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Efficacy and Safety of Alemtuzumab in Patients With RRMS Is Durable Over 10 Years: Follow-up From the CAMMS223 Study

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OBJECTIVE

- **To evaluate the 10-year efficacy and safety profile of alemtuzumab 12 mg in RRMS patients from the phase 2 CAMMS223 study who entered the CAMMS03409 extension study**

INTRODUCTION

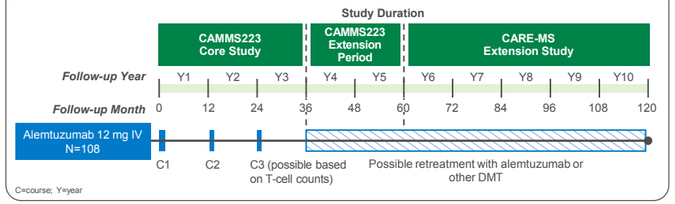
- Alemtuzumab is a humanized monoclonal antibody approved in >60 countries for the treatment of RRMS
- In the phase 2 CAMMS223 trial (NCT00050778), patients with active RRMS who were treatment-naive at baseline demonstrated greater improvements in clinical and MRI outcomes with alemtuzumab compared with SC IFNB-1a[1]
- Five-year data from the CAMMS223 study demonstrated durable efficacy of alemtuzumab in the absence of continuous treatment; notably, most patients did not receive alemtuzumab 12-mg retreatment or other disease-modifying therapy (DMT)[2]
- The most frequent adverse events (AEs) observed with alemtuzumab were infusion-associated reactions (IARs); other AEs of interest included autoimmune AEs[1,2]
- The durable effects of alemtuzumab in the absence of continuous treatment may be due to its selective depletion and repopulation of circulating CD52-expressing T and B lymphocytes[3,4]
  - Following depletion, a distinct pattern of T- and B-cell repopulation begins within weeks, including a relative increase of regulatory T cells and a decrease in proinflammatory cytokines; these pharmacological effects potentially lead to a rebalancing of the immune system[5,6]
  - The exact mechanism of action of alemtuzumab is not known

METHODS

Patients and Procedures

- CAMMS223 was a phase 2, randomized, active-controlled, rater-blinded, 3-year study of alemtuzumab versus SC IFNB-1a (44 µg 3×/week) in treatment-naive patients with active RRMS[1]
  - Patients randomized to alemtuzumab received up to 2 annual courses of 12 mg/day IV (on 5 consecutive days at baseline and on 3 consecutive days 12 months later)
  - In the core study, a third course was possible ≥12 months after the last course, based on T-cell counts
- Patients could participate in an extended follow-up period (minimum additional 2 years) in the CAMMS223 study[2]
  - Retreatment criteria in the extension period were not contingent on evidence of disease activity in all patients
- CAMMS223 patients could then enroll in the same extension study (CAMMS03409 [NCT00930553]) as patients who completed the phase 3 CARE-MS I and CARE-MS II studies, in which they could receive additional alemtuzumab (12 mg on 3 consecutive days ≥1 year after the most recent course; **Figure 1**)[7]
  - Retreatment criteria in the CARE-MS I and II extension study 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
- In the CARE-MS extension study, use of other DMTs was permitted at the investigator's discretion

Figure 1. CAMMS223 and Extension Study Design



Assessments

- Annualized relapse rate (ARR)[a]
- Disability outcomes:
  - Proportion of patients with 6-month confirmed disability worsening (CDW; ≥1-point EDSS increase [or ≥1.5 points if baseline EDSS=0])
  - Mean EDSS scores over time
  - Proportion of patients with improved (≥1-point decrease) or stable (≤0.5-point change) EDSS scores from core study baseline
- Proportion of patients with Gd-enhancing lesions
- Lymphocyte dynamics
  - The kinetics of T- and B-lymphocyte depletion and repopulation were assessed in patients who received the original 2 courses of alemtuzumab and in those who received up to 3 retreatments
  - Blood counts were tested monthly, and lymphocytes were phenotyped by flow cytometry quarterly, and at Months 1 and 13
- Safety was evaluated by review of AEs, serious AEs, medical events of interest, and laboratory tests

Statistical Analysis

- **CAMMS223:** These interim analyses were based on all available data through Year 5 of the CARE-MS extension study (10 total years of follow-up) for those patients who received alemtuzumab 12 mg in the core CAMMS223 study
- **Commercial exposure and post-marketing data:** The frequency of autoimmune AEs in real-world use was estimated using post-marketing safety reports and commercial sales data through February 2017
  - Post-marketing safety data were coded and searched for specific MedDRA Preferred Terms to identify reports of selected autoimmune AEs
  - Frequency rates based on post-marketing safety reports do not have the same precision as clinical trial incidence rates due to limitations associated with post-marketing reporting

CONCLUSIONS

- **Alemtuzumab demonstrated durable clinical efficacy over 10 years in the absence of continuous treatment**
  - **ARR remained low and most patients had improved (≥1-point decrease) or stable (≤0.5-point change) EDSS scores at Year 10 relative to baseline**
  - **The proportion of patients with Gd-enhancing lesions was low in extension Years 1, 2, and 3**
  - **These effects may be due to the distinct pattern of lymphocyte repopulation following treatment with alemtuzumab, which may lead to a rebalancing of the immune system; additional mechanistic studies are required to establish this hypothesis**
- **These results were achieved with 95% of CAMMS223 patients who entered CAMMS03409 remaining on study; the high retention rate supports the robustness of these data**
- **Low annual retreatment rates were maintained, with most patients receiving ≤3 treatment courses**
- **Safety findings were consistent with those of other alemtuzumab clinical trials**
- **Based on these findings, alemtuzumab may provide a unique treatment approach for RRMS patients, offering durable efficacy through 10 years in the absence of continuous treatment**

RESULTS

Patients

- In CAMMS223, 92 of 108 patients who received alemtuzumab 12 mg completed 3 years of follow-up after the first treatment; 72 patients participated in the CAMMS223 2-year extended follow-up period and 60 patients entered the CARE-MS extension study
  - 57 (95%) remained on study at Year 10
- Twenty patients (33%) received only the initial 2 courses of alemtuzumab
  - 26 patients (43%) received a total of 3 alemtuzumab courses, 7 patients (12%) received a fourth course (all after Year 5), and 6 patients (10%) received a fifth course (all after Year 7)
  - Of patients who received retreatment in the CARE-MS extension study, in which retreatment criteria were based on evidence of relapse or radiological activity, relapse was the most common reason given by the investigator (13 [68%] of the 19 courses for which a reason was provided)

Efficacy

- Through 10 years of follow-up, ARR remained low (**Figure 2**)
- Mean EDSS score change from baseline to Year 10 (SD) was +0.12 (1.4) (**Figure 3**)
  - EDSS scores remained stable (≤0.5-point change) or improved (≥1-point decrease) in 78% of patients treated with alemtuzumab
- Most patients (76%) were free of 6-month CDW through 10 years
- At CAMMS223 baseline, 100% of patients had Gd-enhancing lesions
  - After alemtuzumab treatment, the majority of patients were free of Gd-enhancing lesions during the extension (CARE-MS extension baseline: 92%; CARE-MS extension Years 1, 2, and 3 were 94%, 87%, and 95%, respectively)

Pharmacodynamics

- Lymphocytes were depleted after the first course of alemtuzumab, reaching their lowest levels after 1 month; counts then repopulated
  - Depletion and repopulation were similar after up to 5 total treatments (Courses 1–3 shown in **Figure 4**)

Figure 2. Durable Effect of Alemtuzumab on Relapses Through 10 Years

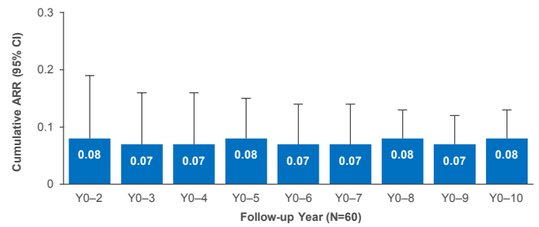


Figure 3. Disability Was Stable Through 10 Years

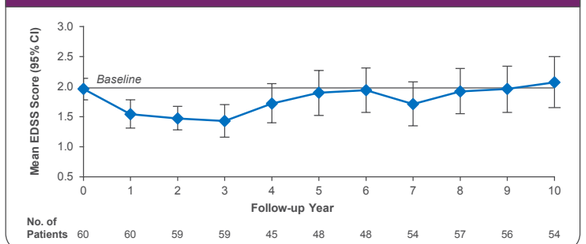
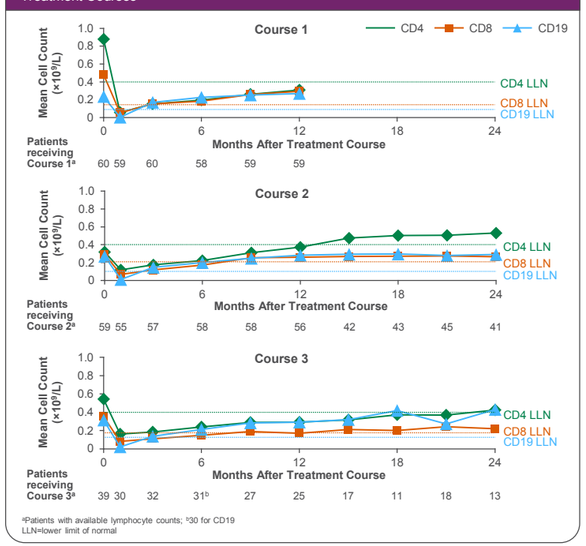


Figure 4. Lymphocyte Depletion and Repopulation Are Similar Across Alemtuzumab Treatment Courses



[a]Patients with available lymphocyte counts; [b]30 for CD19
LLN=lower limit of normal

Safety

- No patients from CAMMS223 withdrew from the CARE-MS extension study due to AEs
- AEs were most prevalent in Year 1 (98.3%) and declined through Year 5 (47.2%)
  - AE incidence increased in Years 6–10 (62%–70%), during which time patients were eligible to receive additional treatment
- The incidence of serious AEs was highest in Year 3 (13.3%)
- The most common AEs in patients who received retreatment were IARs (Course 1, 98.3%; Course 2, 79.7%; Course 3, 76.9%; Course 4, 61.5%; Course 5, 50%) and included rash, headache, pyrexia, and pruritus, the reported incidence of which decreased with additional courses
  - Three serious IARs occurred through 10 years (all in Course 3)
- Infection rate was highest during Year 1 (55.0%), declining thereafter; serious infections occurred in <4% of patients during each year
  - Of those patients who experienced infections, 78% experienced their first infection within 1 year of the last treatment course
- Thyroid AE rates peaked in Year 3 (16.7%) similar to other studies reporting long-term follow-up with alemtuzumab[8,9]
  - Serious thyroid AEs occurred in <4% of patients during each year
- There was a single case of immune thrombocytopenia (ITP) in Year 4, and no cases of nephropathy
- Two patients had malignancy events; both were melanoma (both occurring in Year 10 of follow-up)
  - One patient with a family history of melanoma had Grade 4 malignant melanoma (left foot), deemed related to study drug
  - The other patient was diagnosed with Grade 2 melanoma in situ (abdomen), not related to study drug, and resolved via surgical excision
- Five Grade 4 AEs occurred through 10 years
  - One case of adhesive ileus, diffuse serous peritonitis (Year 1), 3 cases of neutropenia (2 in Year 4, 1 in Year 5), and 1 case of malignant melanoma stage IIB (Year 10)
- One death occurred in the CAMMS223 cohort during the extension study: hemorrhagic shock due to deep left brachial vein damage as a result of an incised wound from an accident unrelated to the study

Safety in Post-Marketing Use

- Through February 2017, ~13,000 patients have been treated worldwide with alemtuzumab for MS
- Post-marketing frequency (AEs and serious AEs [SAEs]) and clinical trial incidence (SAEs only) of key autoimmune events are presented in **Table 1**
- The post-marketing frequency of autoimmune AEs has generally been lower than expected based on the incidence observed in clinical trials
  - Compared with the clinical trial incidence, the post-marketing frequency of neutropenia was higher than the incidence of serious neutropenia events, but lower than the incidence including non-serious neutropenia (2-year incidence: alemtuzumab, 1.7%; SC IFNB-1a, 4.0%)
- Post-marketing frequencies are not directly comparable to clinical trial incidences because of differences in ascertainment methodology and follow-up duration, and limitations of post-marketing reporting
  - Post-marketing reports may include non-serious cases, most cases cannot be confirmed, diagnosis may be inaccurate, there may be duplicate cases or under-reporting, and the amount of clinical detail available is often very limited

Table 1. Key Autoimmune Events; Post-Marketing Frequency, and Clinical Trial Incidence Data

Autoimmune Event	Post-Marketing Estimated Frequency (AEs/SAEs) (%)	Clinical Trials SAEs Incidence (%)[a]
ITP	0.58	1.4
Hemolytic anemia	0.05	0.3
Pancytopenia	0.10	0.2
Nephropathies (including anti-glomerular basement membrane disease)	0.13	0.4
Neutropenia	0.48	0.2

[a]Pooled CAMMS223, CARE-MS I and II, and CAMMS03409 data, with median follow-up of 6.1 years (maximum 12 years)

- Since approval, labeling has included information regarding an increased frequency of infection and the potential for opportunistic infections following treatment with alemtuzumab
  - As anticipated, reports of opportunistic infections have been received in the post-marketing setting; the most commonly reported were *Listeria monocytogenes* (estimated frequency: 0.26%) and cytomegalovirus (estimated frequency: 0.13%)
  - There have been no medically confirmed reports of progressive multifocal leukoencephalopathy attributed to alemtuzumab to date
- The Sponsor performs ongoing evaluation of post-marketing safety reports from multiple sources to refine understanding of the safety and benefit:risk profile of alemtuzumab and to identify potential new safety signals
- Engagement with heath authorities occurs to ensure that alemtuzumab labels are updated to incorporate new information when clinically important:
  - As an example, the LEMTRADA EU Summary of Product Characteristics and labels around the world were updated to reflect the occurrence of *L. monocytogenes* infections following treatment with alemtuzumab and to recommend associated dietary precautions

References

1. Coles AJ, Compston DAS, Selmaj KW, et al. *N Engl J Med* 2008;359:1786-801. 2. Coles AJ, Fox EJ, Vladic A, et al. *Neurology* 2012;78:1069-78. 3. Cox AL, Thompson SAJ, Jones JL, et al. *Eur J Immunol* 2005;35:3332-42. 4. Hu Y, Turner MJ, Shields J, et al. *Immunology* 2009;128:260-70. 5. Zhang X, Tao Y, Chopra M, et al. *J Immunol* 2013;191:5867-74. 6. De Mercanti S, Rolla S, Cucci A, et al. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e194. 7. Fox EJ, Arnold DL, Cohen JA, et al. *Neurology* 2013;80:S41.001. 8. Havrdova E, Arnold DL, Cohen JA, et al. *Mult Scler* 2015;21:Platform 152. 9. Fox E, Arnold DL, Cohen JA, et al. *Mult Scler* 2015;21:P1102.

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CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis

Rebif® is a registered trademark of EMD Serono, Inc.

Previously presented at the 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 14–17, 2016, London, UK.

Alemtuzumab is approved in >60 countries around the world for the treatment of adults with relapsing forms of multiple sclerosis (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.

[a]Relapses were confirmed per the protocol by an independent, blinded relapse adjudication panel in the core study and by the investigator in the extension study.

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