Patients of African Descent With Active RRMS Demonstrate Clinical and Radiologic Benefits With Alemtuzumab Over 5 Years

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on behalf of the CARE-MS I and CARE-MS II Investigators

Presented by Annette Okai

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Disclosures

- **Annette Okai:** Consulting and/or speaking fees (Biogen, EMD Serono, Genentech, Mallinckrodt, Novartis, Sanofi Genzyme, and Teva)
- **Keith R Edwards:** Consulting and/or speaking fees (Biogen, Sanofi Genzyme) and research support (Actelion, Biogen, Eli Lilly, Esai, Forum Pharmaceuticals, Genentech, Hoffman-La Roche, Merz Pharmaceuticals, Novartis, Pfizer, Sanofi Genzyme, and Vaccinex)
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CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis.

African Ancestry Is a Risk Factor for MS Disease Progression

- Patients of African descent have more severe MS disease compared with white patients
  - More rapidly disabling disease[1]
  - Greater MRI lesion volumes[2,3]
  - Greater risk for secondary progression[4]
  - Accelerated retinal nerve fiber layer thinning and ganglion cell/inner plexiform layer thinning[5]
  - Possibly poorer response to disease-modifying therapies (DMTs)[6]

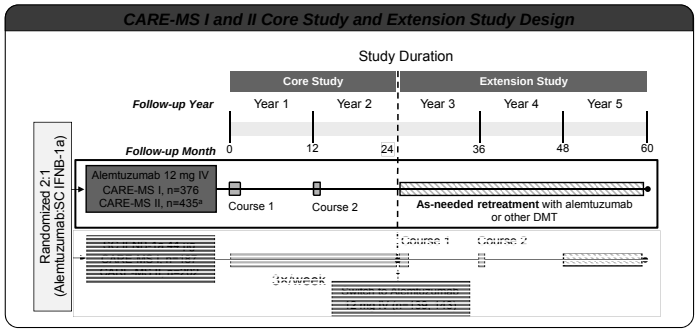
1. Kister I et al. *Neurology* 2010;75:217-23; 2. Howard J et al. *PLoS One* 2012;7:e43061; 3. Weinstock-Guttman et al. *Neurology* 2010;74:538-44; 4. Ferreira Vasconcelos et al. *ISRN Neurol* 2012;410629; 5. Kimbrough DJ et al. *Ann Neurol* 2015;77:228-36; 6. Klineova S et al. *Ethn Dis* 2012;22:221-5.

CARE-MS I and II Study Background (Full Cohort)

- Phase 3 trials in active RRMS patients:
  - Treatment-naive (CARE-MS I)
  - Inadequate response to prior therapy at baseline, defined as at least one relapse (CARE-MS II)
- Alemtuzumab versus SC IFNB-1a over 2 years:
  - Significant decrease in annualized relapse rate (ARR) in both studies[1,2]
  - Significantly reduced risk of 6-month confirmed disability worsening in CARE-MS II[2]
  - MRI outcomes were significantly improved in CARE-MS I and II[1-4]
    - 23% and 68% more patients with no evidence of MRI disease activity[a]
    - 42% and 24% reduction in brain volume loss (BVL)
- Most frequent adverse events (AEs) were infusion-associated reactions (IARs); other AEs of interest included autoimmune AEs[1,2]

[a]Absence of both new gadolinium (Gd)-enhancing T_1 lesions and new/enlarging T_2 hyperintense lesions.
1. Cohen JA et al. *Lancet* 2012;380:1819-28; 2. Coles AJ et al. *Lancet* 2012;380:1829-39; 3. Giovannoni G et al. ENS 2012, 0288; 4. Fisher E et al. *Mult Scler* 2014;20:P103.

CARE-MS I and 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)

[a]As-treated population.

1. Cohen JA et al. *Lancet* 2012;380:1819-28; 2. Coles AJ et al. *Lancet* 2012;380:1829-39; 3. Fox EJ et al. *Neurology* 2013;80:S41.001.

Assessments Through 5 Years

- Relapses
- Expanded Disability Status Scale (EDSS) score was assessed at baseline and quarterly by raters who were blinded to core study treatment assignment
  - Confirmed disability worsening: ≥1-point EDSS increase (≥1.5 point if baseline EDSS=0) confirmed over 6 months
  - Confirmed disability improvement: ≥1-point EDSS decrease from baseline over 6 months, assessed in patients with baseline EDSS ≥2.0
- MRI was conducted at baseline and annually
  - BVL derived by brain parenchymal fraction (BPF) change
- No evidence of disease activity (NEDA) was defined as no evidence of clinical disease activity (relapse and 6-month confirmed disability worsening) and MRI disease activity (new gadolinium-enhancing T_1 and new/enlarging T_2 hyperintense lesions)

General Considerations on Subgroup Analysis

- There must be careful interpretation of any subgroup analysis before making a conclusion
  - Lack of statistical significance does not imply absolute lack of treatment effect
  - Statistical significance does not imply absolutely statistically robust treatment effect
- Relapses and disability worsening are infrequent events, so a few events may influence results
- **Key statistical issues:** not randomized for subgroup, not controlled for multiplicity, subgroup not powered, etc.

CARE-MS I and II Pooled

Patients of African Descent

- 46 patients of African descent in the pooled CARE-MS core studies (SC IFNB-1a and alemtuzumab 12-mg treatment arms)
  - 32 of 35 alemtuzumab-treated patients entered the extension study
- Baseline characteristics were comparable between treatment groups

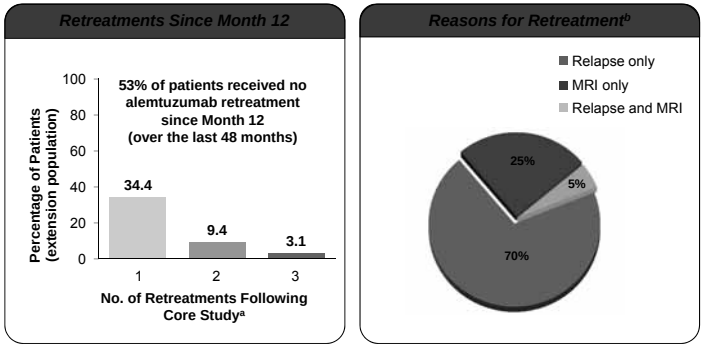
Baseline Characteristics

	SC IFNB-1a (n=11)	Alemtuzumab 12 mg (n=35)
Age, years	33.0 (10.12)	33.4 (8.21)
Female, n (%)	9 (81.8)	26 (74.3)
Country, n (%)		
USA	9 (81.8)	28 (80.0)
Brazil	2 (18.2)	2 (5.7)
UK	0	3 (8.6)
Croatia	0	1 (2.9)
Germany	0	1 (2.9)
EDSS score	2.5 (1.27)	2.2 (1.39)
Time since initial relapse, years	3.66 (2.93)	3.67 (2.50)
Time since most recent relapse, years	0.46 (0.35)	0.40 (0.20)
Number of relapses in year prior to randomization	1.45 (1.04)	1.66 (0.68)

Values are mean (SD) unless otherwise indicated.

Alemtuzumab Retreatment Rate Was Low Through 5 Years in the African Descent Subgroup (n=32)

CARE-MS I and II Pooled



- 88% of patients of African descent did not receive another DMT
- In the overall CARE-MS cohort, 64% did not receive alemtuzumab retreatment since Month 12 and 95% did not receive 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 lesions on MRI.
[b]Over 5 years, there were 20 retreatments in 15 patients.

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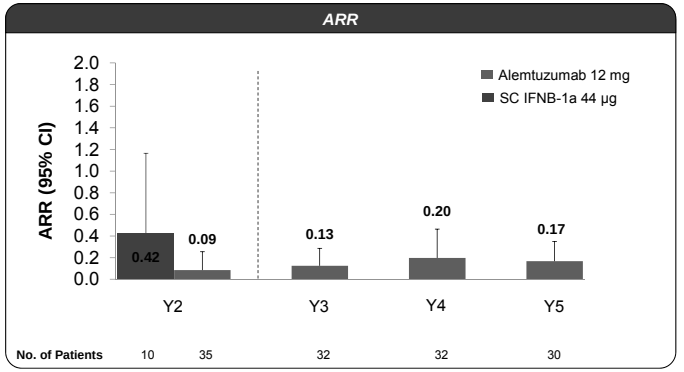
Durable Effect of Alemtuzumab on Relapses Over 5 Years in Patients of African Descent

CARE-MS I and II Pooled



- Cumulative ARR in the alemtuzumab-treated African descent subgroup over Years 0–5 was 0.16 (95% CI, 0.10–0.26)
- 60% of patients were free from relapse in Years 3–5

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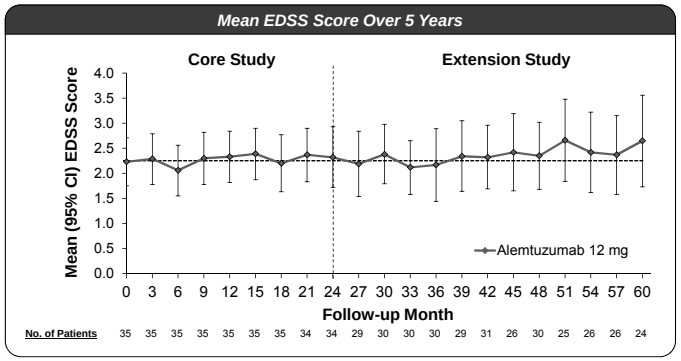
Mean EDSS Score Was Stable Through Year 5 in Patients of African Descent

CARE-MS I and II Pooled



- Mean EDSS score change from baseline to Year 5 was +0.52

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Disability Outcomes Through Year 5 in Alemtuzumab-Treated Patients of African Descent

CARE-MS I and II Pooled

Disability Outcomes

	Patients of African Descent Alemtuzumab 12 mg Years 0–5
6-month confirmed disability worsening	n=32
Patients with no evidence of 6-month confirmed disability worsening, n (%)[a]	23 (71.6)
6-month confirmed disability improvement	n=18
Patients achieving 6-month confirmed disability improvement, n (%)[a]	9 (50.0)

[a]Kaplan-Meier estimate

Confirmed disability worsening: ≥1-point EDSS increase (≥1.5 point if baseline EDSS=0) confirmed over 6 months.
Confirmed disability improvement: ≥1-point EDSS decrease from baseline over 6 months, assessed in patients with baseline EDSS ≥2.0.

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Slowing of BVL Through 5 Years in Alemtuzumab-Treated Patients of African Descent

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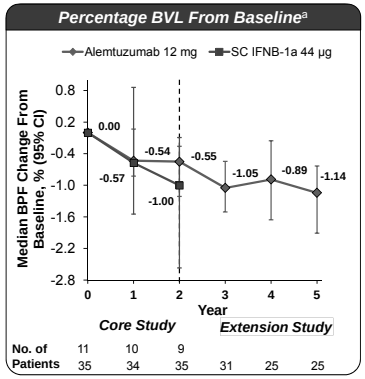

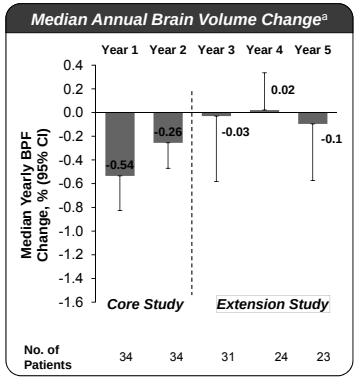

- 53% of patients received no alemtuzumab retreatment since Month 12

[a]Evaluable scans were required for patients to be included in the analysis. 30 patients remained on study through Year 5.

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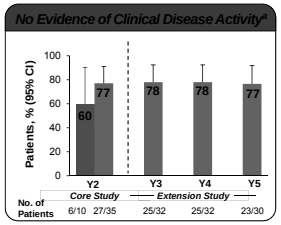
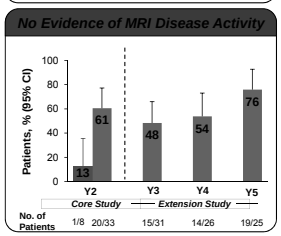
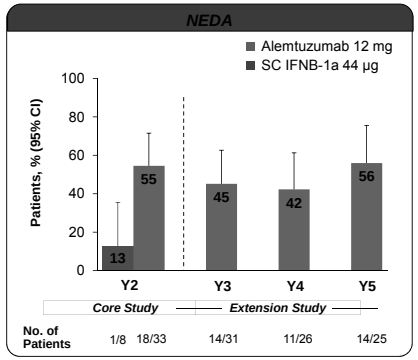
NEDA Was Attained in Many Patients of African Descent in Years 3, 4, and 5

CARE-MS I and II Pooled







- 53% patients received no alemtuzumab retreatment since Month 12

[a]No relapses and no evidence of disability worsening

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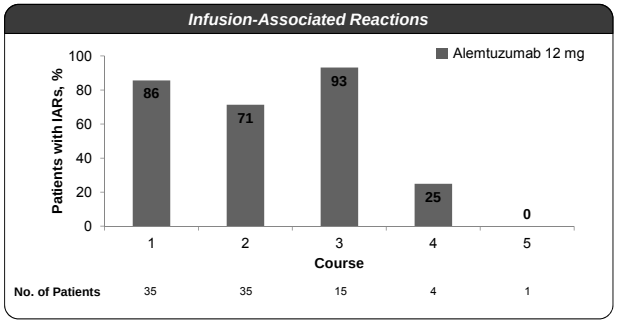
CARE-MS I and II Pooled

IARs in Patients of African Descent



- There were no serious IARs in patients of African descent

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CARE-MS I and II Pooled

Safety Over 5 Years in Patients of African Descent

Adverse Events

	Patients of African Descent Alemtuzumab 12 mg			
Patients with AE, n	Years 1–2 (n=35)	Year 3 (n=33)	Year 4 (n=32)	Year 5 (n=30)
Any AE	34	31	28	26
Serious AEs	8	2	3	2
Any infection	27	17	19	17
Serious infection	2	0	0	0
Thyroid AEs	3	4	2	1
Serious thyroid AEs	0	0	0	0
Immune thrombocytopenia	0	0	1	1
Nephropathies	1	0	0	0
Malignancies	0	0	0	0

- Safety profile was similar to that for the overall cohort

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Conclusions

- In patients of African descent, alemtuzumab had clinical and MRI efficacy comparable with that observed in the overall CARE-MS study population
- Efficacy was durable over 5 years
  - The majority of patients (53%) did not receive alemtuzumab treatment after Month 12
  - Immunomodulation linked to lymphocyte repopulation may contribute to durability of effect
- Further evaluation of MS patients of African descent is warranted

CARE-MS Study Group and Acknowledgments

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Macdonell
McCombe
Paine
Reddel
Schwartz
Vucic

Austria
Vass

Belgium
Dive
Dubois
Sindic

Brazil
Callegaro
Ferreira
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Tilbery

Canada
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Jacques
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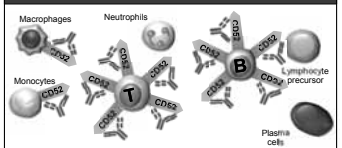
BACK-UP

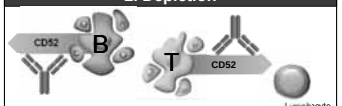
Hypothesis: Alemtuzumab Mechanism of Action May Explain Durability of Effect

1. Selection



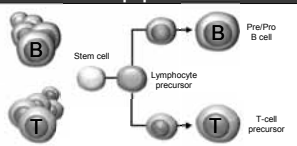
Alemtuzumab binds to CD52, a cell surface antigen present on T and B lymphocytes[1,2]

2. Depletion

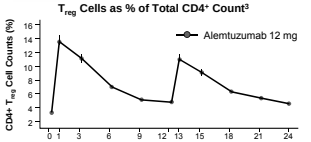


Depletes circulating T and B lymphocytes[1,2]

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.