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Number-Needed-to-Treat Analyses Comparing Clinical Disease Outcomes and Disability Improvement in RMS Patients Treated With Alemtuzumab or Ocrelizumab

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OBJECTIVE

- **To analyze the number needed to treat (NNT) to prevent clinical disease events and improve disability with alemtuzumab versus subcutaneous interferon beta-1a (SC IFNB-1a; CAMMS223, and CARE-MS I and II) and ocrelizumab versus SC IFNB-1a (OPERA I and II) in patients with relapsing-remitting multiple sclerosis (RRMS)**

CONCLUSIONS

- **NNT values to prevent 1 relapse, to prevent CDW, to prevent CDA, and to achieve CDI in 1 patient versus SC IFNB-1a were lower for patients receiving alemtuzumab than for patients receiving ocrelizumab**
- **NNT analyses provide indirect comparative treatment efficacy across trials based on absolute risk reduction versus relative risk reduction, which may be impacted by overall event rates and differences in disease severity between populations[1]**
- **Further data derived from real-world clinical experience will be important to confirm these findings**

INTRODUCTION

- In the absence of head-to-head trials, NNT values may be used to indirectly compare efficacy of disease-modifying therapies (DMTs) across studies[1,2]
- NNT is a well-established, scientifically valid, evidence-based approach for indirect efficacy comparisons across studies that may aid in informing clinical decisions[1]
- Alemtuzumab (a humanized anti-CD52 monoclonal antibody) and ocrelizumab (a humanized anti-CD20 monoclonal antibody) have demonstrated statistically significant improvements in clinical efficacy outcomes in active RRMS patients against the same comparator, SC IFNB-1a, in randomized clinical trials over 2 or 3 years or 96 weeks[3-6] (CAMMS223 [NCT00050778]; CARE-MS I [NCT00530348]; CARE-MS II [NCT00548405]; OPERA I [NCT01247324]; OPERA II [NCT01412333]); both are approved in the USA for patients with RRMS
- Alemtuzumab-treated CARE-MS patients who were followed up for an additional 5 years in 2 extension studies (CAMMS03409 [NCT00930553] and TOPAZ [NCT02255656]) experienced durable efficacy in the absence of continuous treatment; 59% of CARE-MS I and 47% of CARE-MS II patients did not receive additional alemtuzumab or other DMT[7-11]
- The durable effects of alemtuzumab over 7 years in the absence of continuous treatment may be due to its selective depletion and repopulation of circulating CD52-expressing T and B lymphocytes[12,13]
  - Following depletion, a relative increase in regulatory T cells and a decrease in proinflammatory cytokines occurs, potentially leading to a rebalancing of the immune system[14,15]
  - The exact mechanism of action of alemtuzumab is not fully elucidated
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions (IARs); other AEs of interest included autoimmune AEs[3-5]
- Ocrelizumab demonstrated significantly higher efficacy than placebo and intramuscular IFNB-1a over 24 weeks in a phase 2 trial (NCT00676715) and than SC IFNB-1a over 96 weeks in 2 phase 3 trials in patients with RRMS; a majority of phase 3 patients did not receive treatment in 2 years prior to screening[6,16]
- Ocrelizumab selectively targets CD20-positive B lymphocytes for depletion by enhanced antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, antibody-dependent phagocytosis, and apoptosis[17]
  - The precise mechanism of action of ocrelizumab is unknown
- Infections and IARs were the most frequently reported AEs with ocrelizumab; other AEs of interest included increased frequencies of malignancy[6]

METHODS

Patients and Procedures

- CAMMS223, CARE-MS I and II, and OPERA I and II were randomized, clinical studies of alemtuzumab or ocrelizumab versus SC IFNB-1a (44 µg 3×/week) in patients with active RRMS (**Table 1**)[3-6]

Analysis Populations

- All analyses were post hoc
  - 2-year data from CAMMS223 and CARE-MS I were pooled as the patient populations in both studies were treatment-naive and the study designs were similar
  - OPERA I and II data were not pooled with the phase 2 data due to study design differences[16]

Calculation of NNT

- NNT values were derived from post hoc analyses using published data[3-6]
- NNT values were rounded upward to an integer value; a lower NNT indicates a therapeutic intervention with greater benefit
- NNT values to prevent 1 relapse, to prevent clinical disease activity (CDA) in 1 patient, and to achieve confirmed disability improvement (CDI) in 1 patient, versus treatment with SC IFNB-1a were calculated as the reciprocal of the absolute risk difference (ARD) between the investigational group (alemtuzumab or ocrelizumab, p_i) and the comparator group (SC IFNB-1a, p_c)
  - NNT=1/ARD; ARD = $p_i - p_c$
- NNT values to prevent 1 patient from experiencing confirmed disability worsening (CDW) versus treatment with SC IFNB-1a were calculated with an Altman derivation[18] using the estimated proportion of progression events from Kaplan-Meier curves at 2 years (CAMMS223/CARE-MS I and II), and 96 weeks (OPERA I and II)
  - NNT=1/{[$S_c(t)$]^h-$S_c(t)$}, where $S_c(t)$=1 minus the probability of disability progression confirmed for 6 months (CAMMS223, CARE-MS I and II) or 24 weeks (OPERA I and II) in the SC IFNB-1a group, and h is the hazard ratio (calculated using a Cox model) of the investigational group versus the same comparator group (SC IFNB-1a)[18]

Table 1. CAMMS223, CARE-MS I and II, and OPERA I and II Study Designs

	Alemtuzumab			Ocrelizumab	
	CAMMS223[3]	CARE-MS I[4]	CARE-MS II[5]	OPERA I[6]	OPERA II[6]
Design	Phase 2, randomized (1:1), head-to-head, active-controlled, rater-blinded	Phase 3, randomized (2:1), head-to-head, active-controlled, rater-blinded		Phase 3, randomized (1:1), head-to-head, double-blind, double-dummy	
Patient population	Active RRMS in patients who were treatment-naive at baseline		Active RRMS with inadequate response to prior therapy	Active RRMS patients	
Study duration	3 years[a]	2 years		96 weeks	
Intervention	Alemtuzumab 12 mg/day IV (baseline: 5 consecutive days; 12 months later: 3 consecutive days)[b,c] vs SC IFNB-1a (44 µg 3×/week)			Ocrelizumab 300 mg IV on Days 1 and 15, then 600 mg IV at Weeks 24, 48, and 72 vs SC IFNB-1a (44 µg 3×/week)	
Primary outcomes	ARR 6-month CDW[d]			ARR	
Key secondary outcomes	• Proportion of relapse-free patients	• Proportion of relapse-free patients • Change from baseline in EDSS		• 12- and 24-week CDW[e] (pooled OPERA I/II)	

[a]Only outcomes through Year 2 were included in NNT analyses; [b]A third alemtuzumab treatment course was possible ≥12 months after the last course, based on T-cell counts; only Courses 1 and 2 were included in the NNT analyses; [c]Outcomes from patients in CAMMS223 and CARE-MS II who were randomized to receive alemtuzumab 24 mg/day IV were not included in the NNT analyses; [d]CDW previously termed sustained accumulation of disability in the cited reference; [e]CDW termed confirmed disability progression in the cited reference

RESULTS

Patients

- A total of 786 CAMMS223/CARE-MS I, 628 CARE-MS II, 821 OPERA I, and 835 OPERA II patients were included in the NNT analyses
- Within studies, patients were well matched for demographic characteristics including age, sex, and history of relapse[3-6,19]
- Baseline mean Expanded Disability Status Scale (EDSS) scores (CAMMS223/CARE-MS I: 2.0; CARE-MS II: 2.7; OPERA I: 2.9; OPERA II: 2.8); mean MS disease duration (CAMMS223/CARE-MS I: 1.9 years; CARE-MS II: 4.5 years; OPERA I and II: 6.7 years each) and mean number of relapses in the previous 2 years (CAMMS223/CARE-MS I: 2.5; CARE-MS II: 2.8; OPERA I/II: 1.8 in each study) varied across studies[3-6,19]

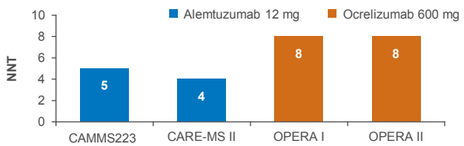
NNT Comparisons

- NNT values with alemtuzumab versus SC IFNB-1a were lower than the NNT values with ocrelizumab versus SC IFNB-1a to:
  - Prevent 1 relapse (**Figure 1**)
  - Prevent 6-month CDW in 1 patient (**Figure 2**)
  - Prevent CDA in 1 patient (**Figure 3**)
  - Achieve CDI in 1 patient (**Figure 4**)

Limitations

- Annualized relapse rates (ARRs) in SC IFNB-1a-treated patients were higher in alemtuzumab trials versus ocrelizumab trials, which may impact the NNT calculations
- Analyses were post hoc using data from published sources; differences in the number of decimal places used to report outcomes between studies may influence the size of the calculated NNT
- Differences across studies in patient populations, study sites, and trial designs

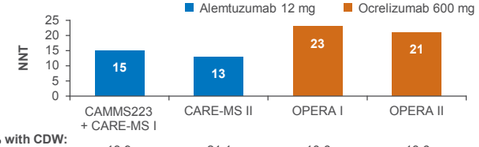
Figure 1. NNT to Prevent 1 Relapse



	CAMMS223 + CARE-MS I	CARE-MS II	OPERA I	OPERA II
ARR with SC IFNB-1a	0.358	0.520	0.292	0.290
ARR with alemtuzumab or ocrelizumab	0.151*	0.260*	0.156*	0.155*
Absolute risk difference	0.207	0.260	0.136	0.135

*P<0.0001

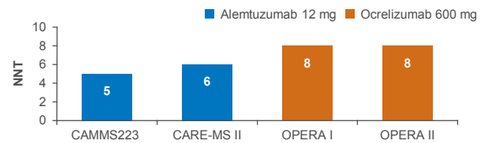
Figure 2. NNT to Prevent 6-Month CDW in 1 Patient



	CAMMS223 + CARE-MS I	CARE-MS II	OPERA I	OPERA II
% with CDW: SC IFNB-1a	13.9	21.1	10.6	13.6
% with CDW: alemtuzumab or ocrelizumab	7.1*	12.7†	6.5‡	8.6§
Absolute risk difference	6.8	8.4	4.1	5.0

CDW: ≥1-point EDSS score increase (or ≥1.5 points if baseline EDSS=0) confirmed over 6 months in alemtuzumab trials[3-5]; ≥1-point EDSS increase (or ≥0.5 point if baseline EDSS >5.5) confirmed at 24 weeks through Week 96 in ocrelizumab trials[6]
*P=0.0024; †P=0.0084; ‡P=0.03; §P=0.04

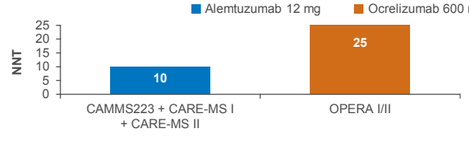
Figure 3. NNT to Prevent CDA in 1 Patient



	CAMMS223 + CARE-MS I	CARE-MS II	OPERA I	OPERA II
% with CDA: SC IFNB-1a	44.6	58.9	37.0	41.0
% with CDA: alemtuzumab or ocrelizumab	24.0*	40.4*	24.0†	27.0†
Absolute risk difference	20.6	18.5	13.0	14.0

CDA: relapse or 6-month CDW[3-5] in alemtuzumab trials and relapse or 24-week CDW in ocrelizumab trials[6]
*P<0.0001; †P-value not available

Figure 4. NNT to Achieve 6-Month CDI in 1 Patient



	CAMMS223 + CARE-MS I + CARE-MS II	OPERA I/II
% with CDI: SC IFNB-1a	16.9	11.6
% with CDI: alemtuzumab or ocrelizumab	27.7*	15.6†
Absolute risk difference[a]	10.8	4.0

CDI: ≥1-point decrease in EDSS score from baseline (patients with baseline score ≥2.0) confirmed over 6 months[3-5]; ≥1-point EDSS decrease (or ≥0.5 point if baseline EDSS >5.5) confirmed at 24 weeks through Week 96 in ocrelizumab trials[6]
[a]CAMMS223/CARE-MS I/CARE-MS II and OPERA I/II were pooled due to a lack of CDI time-to-event analysis for ocrelizumab; Naive absolute risk difference used due to lack of ocrelizumab time-to-event analysis for this endpoint; Only a naive percentage was reported for OPERA I and II patients and a Cochran-Mantel-Haenszel chi-squared test was used for treatment group comparisons
*P=0.0002; †P=0.03

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

OPERA trials are part of the ORCHESTRA clinical development program for ocrelizumab in RRMS (OPERA I and II) and ocrelizumab in primary progressive multiple sclerosis (ORATORIO).

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Alemtuzumab is approved in >65 countries around the world for 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.

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