, Denmark).

### Statistical analysis

On the basis of previous trials and the phase 2 study,[12] we expected at least 20% of patients in the interferon beta 1a group to meet the disability endpoint by 2 years. Therefore, 573 patients, randomly allocated 2:1 to alemtuzumab 12 mg or interferon beta 1a provided 80% or more power to detect a 50% treatment effect in time to sustained disability with a two-sided significance of 5%, assuming 10% discontinuation. This sample size provided 95% or more power to detect a 40% treatment effect on relapse rate, assuming 68% of patients in the interferon beta 1a group relapsed over 2 years. After the protocol amendment, the principal efficacy comparison was between alemtuzumab 12 mg and interferon beta 1a. Safety data are presented for both doses of alemtuzumab. The primary efficacy analysis was adjusted for multiple comparisons with the Hochberg procedure.[18] We assessed treatment effects on relapse rate by the proportional means model,[19] which is an extension of the proportional hazards model to account for recurrent events, and assessed sustained disability with a proportional hazards model with robust variance estimation,[20] including treatment group and geographical region as covariates. We estimated yearly relapse rate with a negative binomial regression model.

We controlled secondary endpoints for multiple comparisons by testing in the following order: proportion of relapse-free patients, changes in EDSS, T2 lesion volume, and MSFC. Formal sequential testing stopped when any p value exceeded 0·05; however, p values and 95% CIs are reported for all endpoints for descriptive purposes. We analysed the proportion of patients who were relapse-free with a proportional hazards model. We analysed changes from baseline in EDSS and MSFC with a mixed model for repeated measures, and treatment comparisons with all available assessments were assessed with a non-parametric test for repeated measures.[21,22] We analysed change in T2-hyperintense lesion volume with a ranked ANCOVA model. We analysed proportions of patients with new or enlarging T2-hyperintense lesions or gadolinium-enhancing lesions, and those who were free from disease activity, with logistic regression. The appendix contains additional details about the statistical methods.

This study is registered with ClinicalTrials.gov, number NCT00548405.

**Role of the funding source**
Genzyme (Sanofi) was involved in the design and undertaking of the trial, data analysis and interpretation, writing of the manuscript, and the decision to submit the manuscript for publication. Bayer Schering Pharma participated in the design of the study, study oversight, review, and approval of the manuscript. Clinical investigators, collaborating with the sponsor, designed and oversaw the study. All authors had full access to data, participated in the analyses, wrote the manuscript, had final responsibility for the decision to submit for publication, and vouch for the accuracy and completeness of the results.

## Results

We included 667 patients in the randomisation when recruitment closed (840 patients including the 24 mg per day alemtuzumab group; figure 1). Overall, we randomly allocated 436 patients to alemtuzumab 12 mg, 173 to alemtuzumab 24 mg, and 231 to interferon beta 1a (figure 1; table 1). 661 (83%) of 798 patients had previously received interferon beta and 274 (34%) had previously received glatiramer; 140 (18%) of patients had received both; and 27 (3%) patients had also been treated with natalizumab. Nine patients originally assigned alemtuzumab 24 mg actually received the 12 mg per day dose; we included these patients in the 24 mg per day group for efficacy but in the 12 mg per day for safety analyses. 755 (90%) of 840 patients randomly allocated treatment remained in the study until month 24 (figure 1). More patients randomly allocated interferon beta 1a than alemtuzumab discontinued the trial before treatment (29 [13%] of 231 patients for interferon beta 1a *vs* 13 [2%] of 609 patients for alemtuzumab) and after starting treatment (27 [12%] of 202 *vs* 16 [3%] of 596). Masking was successful for 5850 (>99%) of 5865 EDSS assessments. Only 12 (2%) of 672 patients had one or more assessments done by an unmasked rater; although included in efficacy analyses, sensitivity studies showed these unmasked data had no effect on outcomes (appendix). For 435 patients treated with alemtuzumab 12 mg at month 0, 188 (43%) received aciclovir prophylaxis and 247 (57%) did not; and for 419 patients treated with alemtuzumab 12 mg at month 12, 278 (66%) received prophylaxis and 141 (34%) did not.

Alemtuzumab 12 mg reduced the rate of relapse compared with interferon beta 1a (table 2, figure 2). Sensitivity analyses of factors that potentially might affect the relapse analysis, including differential dropout before and after treatment initiation, had little influence (appendix). More patients in the alemtuzumab 12 mg group than in the interferon beta 1a group were relapse-free at 2 years (table 2, figure 2). Alemtuzumab 12 mg reduced relapse rate to a greater extent than did interferon beta 1a in all subgroups defined by previous therapy, with or without interferon beta, and those treated specifically at any one time with subcutaneous interferon beta 1a or glatiramer (appendix). Alemtuzumab's superior efficacy compared with interferon beta 1a was unaffected by the presence of anti-interferon antibodies at baseline or month 24 (appendix). Of 654 events that were reviewed by the relapse adjudication committee, 207 (83%) of 250 in the interferon beta 1a group were regarded as relapses, compared with 242 (82%) of 296 in the alemtuzumab 12 mg group, and 88 (81%) of 108 in the alemtuzumab 24 mg group.

Alemtuzumab 12 mg reduced the risk of sustained accumulation of disability compared with interferon beta 1a (table 2, figure 2); sensitivity analyses showed

| | 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 |
| Risk reduction | .. | 49·4% | |
| 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% (39·5–53·5) | 65·4% (60·7–69·7) | <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) | |
| Risk reduction | .. | 42% | 0·0084 |
| Change in EDSS score from baseline | | | |
| 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 T2-hyperintense lesions | –1·23% (–11·13 to 11·39) | –1·27% (–12·70 to 7·78) | 0·14 |
| Patients with new or enlarging T2-hyperintense lesions† | 127/187 (68%) | 186/403 (46%) | <0·0001 |
| Patients with gadolinium-enhancing lesions at 24 months† | 44/190 (23%) | 38/410 (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 clinically disease-free† | 83 (41%) | 254 (60%) | |
| Odds ratio (95% CI) | .. | 2·14 (1·52 to 3·01) | <0·0001 |
| Patients MRI and clinically disease-free† | 25/184 (14%) | 127/396 (32%) | |
| Odds ratio (95% CI) | .. | 3·03 (1·89 to 4·86) | <0·0001 |

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 here for descriptive purposes.

*Table 2:* **Relapse, disability, and MRI outcomes**

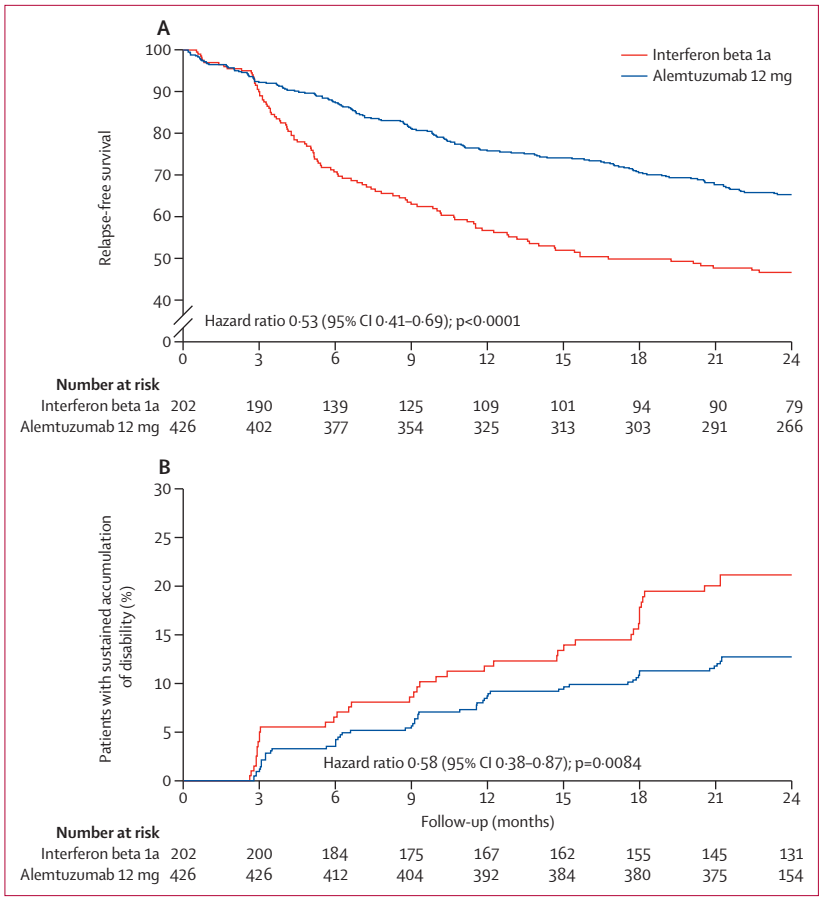



***Figure 2:*** **Clinical efficacy outcome measures**
Kaplan-Meier estimates of time to first relapse (A) and 6 month sustained accumulation of disability (B).

this result to be robust despite variable dropout and some unmasked EDSS assessments (appendix). Alemtuzumab's superior effect on disability was seen in all subgroups defined by previous therapy (appendix) or anti-interferon antibodies (either present at baseline or emerging subsequently; appendix). Mean disability improved from baseline by –0·17 EDSS points after alemtuzumab 12 mg (p=0·004) compared with a 0·24 EDSS point deterioration for interferon beta 1a (p=0·0064), a net benefit for alemtuzumab of 0·41 EDSS point (p<0·0001; table 2, figure 3). More patients in the alemtuzumab 12 mg group had a sustained reduction in disability compared with patients in the interferon beta 1a group (table 2). MSFC scores improved from baseline by 0·08 after alemtuzumab 12 mg and worsened on interferon beta 1a by –0·04, which was not regarded as significant in the hierarchical analysis plan (table 2).

Median T2-hyperintense lesion volume decreased after treatment with interferon beta 1a and alemtuzumab 12 mg, but the relative decrease did not differ between groups (table 2, figure 3). Tertiary analyses suggested that, compared with interferon beta 1a, alemtuzumab 12 mg reduced the proportion of patients who developed new gadolinium-enhancing lesions and new or enlarging T2 lesions (table 2, figure 3). Brain volume loss was reduced after alemtuzumab 12 mg compared with interferon beta 1a (table 2, figure 3).

More patients remained free from clinical disease activity and combined clinical and radiological disease activity in the alemtuzumab 12 mg group than did in the interferon beta 1a group (table 2).

We noted no consistent dose-related differences for alemtuzumab 12 mg compared with 24 mg per day on clinical outcomes, although new MRI lesion formation and brain volume loss were improved for the 24 mg per day group compared with the 12 mg per day group (appendix).

Consistent with previous experience,[23] most patients who were treated with alemtuzumab had mild-to-moderate infusion-associated reactions (most commonly headache, rash, nausea, and pyrexia; table 3). 12 (3%) patients in the alemtuzumab 12 mg group had serious infusion-associated events. None had anaphylaxis. Infusion-related symptoms were more common after 24 mg per day doses of alemtuzumab than after 12 mg per day doses (table 3).

Incidence of serious adverse events did not differ between treatment groups (table 3). Two patients died in the alemtuzumab 12 mg group: one had an automobile accident and one died because of aspiration pneumonia after a brainstem relapse occurring 1 year previously (on-study) left the patient severely disabled. One patient (<1%) in the alemtuzumab 12 mg group, no patients in the alemtuzumab 24 mg group, and six patients (3%) in the interferon beta 1a group discontinued the study because of adverse events. Overall, seven patients developed cancer (table 3).

Infections were more common after receipt of alemtuzumab 12 mg (77% of patients) than they were after receipt of interferon beta 1a (66%), but were predominantly mild or moderate in severity (table 3). Table 3 shows rates of serious adverse infections. Mucocutaneous herpetic and fungal infections were more frequent after alemtuzumab than interferon beta 1a. Segmental herpes zoster infections led to hospital admission for two patients treated with alemtuzumab 24 mg and one patient treated with alemtuzumab 12 mg; we noted no cases of herpetic encephalitis. Prophylactic acivlovir reduced the proportion of patients who had herpes infection in the months after alemtuzumab 12 mg (0·5% versus 2·8% after the first course and 0·4% versus 2·1% after the second course). One patient, from a region endemic for tuberculosis, developed pulmonary tuberculosis after alemtuzumab 24 mg; she discontinued treatment but remained in the study for follow-up. Another patient had a positive tuberculin skin test during the first infusion of alemtuzumab 24 mg but remained on study. Both patients responded to oral antituberculosis therapy.

Thyroid disorders were more common after alemtuzumab (table 3) especially in the second year of treatment, without any cases of ophthalmopathy. All patients with thyroid disorders were managed conventionally; one patient underwent thyroidectomy for goitre and another had radioiodine treatment. Seven patients had immune thrombocytopenia 3–24 months after receipt of alemtuzumab, including five serious cases (table 3). Four cases of disease were initially detected through monthly platelet monitoring and three cases were detected because patients reported symptoms. One patient did not need treatment, six patients received corticosteroids, and two patients had intravenous immunoglobulin. One of these patients also had autoimmune haemolytic anaemia, which resolved spontaneously after 2 months; after 3 months, this patient developed immune thrombocytopenia and underwent a splenectomy. At last assessment, six of seven patients with immune thrombocytopenia were not on treatment and had normal platelet counts; the other patient remained on corticosteroids. We noted no cases of anti-glomerular basement membrane disease. One patient in the alemtuzumab 12 mg group developed membranous nephropathy, with proteinuria detected by routine urinalysis, which improved with furosemide and lisinopril. Autoimmune disorders occurred slightly more frequently after alemtuzumab 24 mg than with alemtuzumab 12 mg (table 3).

Alemtuzumab reduced circulating lymphocyte counts after each treatment course but had little effect on other leucocytes (appendix). B cells repopulated within 6 months whereas T cells reconstituted slowly, approaching the lower limit of normal at 1 year after treatment, as noted previously.[9,24] Lymphocyte reconstitution was much the same with each alemtuzumab administration.

We noted alemtuzumab-binding antibodies in 29% of patients before the second treatment compared with 81% 1 month after this treatment. Presence and concentration of anti-alemtuzumab antibodies did not influence lymphocyte depletion or repopulation, efficacy, or safety. Neutralising anti-interferon beta antibodies were present in 34 (18%) of 193 patients receiving interferon beta-1 at baseline and 23 (13%) of 178 of these patients at 24 months.

## Discussion

Individuals with relapsing-remitting multiple sclerosis that remains active after first-line disease-modifying therapy have a poor prognosis for future disability.[2,3,25] Switching to a more potent therapy is logical in the face of aggressive disease; but considerable uncertainty and variation in practice exists in terms of how best to manage patients who relapse on first-line therapy. In our phase 3 trial, which exclusively enrolled patients who remained clinically active despite interferon beta or glatiramer treatment, escalation to alemtuzumab

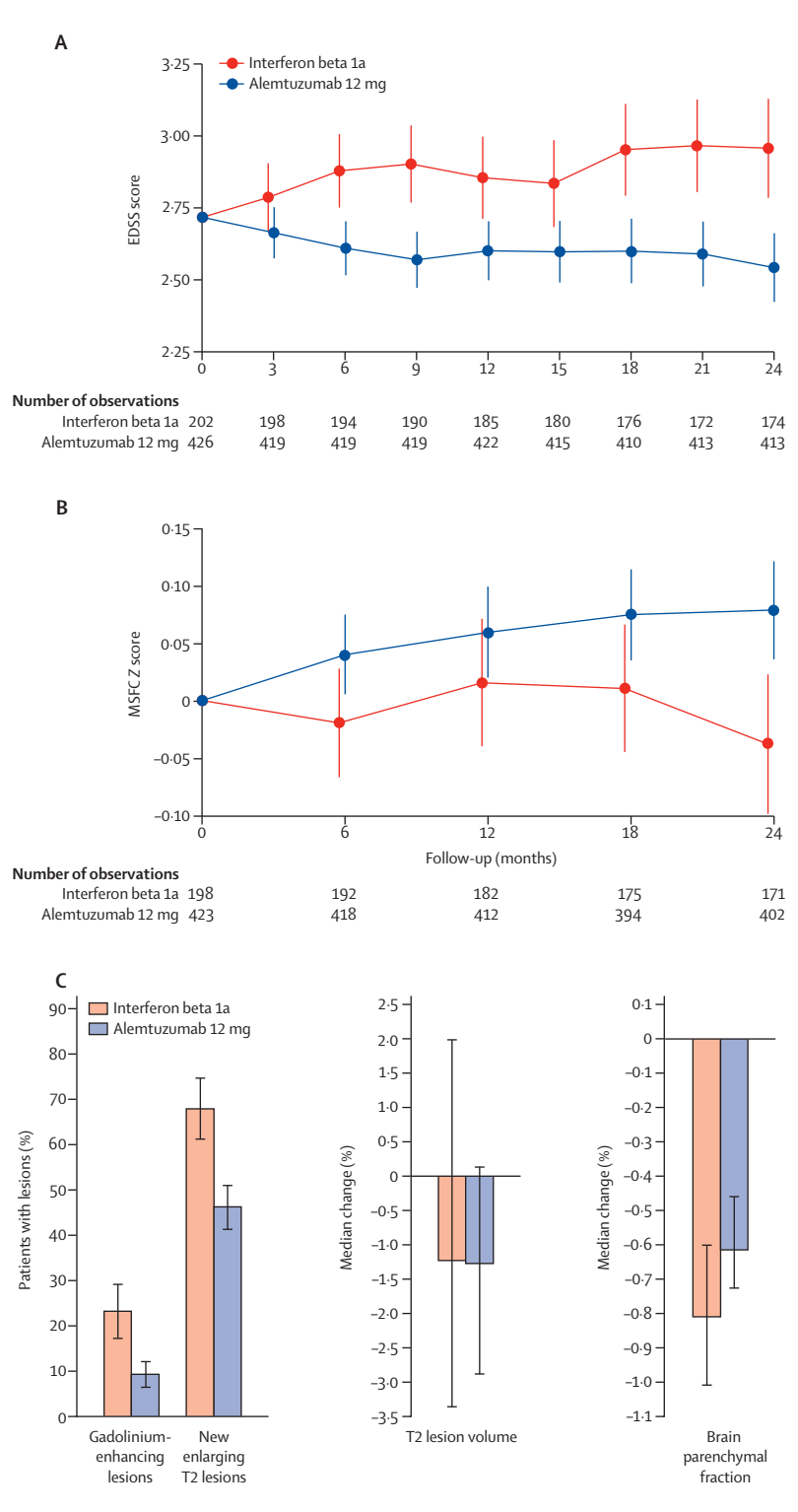



***Figure 3:*** **Secondary and exploratory clinical and MRI outcome measures**
(A) Mean change of expanded disability status scale (EDSS) from baseline; bars show 95% CIs. (B) Mean change from baseline in multiple sclerosis functional composite (MSFC) *Z* score; bars show 95% CIs. (C) MRI outcomes over 2 years: proportion of patients with new or enlarging T2 hyperintense lesions; proportion with gadolinium-enhancing lesions; median percentage change in volume of T2-hyperintense lesions, and brain parenchymal fraction.

| | Interferon beta 1a (n=202) | Alemtuzumab 12 mg (n=435) | Alemtuzumab 24 mg (n=161) |
|---|---|---|---|
| **All adverse events** | | | |
| Events (events per person-year) | 2128 (5·69) | 7513 (8·66) | 3715 (11·57) |
| Patients with ≥1 event | 191 (95%) | 428 (98%) | 159 (99%) |
| Study drug discontinuation because of adverse event* | 15 (7%) | 14 (3%) | 6 (4%) |
| **Serious adverse events** | | | |
| Events (events per person-year) | 77 (0·21) | 138 (0·16) | 53 (0·17) |
| Patients with ≥1 event | 44 (22%) | 85 (20%) | 30 (19%) |
| Multiple sclerosis relapse† | 25 (12%) | 33 (8%) | 3 (2%) |
| Excluding MS relapses | 26 (13%) | 58 (13%) | 27 (17%) |
| Deaths | 0 | 2 (<1%) | 0 |
| **Infusion-associated reactions** | | | |
| Any event | NA | 393 (90%) | 156 (97%) |
| Events affecting >10% in any group | | | |
| Headache | NA | 188 (43%) | 92 (57%) |
| Rash | NA | 168 (39%) | 86 (53%) |
| Nausea | NA | 72 (17%) | 38 (24%) |
| Pyrexia | NA | 69 (16%) | 32 (20%) |
| Urticaria | NA | 64 (15%) | 38 (24%) |
| Pruritus | NA | 50 (11%) | 31 (19%) |
| Insomnia | NA | 44 (10%) | 18 (11%) |
| Fatigue | NA | 39 (9%) | 21 (13%) |
| Chills | NA | 32 (7%) | 22 (14%) |
| Chest discomfort | NA | 27 (6%) | 23 (14%) |
| Dyspnoea | NA | 27 (6%) | 18 (11%) |
| Myalgia | NA | 24 (6%) | 17 (11%) |
| Serious adverse events | NA | 12 (3%) | 5 (3%) |
| Pyrexia | NA | 2 (<1%) | 0 |
| Urticaria | NA | 2 (<1%) | 0 |
| Chest discomfort | NA | 1 (<1%) | 0 |
| Hypothyroidism | NA | 1 (<1%) | 0 |
| Nausea | NA | 1 (<1%) | 0 |
| Vomiting | NA | 1 (<1%) | 0 |
| Chest pain | NA | 1 (<1%) | 0 |
| Infusion related reaction | NA | 1 (<1%) | 0 |
| Non-cardiac chest pain | NA | 1 (<1%) | 0 |
| Status migrainosus | NA | 1 (<1%) | 0 |
| Cough | NA | 1 (<1%) | 0 |
| Dyspnoea | NA | 1 (<1%) | 0 |
| Haemoptysis | NA | 1 (<1%) | 0 |
| Gastritis | NA | 0 | 1 (1%) |
| Peripheral oedema | NA | 0 | 1 (1%) |
| Pneumonia | NA | 0 | 1 (1%) |
| Migraine | NA | 0 | 1 (1%) |
| Sinus tachycardia | NA | 0 | 1 (1%) |
| Rash | NA | 0 | 1 (1%) |
| Hypertension | NA | 0 | 1 (1%) |

(Continues in next column)

| | Interferon beta 1a (n=202) | Alemtuzumab 12 mg (n=435) | Alemtuzumab 24 mg (n=161) |
|---|---|---|---|
| (Continued from previous column) | | | |
| **Infections** | | | |
| Any event | 134 (66%) | 334 (77%) | 134 (83%) |
| Events affecting >10% in any group | | | |
| Nasopharyngitis | 48 (24%) | 128 (29%) | 52 (32%) |
| Urinary tract infection | 23 (11%) | 93 (21%) | 37 (23%) |
| Upper respiratory tract infection | 25 (12%) | 71 (16%) | 34 (21%) |
| Herpes viral infections | 8 (4%) | 68 (16%) | 26 (16%) |
| Herpes simplex‡ | 4 (2%) | 42 (10%) | 13 (8%) |
| Herpes zoster§ | 3 (1%) | 26 (6%) | 12 (7%) |
| Herpes dermatitis | 0 | 1 (<1%) | 0 |
| Varicella | 0 | 1 (<1%) | 1 (1%) |
| Herpes virus infection | 1 (<1%) | 0 | 1 (1%) |
| Sinusitis | 20 (10%) | 58 (13%) | 20 (12%) |
| Influenza | 11 (5%) | 41 (9%) | 18 (11%) |
| Serious adverse events | 3 (1%) | 16 (4%) | 6 (4%) |
| Pneumonia | 0 | 4 (1%) | 1 (1%) |
| Gastroenteritis | 0 | 3 (1%) | 1 (1%) |
| Appendicitis | 0 | 2 (<1%) | 0 |
| Febrile infection | 0 | 1 (<1%) | 0 |
| Herpes zoster | 0 | 1 (<1%) | 2 (1%) |
| Influenza | 0 | 1 (<1%) | 0 |
| Labyrinthitis | 0 | 1 (<1%) | 0 |
| Oesophageal candidiasis | 0 | 1 (<1%) | 0 |
| Pasteurella infection | 0 | 1 (<1%) | 0 |
| Pyelonephritis | 0 | 1 (<1%) | 0 |
| Tooth infection | 0 | 1 (<1%) | 0 |
| Upper respiratory tract infection | 0 | 1 (<1%) | 0 |
| Urinary tract infection | 0 | 1 (<1%) | 0 |
| Bronchitis | 0 | 0 | 1 (1%) |
| Diverticulitis | 0 | 0 | 1 (1%) |
| Pulmonary tuberculosis | 0 | 0 | 1 (1%) |
| Catheter site infection | 1 (<1%) | 0 | 0 |
| Injection site abscess | 1 (<1%) | 0 | 0 |
| Pyelonephritis chronic | 1 (<1%) | 0 | 0 |
| **Thyroid disorders** | | | |
| Any event¶ | 10 (5%) | 69 (16%) | 31 (19%) |
| Hyperthyroidism | 1 (<1%) | 22 (5%) | 6 (4%) |
| Hypothyroidism | 3 (1%) | 19 (4%) | 12 (7%) |
| Thyroiditis | 0 | 7 (2%) | 4 (2%) |
| Goitre | 1 (<1%) | 6 (1%) | 4 (2%) |
| Serious adverse event | 0 | 2 (<1%) | 2 (1%) |
| Hypothyroidism | 0 | 2 (<1%) | 1 (1%) |
| Hyperthyroidism | 0 | 1 (<1%) | 0 |
| Goitre | 0 | 0 | 1 (1%) |

(Continues in next column)

| | Interferon beta 1a (n=202) | Alemtuzumab 12 mg (n=435) | Alemtuzumab 24 mg (n=161) |
|---|---|---|---|
| (Continued from previous column) | | | |
| **Blood and lymphatic system disorders** | | | |
| Any event | 28 (14%) | 59 (14%) | 25 (16%) |
| Serious adverse events | 0 | 3 (1%) | 5 (3%) |
| Autoimmune thrombocytopenia‖ | 0 | 3 (1%) | 2 (1%) |
| Thrombocytopenia | 0 | 0 | 1 (1%)** |
| Anaemia | 0 | 0 | 1 (1%) |
| Febrile neutropenia | 0 | 0 | 1 (1%) |
| **Malignant disease** | | | |
| Basal cell carcinoma | 1 (<1%) | 1 (<1%) | 1 (1%) |
| Thyroid cancer | 0 | 1 (<1%) | 0 |
| Acute myeloid leukemia | 1 (<1%) | 0 | 0 |
| Vulval cancer | 0 | 0 | 1 (1%) |
| Colon cancer | 0 | 0 | 1 (1%) |
| **Liver toxicity** | | | |
| Any event | 13 (6%) | 19 (4%) | 5 (3%) |
| Serious adverse event | 5 (2%) | 4 (1%) | 1 (1%) |
| **Administration-site reactions** | | | |
| Any event | 56 (28%) | 40 (9%) | 17 (11%) |
| **Other events affecting >10% of patients in any group††** | | | |
| General condition | | | |
| Pyrexia | 18 (9%) | 95 (22%) | 47 (29%) |
| Fatigue | 26 (13%) | 81 (19%) | 35 (22%) |
| Chills | 9 (4%) | 35 (8%) | 22 (14%) |
| Pain | 8 (4%) | 35 (8%) | 16 (10%) |
| Chest discomfort | 1 (<1%) | 33 (8%) | 27 (17%) |
| Influenza-like illness | 47 (23%) | 31 (7%) | 13 (8%) |
| Injection site erythema | 28 (14%) | 0 | 0 |
| Nervous system disorders | | | |
| Headache | 36 (18%) | 230 (53%) | 102 (63%) |
| Multiple sclerosis relapse† | 99 (49%) | 143 (33%) | 53 (33%) |
| Paraesthesia | 20 (10%) | 50 (11%) | 18 (11%) |
| Dizziness | 11 (5%) | 48 (11%) | 26 (16%) |
| Hypoaesthesia | 16 (8%) | 35 (8%) | 19 (12%) |
| Skin and subcutaneous tissue disorders | | | |
| Rash | 11 (5%) | 193 (44%) | 96 (60%) |
| Urticaria | 2 (1%) | 75 (17%) | 43 (27%) |
| Pruritus | 5 (2%) | 66 (15%) | 35 (22%) |
| Generalised rash | 2 (1%) | 33 (8%) | 16 (10%) |

(Continues in next column)

Data are incidence in patients, n (%), unless otherwise stated. NA=not applicable. *Includes events occurring in patients whose primary reason for discontinuing the study drug was an adverse event (including abnormal laboratory findings). †Includes only events with preferred term multiple sclerosis relapse, and might not correspond to relapse tally for efficacy endpoints. ‡Includes the preferred terms herpes simplex, oral herpes, genital herpes, and herpes simplex ophthalmic. §Includes the preferred terms herpes zoster and herpes zoster multi-dermatomal. ¶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. ‖Autoimmune thrombocytopenia includes terms autoimmune thrombocytopenia and idiopathic thrombocytopenic purpura. **Grade 1 thrombocytopenia, not related to study drug. ††Events that were not infusion-associated reactions.

***Table 3:*** **Adverse event summary (safety population)**

significantly reduced the relapse rate and risk of 6 month sustained accumulation of disability by more than 40% compared with treatment with interferon beta 1a. No phase 3 monotherapy trial has previously shown superior efficacy on EDSS disability measures against an active comparator. Although mean disability deteriorated after interferon beta 1a, it improved with alemtuzumab 12 mg; and more patients had a sustained reduction in disability after alemtuzumab. The clinical evidence for efficacy is supported by alemtuzumab's significantly greater effects on several MRI measures compared with interferon beta 1a. Adjustment for specific previous treatments, participant withdrawals before treatment, and anti-interferon antibodies present at baseline or study end, did not change the evidence for improved efficacy of alemtuzumab. Previous therapy or the presence of anti-interferon antibodies did not affect the results, although the study was not powered to detect an interaction.

These results extend the experience of alemtuzumab from the phase 2 trial[12] and accompanying phase 3 trial[13] in previously untreated patients to those with disease activity on first-line therapy and increased disease duration and disability at baseline; however, compared with phase 3 trials of other compounds, this population is still at the lower end of disease duration and has typical relapse rates and disability at entry (panel). We regard subcutaneous high-dose, high-frequency interferon beta 1a as an appropriate comparator for this study because it is a common escalation choice for patients with disease activity during treatment with another first-line disease modifying therapy both in the USA and Europe.[29,30]

Our trial supports previous experience of the safety profile of alemtuzumab accumulated for 3–5 years;[8,11,12] our cohort and others are under extended review to collect long-term safety data. In our study, infusion-associated reactions were effectively managed with methylprednisolone, antipyretics, and antihistamines. Incidence of mild-to-moderate infections and superficial herpetic infections were more common after alemtuzumab than interferon beta 1a, but were treatable with aciclovir. We did not note any serious opportunistic infections, perhaps because of intact innate immunity, sequestered lymphocytes, and maintained levels of serum immunoglobulins[9] or tissue-resident effector memory T cells.[31] We identified secondary autoimmune diseases promptly by monitoring, allowing effective therapy. At 2 years, 16% of patients

### *Panel:* Research in context

#### Systematic review

We identified references for this study in the authors' files and by searching PubMed for trials without language or date restriction with the terms "multiple sclerosis" AND "clinical trials", "alemtuzumab", OR "interferon". One previous phase 3 trial assessed patients with multiple sclerosis that remained active despite previous therapy.[26] The trial tested the combination of intravenously natalizumab once every 4 weeks and interferon beta 1a once per week against interferon beta 1a alone. Two other phase 3 trials that included weekly interferon beta used relapse rate as their primary outcome measure and were not powered to detect effects on disability outcomes.[27,28]

#### Interpretation

Our trial explored the effects of alemtuzumab in a population with relapsing-remitting multiple sclerosis with at least one relapse on previous interferon beta or glatiramer therapy; therefore this group had a longer disease duration and greater mean disability than in the phase 2 trial[12] and accompanying phase 3 trials of previously untreated patients.[13] Alemtuzumab 12 mg per day, given intravenously for 5 days at baseline and 3 days at 12 months, was more effective than was interferon beta 1a 44 μg subcutaneously three times weekly in reducing clinical relapses, slowing disability accumulation and brain volume loss, and inducing sustained improvement in disability. Alemtuzumab is the only drug to have been shown to have superiority over interferon beta 1a in disability outcomes in a monotherapy phase 3 trial. The risk management programme employed in the study identified the main adverse effects of alemtuzumab; including treatable autoimmunity, chiefly against the thyroid but also immune thrombocytopenia, infusion-related symptoms, and increased frequency of common infections.

treated with alemtuzumab 12 mg had autoimmune thyroid disease; our previous experience suggests that this figure might rise to about 33%, with annual incidence reducing after the third year.[32]

Alemtuzumab is the first treatment for multiple sclerosis to show improved efficacy on clinical endpoints against an active comparator in one phase 2 and two phase 3 trials.[12,13] Significant effects on clinical and MRI indicators of inflammatory disease activity were accompanied in this study by slowing of cerebral atrophy and accumulation of physical disability and, for many patients, by improvements in disability. We conclude that, with appropriate monitoring to reduce the risk of potentially serious but nonetheless treatable adverse effects, alemtuzumab offers the prospect for effective immunotherapy in patients with relapsing-remitting multiple sclerosis whose disease has advanced despite use of a first-line treatment.

#### Contributors

AJC wrote the first draft of the manuscript and coordinated all reviews and submissions. The writing committee (AJC, DLA, JAC, CC, EJF, H-PH, EH, KS, HLW, DHM, MP, and DASC) met to review data outputs, suggest additional analyses, edit, and approve manuscript drafts. Statistical support was led by SLL. Final versions of the manuscript were edited and approved by representatives of the investigators (CLT, TM, and EF) and sponsors (RS and PO).

#### Conflicts of interest

AJC reports receiving consulting fees from Genzyme, lecture fees from Merck Serono, and research support paid to his institution from Genzyme. CLT reports receiving compensation from clinical trials with Genzyme, Sanofi-Aventis, Eli Lilly, Opexa Therapeutics, Biogen Idec, Teva, Roche, Novartis, Xenoport, Acorda, and Pfizer Pharmaceuticals and compensation for speaker activities and consultation activities from Acorda, Biogen Idec, Novartis, Forrest, and Teva. DLA served on advisory boards, received speaker honoraria, and served as a consultant or received research support from Bayer, Biogen Idec, Coronado Biosciences, Consortium of Multiple Sclerosis Centers, Eli Lilly, EMD Serono, Genentech, Genzyme, GlaxoSmithKline, MS Forum, NeuroRx Research, Novartis, Opexa Therapeutics, Roche, Merck Serono, SA Serono Symposia International Foundation, Teva, the Canadian Institutes of Health Research, and the Multiple Sclerosis Society of Canada; and holds stock in NeuroRx Research. JAC reports receiving consulting fees from Biogen Idec, Elan, Five Prime Therapeutics, Eli Lilly, Novartis, Teva, Vaccinex, lecture fees from Novartis and Waterfront Media, and research support paid to his institution from Biogen Idec, Genzyme, Novartis, and Teva. CC reports receiving consulting fees from Biogen Idec, Gemacbio, Genzyme, Novartis, Sanofi-Aventis, Teva, UCB; lecture fees from Bayer-Schering, Biogen Idec, Genzyme, Merck-Serono, Novartis, Octopharma, Sanofi-Aventis, Teva; research support paid to his institution from Bayer-Schering, Biogen Idec, Merck-Serono, Novartis, Sanofi-Aventis, Teva. EJF reports receiving consulting fees, honoraria, travel, and research support from Acorda, Bayer, Biogen Idec, Eli Lilly, EMD Serono, Genzyme, GlaxoSmithKline, Novartis, Ono, Opexa, Pfizer, Roche, Sanofi, and Teva. H-PH reports receiving honoraria for consulting and speaking, with approval by the rector of Heinrich-Heine-University from Bayer, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi, and Teva. EH reports receiving consulting fees, honoraria, travel, and research support from Bayer, Biogen Idec, Genzyme, GSK, Merck Serono, Novartis, Roche, and Teva. KJ reports receiving consulting fees from Genzyme, Novartis, Biogen Idec, and Roche; he has received lecture fees from Novartis, Merck-Serono, Biogen Idec, and Bayer; and received financial compensation including travel from Genzyme for presentation at ECTRIMS 2010. HLW reports receiving consulting fees from Biogen Idec, EMD Serono, Nasvax, Novartis, Teva, and research support paid to his institution from Biogen Idec and EMD Serono. TM has received compensation for speaker activities for Acorda, Allergan, Bayer, Biogen Idec, Eli Lilly, Forest, Novartis, Pfizer, Questcor, Teva and National MS Society; until clinical trial closure, TM was an independent contractor for Allergan, Biogen Idec, Genzyme, Elan, Teva, Ono, Pfizer, Novartis, Sanofi-Aventis, EMD Serono, and Roche/Genentech. EF reports receiving consulting fees from Biogen Idec, Genzyme, Pfizer, and Wyeth, lecture fees from Biogen Idec and Teva, and research support paid to her institution from Biogen Idec, Genzyme, and Wyeth. RS receives personal compensation as an employee of Bayer HealthCare, Berlin, Germany. ASC reports receiving consulting fees, lecture fees and grant support from Genzyme and lecture fees from Bayer Schering Pharma, on behalf of the University of Cambridge. DHM, SLL, PO, and MP receive personal compensation as employees of Genzyme (a Sanofi company).

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