DX07

Durable Clinical Improvements With Alemtuzumab in RRMS Patients in the Absence of Continuous Treatment: 7-Year Follow-up of CARE-MS II Patients (TOPAZ Study)

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OBJECTIVE

- **To evaluate the efficacy and safety of alemtuzumab 12 mg over 7 years in RRMS patients from the CARE-MS II core study who entered the CARE-MS extension and TOPAZ studies**

CONCLUSIONS

- **Alemtuzumab demonstrated clinical efficacy through Year 7 in patients with active RRMS who had an inadequate response to prior therapy**
  - **The majority of patients maintained a low ARR, showed stabilized or improved disability, and achieved NEDA in each year**
- **The robustness of these results is supported by the high retention rate (73%) from core study baseline, and is further underscored by the observation that 47% of patients received no additional alemtuzumab courses and no other DMTs in the extension through Year 7**
- **Alemtuzumab had a consistent safety profile through Year 7, and the overall incidence of AEs decreased over time**

INTRODUCTION

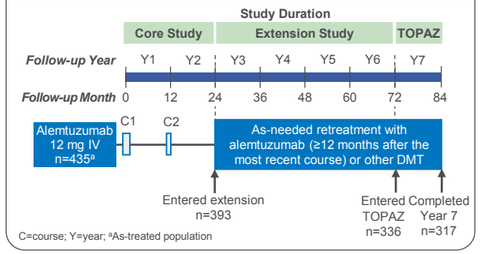
- In CARE-MS II (NCT00548405), 2 courses of alemtuzumab demonstrated significantly greater improvements in clinical and MRI outcomes versus SC IFNB-1a over 2 years[1]
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions (IARs); other AEs of interest included autoimmune AEs[1]
- Alemtuzumab-treated patients who were followed up for an additional 4 years in an extension study (NCT00930553) experienced efficacy in the absence of continuous treatment; 50% of patients did not receive additional alemtuzumab or other disease-modifying therapy (DMT) over 6 years after the initial 2 courses[2-4]
- The effects of alemtuzumab may be due to its selective depletion and distinct pattern of repopulation of circulating CD52-expressing T and B lymphocytes[5,6]
  - 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[7,8]
  - The exact mechanism of action of alemtuzumab is not fully elucidated
- Patients completing the extension study could enroll in the 5-year TOPAZ study (long-Term follow-up study for multiple sclerOsis Patients who have completed the AlemtuZumab extension study; NCT02255656) for further evaluation

METHODS

Patients and Treatment

- In CARE-MS II, patients with active RRMS and an inadequate response to prior therapy received 2 annual courses of alemtuzumab 12 mg/day IV (on 5 consecutive days at baseline and on 3 consecutive days 12 months later)
- In the extension study, patients could receive additional treatment with alemtuzumab (12 mg/day on 3 consecutive days ≥12 months after the most recent course) as needed for relapse or MRI activity, or receive other licensed DMTs at the investigator's discretion
- In TOPAZ, patients can receive alemtuzumab retreatment (12 mg/day on 3 consecutive days ≥12 months after the most recent course) or other DMT at any time point, both at the investigator's discretion (no criteria)

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



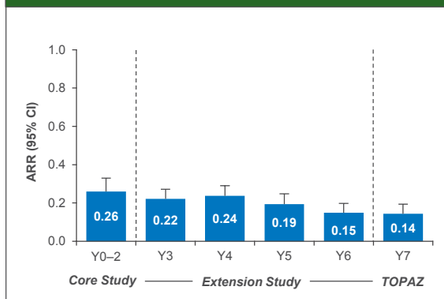
C=course; Y=year; [a]As-treated population

RESULTS

Patients and Retreatment

- 317 (73%) patients remained on study from core study baseline until end of Year 7 (data cutoff date: October 4, 2016; **Figure 1**)
- Of the 393 patients who entered the extension study
  - 185 (47%) received no additional treatment (no additional alemtuzumab courses and no other DMTs) in the extension through Year 7
  - 206 (52%) received no alemtuzumab retreatment
  - 347 (88%) received no other DMT
  - 112 (28%) received 1 alemtuzumab retreatment through Year 7, 58 (15%) received 2 retreatments, 9 (2%) received 3 retreatments, 6 (1.5%) received 4 retreatments, and 2 (0.5%) received 5 retreatments
- Most common reasons for retreatment included relapse (57%), MRI activity (19%), and both relapse and MRI activity (21%)

Figure 2. Effect of Alemtuzumab on Relapses

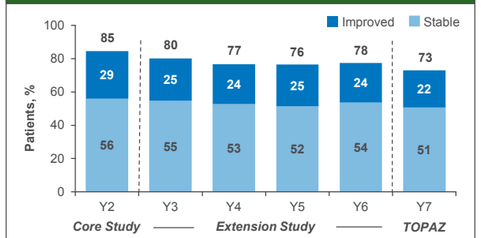


ARR was estimated using a negative binomial model

Clinical Efficacy

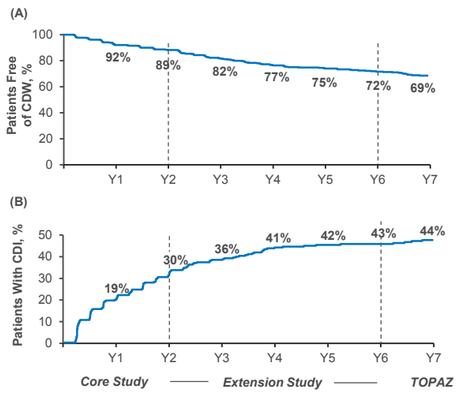
- Alemtuzumab-treated patients maintained a low annualized relapse rate (ARR) over 7 years (**Figure 2**), with a cumulative ARR (Years 3–7) of 0.19 (95% CI, 0.17–0.22)
  - 51% of patients were relapse-free in Years 3–7
- At Year 7, 73% of patients had improved or stable Expanded Disability Status Scale (EDSS) scores compared with baseline (improved, 22%; stable, 51%; **Figure 3**); the mean change in EDSS score from baseline to Year 7 was 0.17
- Through Year 7, 69% were free of 6-month confirmed disability worsening (CDW; **Figure 4A**); 44% experienced 6-month confirmed disability improvement (CDI; **Figure 4B**)
- The majority of patients achieved no evidence of disease activity (NEDA) in each year (**Figure 5**); 20% achieved NEDA sustained over Years 3–7

Figure 3. Majority of Patients Had Improved or Stable EDSS Scores Over 7 Years



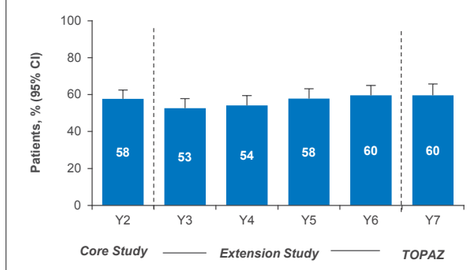
Sum of percentages may differ due to rounding; Improved EDSS score: ≥1.0-point decrease from core study baseline; Stable EDSS score: ≤0.5-point change in either direction from core study baseline

Figure 4. Patients (A) Free of 6-Month CDW and (B) Achieving 6-Month CDI



Kaplan-Meier estimates were used to assess proportions of patients with 6-month CDW and 6-month CDI; CDW: ≥1.0-point EDSS increase (or ≥1.5 points if baseline EDSS=0) confirmed over 6 months; CDI: ≥1.0-point EDSS decrease from baseline confirmed over 6 months; CDI is assessed only in patients with baseline EDSS score ≥2.0

Figure 5. Majority of Patients Achieved NEDA in Each Year



	Y2	Y3	Y4	Y5	Y6	Y7
Free of clinical disease activity	73%	76%	74%	79%	85%	85%
Free of MRI disease activity	76%	68%	70%	68%	69%	67%

NEDA: absence of clinical disease activity (relapses and 6-month CDW) and MRI disease activity (new gadolinium-enhancing T1 and new/enlarging T2 hyperintense lesions)

Safety

- The incidence of AEs was reduced in Years 3–7 compared with the core study (Years 1–2), and declined over time (**Table 1**)
  - Thyroid AE incidence peaked in Year 3 as reported previously, and declined subsequently through Year 7; cumulative thyroid incidence in Years 1–7 was 43%
  - No immune thrombocytopenia events occurred outside the 48-month monitoring period following the last alemtuzumab dose
  - One renal genitourinary (anti-glomerular basement membrane type IV positive; asymptomatic) event was reported, which was assessed as treatment-related; no corrective treatment was administered, and the event had not been resolved at most recent known follow-up (8 days after the event); further follow-up for details and confirmation of the diagnosis is ongoing
  - The incidence of malignancies was <1% per year through 7 years
  - The incidence of infections declined from Years 4–7; the incidence of serious infections was <3.5% per year through 7 years
- Through Year 7, the most commonly reported AEs were IARs, the incidence of which declined after the first course of alemtuzumab (Course 1: 84%; Course 2: 71%; and Course 3: 61%); IARs were reported in 50, 9, and 5 patients after Courses 4, 5, and 6, respectively, and in 1 patient after Course 7
  - The incidence of serious IARs was low (Course 1: 1.4%; Course 2: 1.4%; and Course 3: 1.1%); 1 patient had a serious IAR after Course 4, and no patients reported serious IARs after Courses 5, 6, and 7; no alemtuzumab patients discontinued from the extension study or TOPAZ due to IARs
- Two deaths were reported in Year 7 that were assessed as not related to alemtuzumab (one case of suicide occurring approximately 40 months after the last dose of alemtuzumab; and one death due to an unknown cause [patient was found dead at home; study period was not completed per protocol at time of death; autopsy was performed but results were not provided])

Table 1. Incidence of AEs by Year

	Incidence, %							Exposure-Adjusted Incidence Rate Per 100 Patient-Years[a]		
	Y1 (N=435)	Y2 (N=434)	Y3 (N=412)	Y4 (N=387)	Y5 (N=367)	Y6 (N=357)	Y7 (N=336)	Y0–2 (N=435)	Y3–7 (N=412)	Y0–7 (N=435)
Any AE	94.7	92.6	83.3	81.4	79.8	77.0	62.2	871.4	179.8	673.0
Serious AEs	12.6	9.9	10.2	14.5	10.4	9.0	9.5	11.1	9.7	9.3
AEs excluding IARs	85.7	87.3	83.0	80.6	79.8	75.9	61.3	252.5	176.0	204.1
Infections	63.2	61.8	50.0	50.6	44.7	43.7	34.2	89.0	45.8	58.5
Serious infections	2.1	1.8	1.2	2.3	1.9	1.7	3.3	1.9	1.8	1.7
Autoimmune AEs[b]										
Thyroid AEs	5.1	8.8	17.2	5.4	3.3	4.2	2.4	7.3	9.3	9.6
Serious thyroid AEs	0	0.5	3.2	1.3	0	0.3	0.3	0.2	1.2	0.9
Immune thrombocytopenia	0.2	0.7	0.5	1.8	0.3	0.6	0	0.5	0.7	0.6
Nephropathies	0	0.2	0	0	0	0	0.3	0.1	0.1	0.1
Malignancies	0	0.5	0.5	0	0	0.6	0.3	0.2	0.2	0.2

[a]Exposure-adjusted incidence rate=(Number of patients with first AE in the time interval)/(Total follow-up duration [year] of all patients within the time interval, censoring at the time of AE for patients counted in the numerator)
[b]First occurrence of AE for a patient

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TOPAZ=a long-Term follow-up study for multiple sclerOsis Patients who have completed the AlemtuZumab extension study
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