Table 1. Clinical End Points at Month 9

	GTR (n = 353)	GA (n = 357)	Placebo (n = 84)
Annualized relapse rate [95%CI]	0.31 (0.20 to 0.48)	0.41 (0.27 to 0.63)	0.39 (0.22 to 0.67)
Subjects without relapse (%)	281 (79.6%)	263 (73.7%)	62 (73.8%)
Change in EDSS (Median (min–max))	0.0 (–2.5 to 2.0)	0.0 (–3.0 to 4.5)	0.0 (–2.0 to 1.5)
Free from disease activity (%)	33 (9.3%)	32 (9.0%)	6 (7.1%)

EDSS, Extended Disability Status Scale; GA, glatiramer acetate; GTR, a generic form of GA.

There were no differences between the 2 active treatments in other MRI end points at 9 months: change in T2 lesion number or volume (mm^3), change in T1-hypo lesion volume (mm^3), or change in brain volume (cm^3). Clinical end points were similar between GTR and GA (Table 1).

Overall safety and tolerability were excellent and similar for GTR and GA. The most common drug-related AEs were injection site reaction (16.4% of GTR-treated patients vs 17.1% of GA-treated patients) and immediate postinjection reaction (6.8% and 5.0%, GTR vs GA, respectively). The rate of serious or severe AEs was low. Drug-related serious AEs were reported by 3 (0.8%) GTR-treated patients and 4 (1.1%) GA-treated patients. No patients died. Local tolerability (pain, itchiness, redness, swelling, lumps) was similar between the GTR and GA groups.

Data from the open-label study is expected in 2015 and will include 2-year safety and efficacy data, data on switching (from GA to GTR), and immunogenicity data for both the core and open-label portions of the study.

Postrelapse MS Treatment With Alemtuzumab Better Than SC IFN-β-1a

Written by Brian Hoyle

Subgroup analyses, entitled An Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab [NCT00930553; Barkhof F et al. ACTRIMS/ECTRIMS 2014 (poster P075)], of an ongoing, open-label extension of the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis, Study Two [CARE-MS II; Coles AJ et al. *Lancet.* 2012], have confirmed the superiority of treatment of MS using the anti-CD52 humanized monoclonal antibody, alemtuzumab, over subcutaneous interferon beta-1a (SC IFN-β-1a) in magnetic resonance imaging (MRI) outcomes. The subgroup analyses were based on baseline demographics and disease characteristics, as well as prior use of SC IFN-β-1a. Alemtuzumab's superiority was, in most cases, a holdover from treatment received 2 years previously.

The latest findings from the subgroup analyses based on the phase 3, randomized, rater-blinded, active-controlled, head-to-head CARE-MS II study were presented by Frederik Barkhof, MD, VU University Medical Center, Amsterdam, the Netherlands.

CARE-MS II has established the significant superiority of alemtuzumab throughout 2 years compared with SC IFN-β-1a at reducing the risk of the development or enlargement of gadolinium-enhancing (Gd+) lesions and reducing brain volume loss [Coles AJ et al. *Lancet.* 2012], and in lessening the number of hypointense lesions [Arnold DL et al. ECTRIMS 2012). Eligible patients (n = 667) aged 18 to 55 years with active relapsing-remitting MS and a baseline Expanded Disability Status Scale (EDSS) score ≤ 5 (n = 667) were randomized 2:1 to receive alemtuzumab 12 mg/d intravenously for 5 consecutive days at baseline and 3 consecutive days 12 months later (n = 426), or to receive SC IFN-β-1a 44 µg 3 times a week on an ongoing basis (n = 202) [Coles AJ et al. *Lancet.* 2012]. The groups were similar at baseline concerning demographic and relevant clinical parameters.

The core phase ran for 2 years. In the subsequent extension phase, patients initially randomized to alemtuzumab could continue their treatment if they relapsed or presented with MRI signs of progression. This retreatment was unnecessary in 80% of cases.

The proportion of patients with new or enlarged Gd+, T2 lesions, and T1 lesions was significantly lower with alemtuzumab (≤20%) than IFN-β-1a in the core portion of the study (all $P<.0001$) [Coles AJ et al. *Lancet*. 2012], and the proportion in the extension phase in the 20% of patients who received alemtuzumab was comparable. Furthermore, the mean change in brain parenchymal fraction (BPF) from baseline through year 3 was significantly less in alemtuzumab-treated patients, with the year 2 value maintained at year 3, than in IFN-β-1a-treated patients ($P=.012$).

Subgroup analyses revealed that the risk of Gd+ lesions was significantly lower with alemtuzumab compared with IFN-β-1a ($P<.05$ for overall population) for most parameters, with only nonwhite race and Latin American geographic region being equivocal.

Other subgroup analyses based on the same parameters revealed that, compared with SC IFN- β -1a, alemtuzumab significantly lessened the risk of new or enlarging T2 lesions ($P<.01$) and new T1 lesions ($P<.05$) at year 2. Also, the subgroup analysis of the change from baseline in BPF consistently revealed the reduced loss in volume associated with alemtuzumab-treated patients. The difference in volume loss between the alemtuzumab and IFN-β-1a groups was significant for the parameters of patients aged <34 years ($P=.0126$), white race ($P=.0285$), baseline EDSS score ≥2.5 ($P=.0437$), baseline BPF ≥0.816105 ($P=.0359$), baseline T2 lesion volume <5.7135 cm^3, disease duration <3.8 years ($P=.0142$), and no prior SC IFN-β-1a use ($P=.0076$).

The latest findings strengthen support for the superiority of using alemtuzumab in the treatment of active relapsing-remitting MS in patients who have relapsed.

Results of DECIDE: DAC HYP Superior to IFN-β-1a for RRMS

Written by Brian Hoyle

Ludwig Kappos, MD, University Hospital, Basel, Switzerland, described the results of the phase 3, randomized, double-blind, double-dummy, active-controlled Efficacy and Safety of Daclizumab High Yield Process Versus Interferon β 1a in Patients With Relapsing-Remitting Multiple Sclerosis trial [DECIDE; NCT01064401] establishing the superiority of the humanized monoclonal antibody, daclizumab high-yield process (DAC HYP), to interferon beta-1a (IFN-β-1a) in the treatment of relapsing-remitting multiple sclerosis (RRMS).

DAC HYP selectively binds to a subunit of CD25 that is exuberantly expressed on T-cells that become abnormally activated in MS [Perry JSA et al. *Sci Transl Med*. 2012; Wuest SC et al. *Nat Med*. 2011; Martin JF et al. *J Immunol*. 2010; Bielekova B et al. *Proc Natl Acad Sci USA*. 2004; McDyer JF et al. *J Immunol*. 2002]. DAC HYP modulates interleukin-2 signaling without causing general immune cell depletion.

DECIDE was designed to determine if DAC HYP would provide superior outcomes for identified clinical end points compared with IFN-β-1a in greater than 1800 people with RRMS in 28 countries randomized to treatment with subcutaneous DAC HYP 150 mg every 4 weeks (n=919) or intramuscular injection of IFN-β-1a 30 µg QW (n=922). The primary end point was the reduction in annualized relapse rate (ARR). Secondary end points included the number of new or newly enlarging T2 hyperintense lesions on magnetic resonance imaging (MRI), the proportion of patients with sustained disability progression as determined by Extended Disability Severity Scale (EDSS) scores, the proportion of relapse-free patients, and a worsening physical impact score on the MS Impact Scale (MSIS-29).

Baseline demographic and clinical characteristics (duration of RRMS, relapses in previous year, EDSS score, prior treatment, the presence and number of gadolinium-enhancing [Gd+] lesions, and T2 lesions) were similar in both study arms.

The primary end point was met. ARR in the DAC HYP arm was 45% less than in the IFNβ-1a arm (0.216 vs 0.393; 95% CI, 35.5% to 53.1%; $P<.0001$). Significantly, more patients receiving DAC HYP remained relapse-free throughout the trial (overall RR 41%, $P<.0001$), with increasing divergence between the arms with time.

Week 96 MRI data revealed a reduction in the mean number of new and newly enlarged T2 lesions with DAC HYP (9.4 with IFN-β-1a, n=841 vs 4.3 with DAC HYP, n=864; 54% reduction), new Gd+ lesions (1.0 with IFN-β-1a, n=909 vs .4 with DAC HYP, n=900; 65% reduction), and new T1 hypointense lesions (4.4 with IFN-β-1a, n=908 vs 2.1 with DAC HYP, n=899; 52% reduction; all $P<.0001$).

Confirmed disability progression was lower in the DAC HYP arm vs IFN-β-1a, with a risk reduction of 16% ($P=.16$) at 3 months in patients with suspected disease progression and 27% ($P=.0332$) at 6 months in patients with confirmed disease progression; a similar pattern was seen in patients with suspected and confirmed progression with further divergence of the study arms out to week 144. More patients treated with IFN-β-1a than with DAC HYP had MSIS-29 scores that were indicative of a clinically meaningful worsening of symptoms (23% vs 19%; 24% reduction; $P=.0176$). Finally, annualized brain volume change for weeks 0 to 24 and weeks 24