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RRMS Patients With an Inadequate Response to a Prior Therapy Demonstrate Slowing of Brain Volume Loss Over 5 Years Following Alemtuzumab Treatment

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OBJECTIVES

- **To evaluate brain volume loss (BVL) over 5 years in patients who received alemtuzumab in CARE-MS II and continued in an ongoing extension study**
- **To evaluate the possible impact of baseline brain parenchymal fraction (BPF) on 5-year BVL**

INTRODUCTION

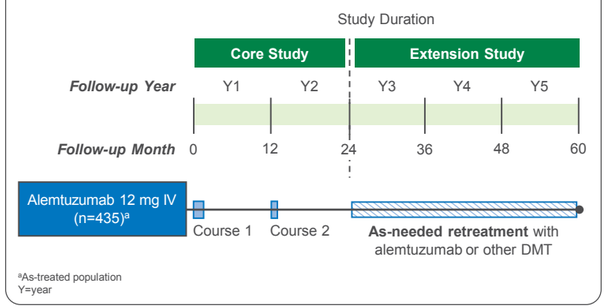
- Alemtuzumab is a humanized anti-CD52 monoclonal antibody that is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) in >50 countries
- In patients with active RRMS who had an inadequate response (≥1 relapse after ≥6 months of treatment) to prior therapy at baseline (CARE-MS II, NCT00548405), alemtuzumab demonstrated greater improvements on clinical and MRI outcomes versus SC IFNB-1a over 2 years, and alemtuzumab patients were more likely to have no evidence of disease activity versus SC IFNB-1a patients[1]
- The most frequent adverse events (AEs) observed with alemtuzumab were infusion-associated reactions; other AEs of interest included autoimmune AEs[1]
- Alemtuzumab-treated patients who have been followed through 5 years in the ongoing open-label extension study (NCT00930553)[2] continue to show durable efficacy outcomes despite most receiving no alemtuzumab since Month 12 and no other disease-modifying therapy (DMT)[3,4]
- Brain atrophy is a marker for neurodegeneration in RRMS patients and has been correlated with disability worsening and cognitive dysfunction[5-8]
- Recent literature shows that irreparable BVL, in excess of that observed in healthy individuals (0.1%–0.3% per year based on structural image evaluation using normalization of atrophy [SIENA] analysis),[9] occurs early in the MS disease course[10,11]

METHODS

Study Design

- CARE-MS II was a phase 3, randomized, head-to-head, rater-blinded, 2-year study of alemtuzumab versus SC IFNB-1a (44 µg 3 times per week) in patients with active RRMS who had an inadequate efficacy response to prior therapy (≥1 relapse) at baseline (**Figure 1**)[1]
  - Patients randomized to alemtuzumab received 2 annual courses of 12 mg/day (on 5 consecutive days at baseline and on 3 consecutive days 12 months later)
- In the ongoing extension study, patients could receive alemtuzumab retreatment (12 mg on 3 consecutive days ≥1 year after the most recent course) for relapse or MRI activity[2]
  - Retreatment criteria were ≥1 protocol-defined relapse, or ≥2 new/enlarging T_2 hyperintense and/or new gadolinium-enhancing T_1 brain or spinal cord lesions on MRI
- Use of other DMTs was permitted at the investigator's discretion

Figure 1. CARE-MS II Core and Extension Study Design



[a]As-treated population
Y=year

Efficacy Assessments

- MRI scans were obtained at baseline and annually thereafter, and analyzed centrally at NeuroRx Research (Montréal, Canada) by experts masked to treatment group assignment
- BVL was derived by BPF change, and scans were read by Cleveland Clinic (Cleveland, OH, USA)
- BVL was compared in patient subgroups stratified by baseline median BPF value
  - Subgroup analysis was performed on patients with available BPF value at baseline

Statistical Analyses

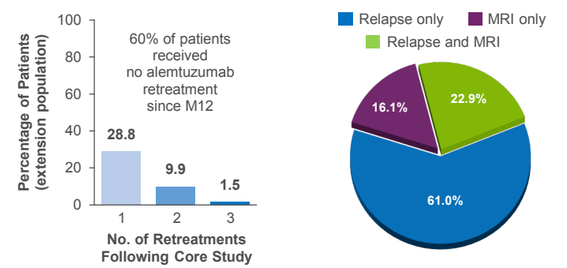
- Percentage changes in BPF were analyzed using the Wilcoxon signed rank test
- Interim analyses were based on all available data through Year 3 of the ongoing extension study

RESULTS

Patients

- A total of 435 patients received alemtuzumab 12 mg in CARE-MS II; of the 423 alemtuzumab patients who completed CARE-MS II, 393 (93%) patients entered the extension study
- Of those patients who enrolled in the extension, 357 (91%) remained on study through Month 60 (Year 5)
- Through 5 years, 218 (55%) patients did not receive retreatment with alemtuzumab or other DMT since the initial 2 courses at core study baseline and Month 12
  - 235 (60%) patients did not receive retreatment with alemtuzumab (**Figure 2A**); of those patients who received alemtuzumab retreatment, relapse was the most common reason given by the investigator (**Figure 2B**)
  - 363 (92%) patients did not receive another DMT

Figure 2. Alemtuzumab Retreatment Rate in CARE-MS II Was Low Through 5 Years

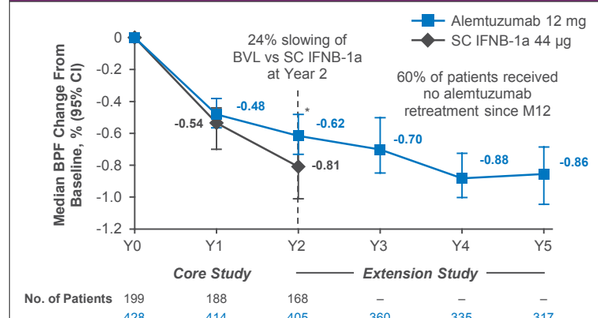


[a]No reason was provided for 4 retreatments; over 5 years, there were 209 retreatments in 158 patients
M=month

Brain Volume Change by Year

- Alemtuzumab slowed BVL by 24% over 24 months versus SC IFNB-1a at the end of the core CARE-MS II study (**Figure 3**)[1]
- The slowing of BVL in alemtuzumab patients was maintained through 5 years

Figure 3. Slowing BVL Through 5 Years in Alemtuzumab-Treated Patients

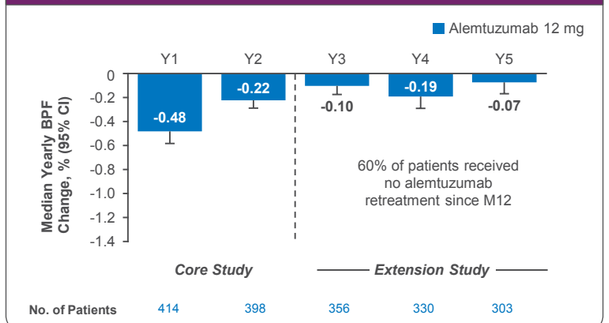


No. of Patients	Y0	Y1	Y2	Y3	Y4	Y5
	199	188	168	–	–	–
	428	414	405	360	335	317

*Alemtuzumab vs SC IFNB-1a, *P*=0.0121

- Median yearly BVL was decreased at Year 2 in CARE-MS II alemtuzumab-treated patients and this decrease was maintained through Year 5 (**Figure 4**)

Figure 4. Median Yearly BVL in Alemtuzumab-Treated Patients Remained Low Through 5 Years

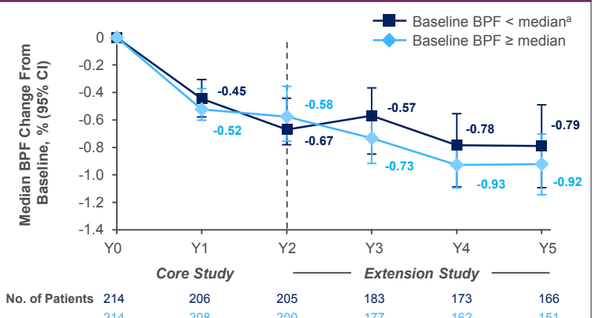


No. of Patients	Y1	Y2	Y3	Y4	Y5
	414	398	356	330	303

BVL by Baseline Subgroup

- Comparison of BVL in subgroups stratified by baseline median BPF revealed that baseline BPF status had no impact on BVL through Year 5 (**Figure 5**) or median yearly BVL (**Figure 6**)

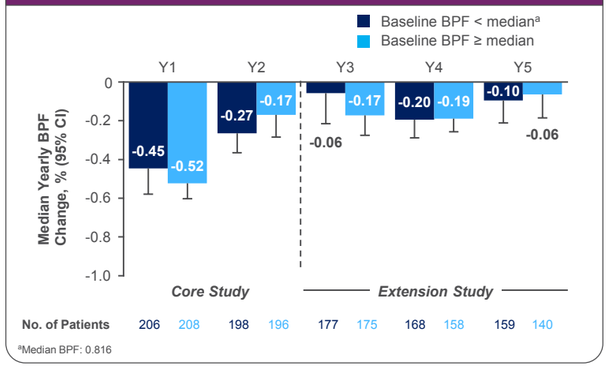
Figure 5. Baseline BPF Did Not Impact BPF Change From Baseline Through 5 Years in Alemtuzumab-Treated Patients



No. of Patients	Y0	Y1	Y2	Y3	Y4	Y5
	214	206	205	183	173	166
	214	208	200	177	162	151

[a]Median BPF: 0.816

Figure 6. Baseline BPF Did Not Impact Median Yearly BPF Change Through 5 Years in Alemtuzumab-Treated Patients



No. of Patients	Y1		Y2		Y3		Y4		Y5	
	206	208	198	196	177	175	168	158	159	140

[a]Median BPF: 0.816

CONCLUSIONS

- **Alemtuzumab slowed BVL through Year 5 in patients with active RRMS who had an inadequate response to prior therapy at baseline**
  - **For the overall alemtuzumab-treated population, median annual BVL was ≤0.22% in Years 2, 3, 4, and 5**
  - **Baseline BPF did not impact BVL through 5 years**
- **Most patients did not receive alemtuzumab retreatment after the initial 2 courses in the core study through Year 5**
- **Based on these findings, alemtuzumab may provide a unique treatment approach with durable efficacy through 5 years in the absence of continuous treatment for RRMS patients**

References

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Alemtuzumab is approved in many countries around the world for treatment of adults with relapsing forms of MS. In the US, the indication provides that, because of its safety profile, the use of alemtuzumab should be reserved for patients who generally have had an inadequate response to 2 or more therapies indicated for the treatment of MS. In the EU, it is approved to treat patients with relapsing-remitting MS with active disease defined by clinical or imaging features. This material may contain information that is outside of the approved labeling in some countries.

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