Patients With Active RRMS and Inadequate Response to Therapy at Baseline Show Durable Disability Improvement Over 5 Years With Alemtuzumab: CARE-MS II

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on behalf of the CARE-MS II Investigators

Presented by Christopher LaGanke

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- **Christopher LaGanke:** Compensation for consulting (Acorda Therapeutics, Bayer, Biogen, Cephalon, EMD Serono, Novartis, Pfizer, Questcor, Sanofi Genzyme, Strativa, Teva, and UCB).
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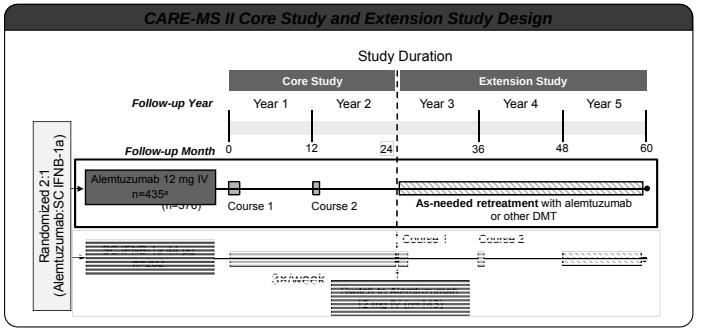
CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis.

CARE-MS II Study Background

- Phase 3 trial in patients with active RRMS and an inadequate response to prior therapy at baseline, defined as at least one relapse
- Alemtuzumab versus SC IFNB-1a over 2 years:
  - Significant 49% decrease in annualized relapse rate[1]
  - Significant 42% reduction in risk of 6-month confirmed disability worsening[1]
  - 68% more patients with no evidence of MRI disease activity[2]
  - Significant 24% reduction in brain volume loss[1]
- Most frequent adverse events (AEs) were infusion-associated reactions; other AEs of interest included autoimmune AEs[1]

No evidence of MRI disease activity defined as absence of gadolinium (Gd)-enhancing T_1 lesions and new/enlarging T_2 hyperintense lesions.
1. Coles AJ et al. *Lancet* 2012;380:1829-39; 2. Fisher E et al. *Mult Scler* 2014;20:P103.

CARE-MS II Core and Extension Study Design



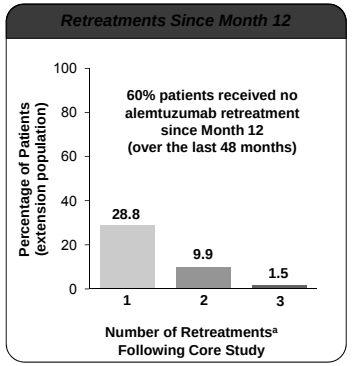
- Ongoing, open-label, rater-blinded extension study provides follow-up, retreatment where necessary, and reassessment of outcomes through Month 60 (Year 5)
  - 393 (93%) of alemtuzumab patients completing CARE-MS II (Years 1 and 2) enrolled in the extension (Year 3–5)
  - 357 (91%) remained on study through Month 60 (end of Year 5)

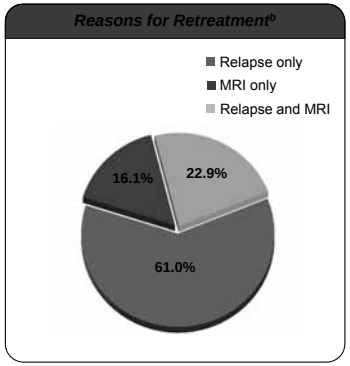
[a]As-treated population.

Disability Assessments Through 5 Years

- Expanded Disability Status Scale (EDSS) scores were assessed at baseline and quarterly by raters who were blinded to core study treatment assignment
  - EDSS mean change from baseline
  - 6-Month confirmed disability worsening: ≥1-point EDSS increase (≥1.5 point if baseline EDSS=0)
  - Confirmed disability improvement: ≥1-point EDSS decrease from baseline over 3, 6, or 12 months, assessed in patients with baseline EDSS ≥2.0

Alemtuzumab Retreatment Rate Was Low Through 5 Years

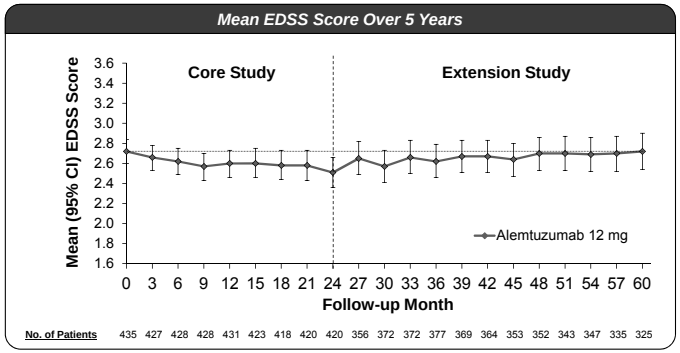




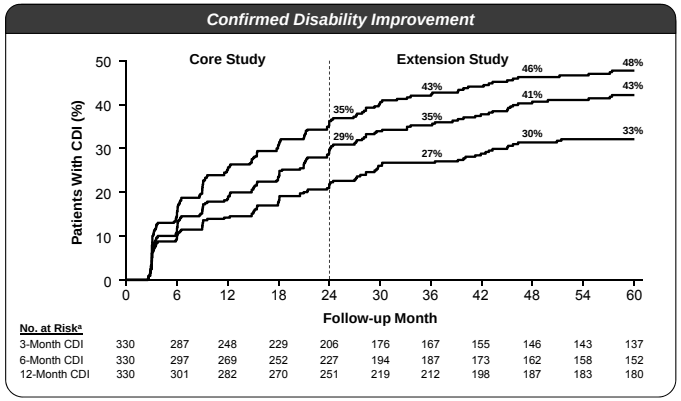
- 7.6% of patients (n=30) received another DMT

[a]Retreatment criteria were ≥1 protocol-defined relapse, or ≥2 new/enlarging T_2 hyperintense and/or new gadolinium (Gd)-enhancing T_1 brain or spinal cord lesions on MRI.
[b]No reason was provided for 4 cases. Over 5 years, there were 209 retreatments in 158 patients.

Mean EDSS Score Was Stable Through Year 5



Confirmed Disability Improvement Was Newly Achieved Through Year 5



- Number at risk is the number of patients who remained on study and who had yet to achieve CDI
- Of patients who entered the extension study, 91% remained on study through Year 5

CDI=confirmed disability improvement.

Most Alemtuzumab-Treated Patients Had Improved or Stable EDSS Scores From Baseline to Year 5

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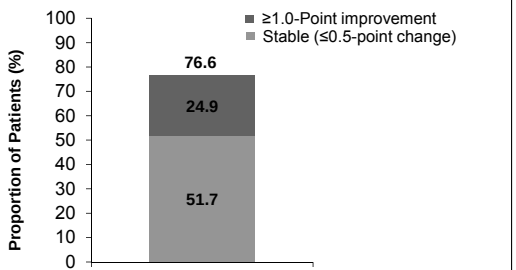
1.0-Point Improved or Stable EDSS Score From Baseline to Year 5 (Month 60)



Through Year 5:

- 75% were free from 6-month confirmed disability worsening[a]
- 43% achieved 6-month confirmed disability improvement[a]
  - Of these, 96% were free from 6-month confirmed disability worsening

[a]Kaplan-Meier estimate.

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Most Alemtuzumab-Treated Patients Had Improved or Stable Functional Systems Scores From Baseline to Year 5

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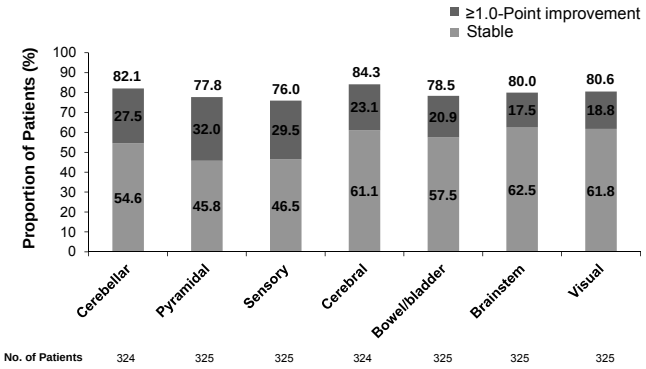
1.0-Point Functional System Score Improvement or Stability



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Hypothesis: Alemtuzumab Mechanism of Action May Explain Durability of Effect

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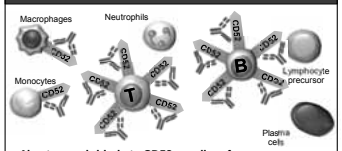
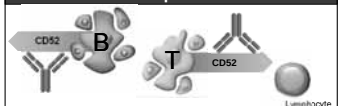
1. Selection



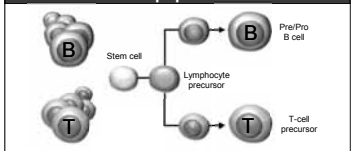
Alemtuzumab binds to CD52, a cell surface antigen present on T and B lymphocytes[1,2]

2. Depletion

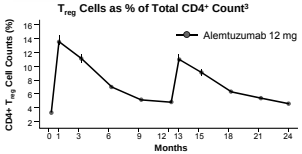


Depletes circulating T and B lymphocytes[1,2]

3. Repopulation



T_{reg} Cells as % of Total CD4+ Count[3]



T_{reg} Phenotype: $CD4^+/CD25int/br^+/CD127lo-$

Lymphocytes repopulate over time[4,5]

- **Distinctive repopulation pattern, resulting in a relative increase of cells with memory and regulatory phenotype and a decrease in cells with a pro-inflammatory signature[4,6]**

1. Hu Y et al. *Immunology* 2009;128:260-70; 2. Rao SP et al. *PLoS One* 2012;7:e39416; 3. Hartung HP et al. ECTRIMS 2012; P935; 4. Cox AL et al. *Eur J Immunol* 2005;35:3332-42; 5. Hill-Cawthorne GA et al. *J Neurol Neurosurg Psychiatry* 2012;83:298-304; 6. Zhang X et al. *J Immunol* 2013;191:5867-74.

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Conclusions

CARE-MS II

- Alemtuzumab is administered as 2 courses (5 days at Month 0 and 3 days at Month 12)
  - Most patients did not receive any additional treatment (no alemtuzumab retreatment since the initial 2 courses or other DMT)
- EDSS-based disability was improved or stable for most patients over 5 years
  - Improvement was evident across all functional systems
- Immunomodulation linked to lymphocyte repopulation may contribute to durability of effect
  - Shift from a pro-inflammatory to anti-inflammatory profile
- Based on these findings, alemtuzumab may provide a unique treatment approach with durable efficacy in the absence of continuous treatment for RRMS patients

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CARE-MS Study Group and Acknowledgments

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