Long-term Efficacy of Ofatumumab in Patients With Relapsing Multiple Sclerosis

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1

Disclosures

Stephen Hauser serves on the board of trustees for Neurona and serves on scientific advisory boards for Accure, Alector and Annexon, received travel reimbursement and writing assistance for CD-20 related meeting and presentations from Roche and Novartis.

Edward Fox has received fees for consulting, contracted research, speaker's bureau and advisory work from Biogen, Celgene, Chugai, EMD Serono, Genentech/Roche, MedDay, Novartis, Sanofi, Genzyme, Teva; contracted research and advisory work for TG Therapeutics.

Angela Aungst has nothing to disclose.

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Derrick Robertson has received fees for consulting, contracted research and speaker's bureau from Biogen, Celgene, EMD Serono, Genentech, Sanofi Genzyme, Janssen, TG therapeutics; consulting fees and speakers bureau for Bristol Myers Squibb, Horizon, and Alexion; consulting fees and contracted research for Novartis; consulting fees for Greenwich biosciences; contracted research for GW Pharmaceuticals, PCORI, Atara Biotherapeutics and CorEvitas.

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Ludwig Kappos has received consultancy fees from Actelion, Bayer HealthCare, Biogen, BMS, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Santhera, and TG therapeutics; contracted research from Bayer HealthCare, Biogen, European Union, InnoSwiss, Merck, Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation; speaker fees from Bayer HealthCare, Biogen, Merck, Novartis, Roche, and Sanofi; serves on the steering committee for Actelion, Bayer HealthCare, Biogen, BMS, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Santhera, TG Therapeutics; Support of educational activities from Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire, and Teva; License fees for Neurostatus products

- Early initiation of high-efficacy therapies for the treatment of relapsing multiple sclerosis (RMS) has been shown to improve long-term outcomes versus initiating, or escalating from, lower efficacy therapies[1–3]

- The high-efficacy therapy ofatumumab, is a fully human anti-CD20 monoclonal antibody with a 20 mg subcutaneous monthly dosing regimen[4] and is approved in 69 countries for treating RMS in adults

- The Phase 3 ASCLEPIOS I/II trials demonstrated the superiority of ofatumumab compared to teriflunomide in reducing the annualized relapse rate (ARR), suppressing MRI lesion activity and delaying disability worsening, while maintaining a favorable safety profile in patients with RMS[4,5]

- Assessment of the long-term efficacy and safety of ofatumumab is important to further understand its benefit-risk profile in patients with RMS

  o The long-term safety of ofatumumab is being discussed separately at this congress in the platform presentation S14.004 and poster P7.011

ARR, annualized relapse rate; MRI, magnetic resonance imaging; RMS, relapsing multiple sclerosis.

1. He A, et al. *Lancet Neurol*. 2020;19:307–316; 2. Harding K, et al. *AMA Neurol*. 2019;76:536–541; 3. Iaffaldano P, et al. *Ther Adv Neurol Disord*. 2021;14:17562864211019574; 4. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed March 29, 2022); 5. Hauser SL, et al. *N Engl J Med*. 2020;383:546–57.

To assess the long-term efficacy of ofatumumab treatment for up to 4 years* in patients with RMS in the ongoing ALITHIOS open-label extension study

*Data cut-off: 25-Sep-2021.
RMS, relapsing multiple sclerosis.

Background | Objectives | Methods | Results | Conclusions

- Annualized relapse rate (ARR)

- 3- and 6-month confirmed disability worsening (3mCDW, 6mCDW)

  o Confirmed disability worsening is an increase from baseline in EDSS score sustained for at least 3 or 6 months

- Brain MRI outcomes

  o Mean number of Gd-enhancing T1 lesions per scan

  o Number of new or enlarging T2 lesions per year

ARR, annualized relapse rate; 3mCDW, 3-month confirmed disability worsening; 6mCDW, 6-month confirmed disability worsening; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging.

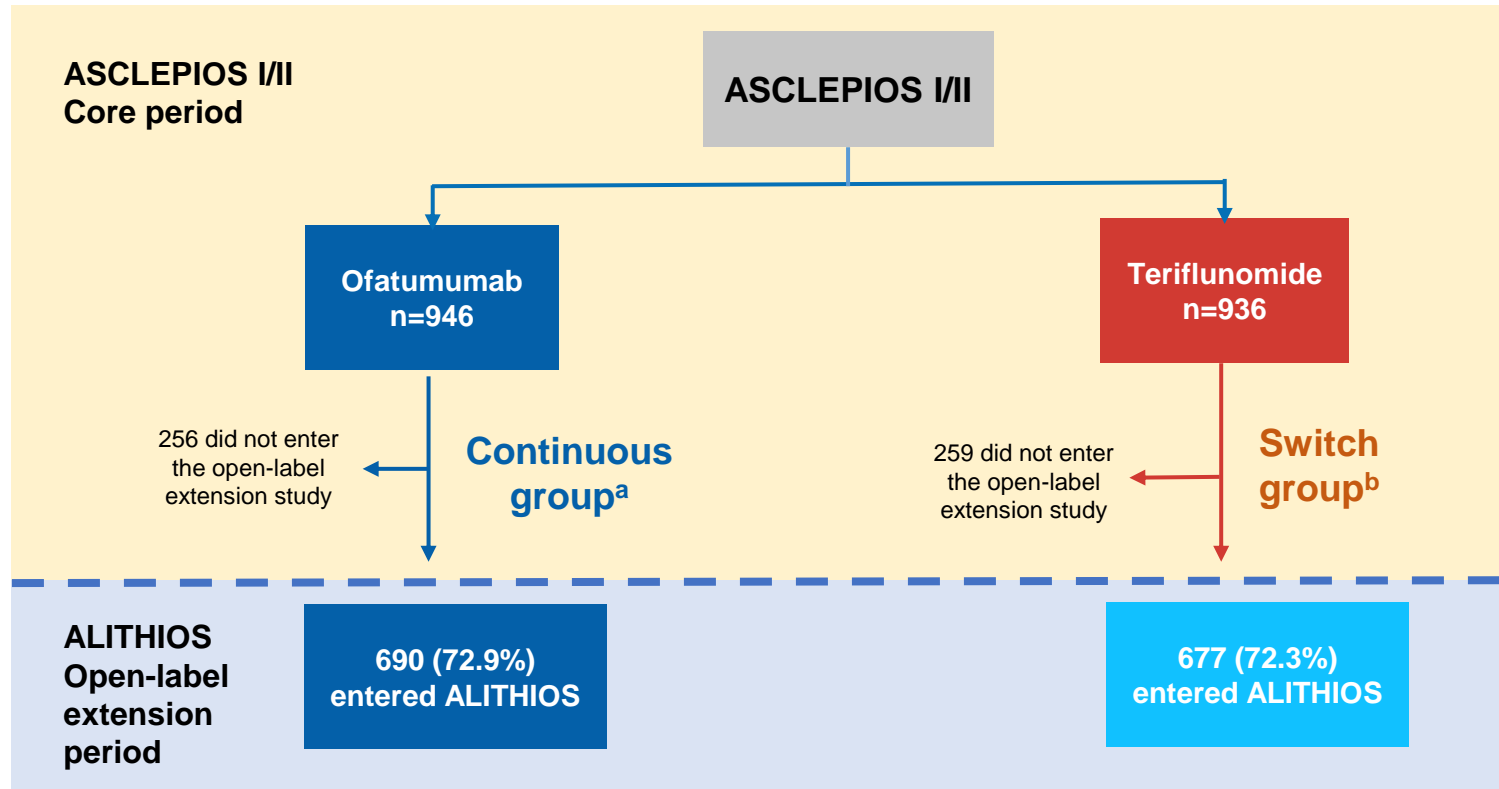**As of data cut-off*, total exposure to ofatumumab was: 2761.4 PYs in continuous group[a] and 1271.1 PYs in switch group[b]**

ASCLEPIOS I/II Core period

ASCLEPIOS I/II

Ofatumumab
n=946

Teriflunomide
n=936

256 did not enter the open-label extension study

Continuous group[a]

259 did not enter the open-label extension study

Switch group[b]

ALITHIOS Open-label extension period

690 (72.9%) entered ALITHIOS

677 (72.3%) entered ALITHIOS

- Of 1882 patients randomized in the ASCLEPIOS I/II trials, 1367 (72.6%) patients enrolled into the ALITHIOS open-label extension study and received ofatumumab for up to 4 years cumulatively

- Of these, 1214/1367 (88.8%) patients were still receiving ofatumumab treatment at the time of data cut-off*

  o The main reasons for discontinuing treatment were the occurrence of AEs (4.0%) and patient/guardian decision (4.0%)

All percentages are calculated based on the number of patients in full analysis set in the corresponding column. Dotted line represents the first dose of ofatumumab in extension phase. Core period is period before the dotted line.
Only patients from the ASCLEPIOS I/II studies are included in the analyses presented here. *Data cut-off: 25-Sep-2021; [a]randomized to ofatumumab in the core; [b]Switch group refers to the patients who were randomized to teriflunomide in the core and switched to ofatumumab during the extension phase. AE, adverse event; PY, patient-years.

| Background | Objectives | Methods | Results | Conclusions |

| Demographics and clinical characteristics[a]	Ofatumumab continuous (N=946)	Switch from teriflunomide to ofatumumab (N=936)	
		Baseline from core study (N=936)	Baseline from extension study (N=677)
Age, years	38.4±9.04	38.0±9.22	40.1±9.21
Female, n (%)	637 (67.3)	636 (67.9)	456 (67.4)
BMI, kg/m^2	25.86±6.22	25.93±6.02	25.61±5.85
Treatment-naive patients[b], n (%)	386 (40.8)	363 (38.8)	Not applicable[c]
EDSS score at baseline	2.93±1.35	2.90±1.36	2.81±1.46[d]
Number of relapses in the last 12 months prior to screening	1.2±0.69	1.3±0.71	0.2±0.49[d]
Number of Gd+ T1 lesions	1.7±4.51	1.3±3.43	0.8±2.37[d]
Total volume of T2 lesions, cm^3	13.72±13.80	12.55±13.81	Not available

[a]Values are represented as mean±SD unless specified otherwise; [b]Treatment naive patients are those who have not received a prior multiple sclerosis disease modifying therapy; [c]not applicable since all patients have been pre-treated with teriflunomide; [d]The baseline from the extension study in the ofatumumab switch from teriflunomide group reflects the teriflunomide treatment effect during the double-blind treatment phase in the ASCLEPIOS studies.

BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing.

Background   Objectives   Methods   Results   Conclusions

**Within-group comparison during
the core and extension phase**
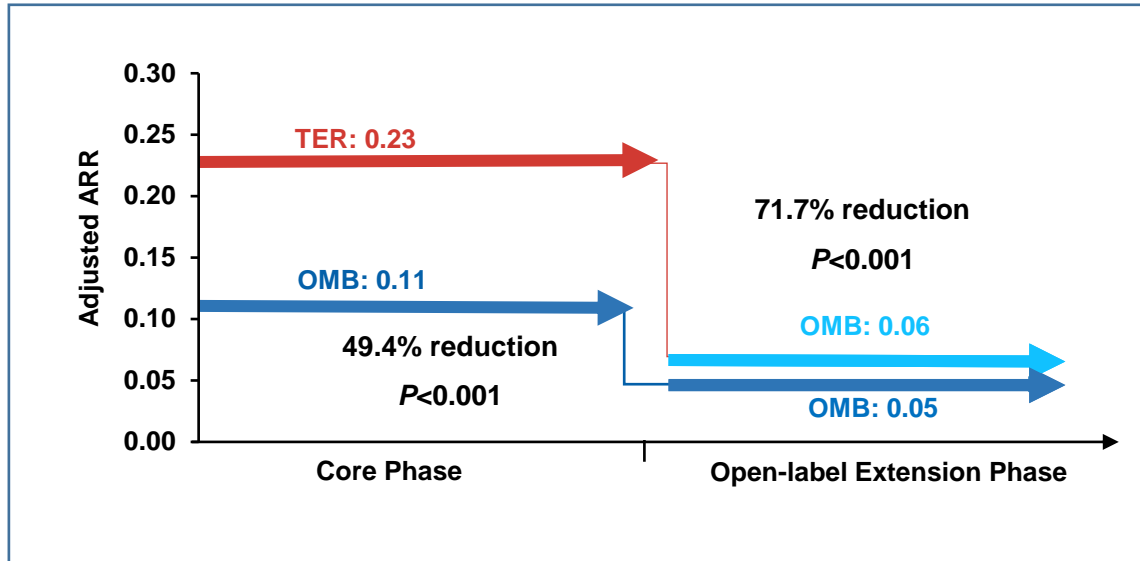
**Between-group comparison
Cumulative number of relapses**
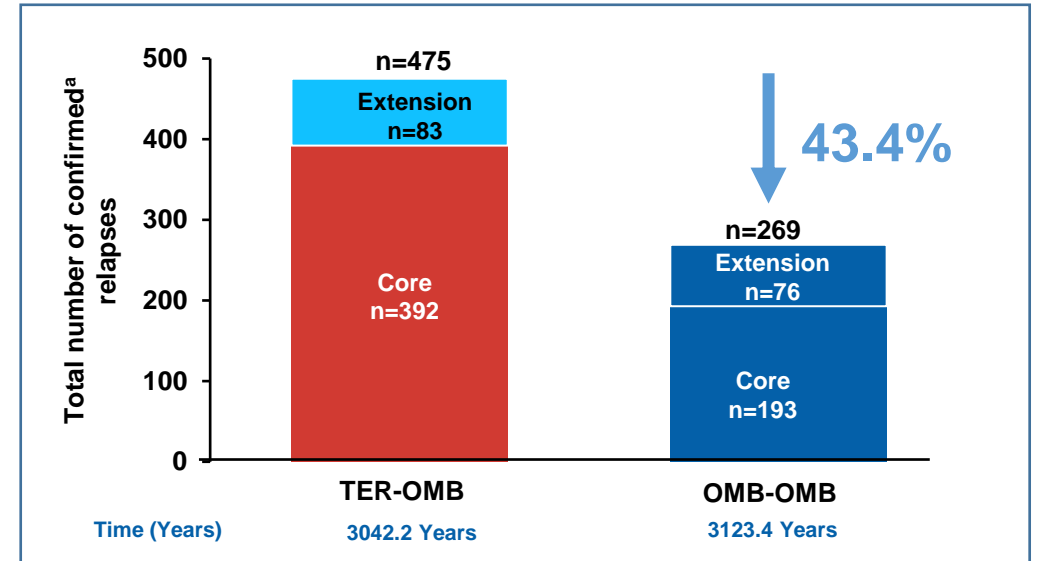
- **The between-group analysis over a period of up to 4 years shows a cumulative benefit with the earlier initiation of ofatumumab**
- **ARR in the continuous ofatumumab group remained low for up to 4 years after treatment initiation which resulted in an adjusted rate of 1 relapse every 20 years during the extension phase**
- **Switch from teriflunomide to ofatumumab resulted in a pronounced reduction in ARR**

All P values are nominal P values; additional details including the confidence intervals are presented in the backup slides.
[a]Confirmed relapses are those accompanied by a clinically relevant change in the EDSS.
ARR, annualized relapse rate; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Background   Objectives   Methods   Results   Conclusions

8

Time to first 3-month confirmed disability worsening (3mCDW) – Kaplan-Meier estimates
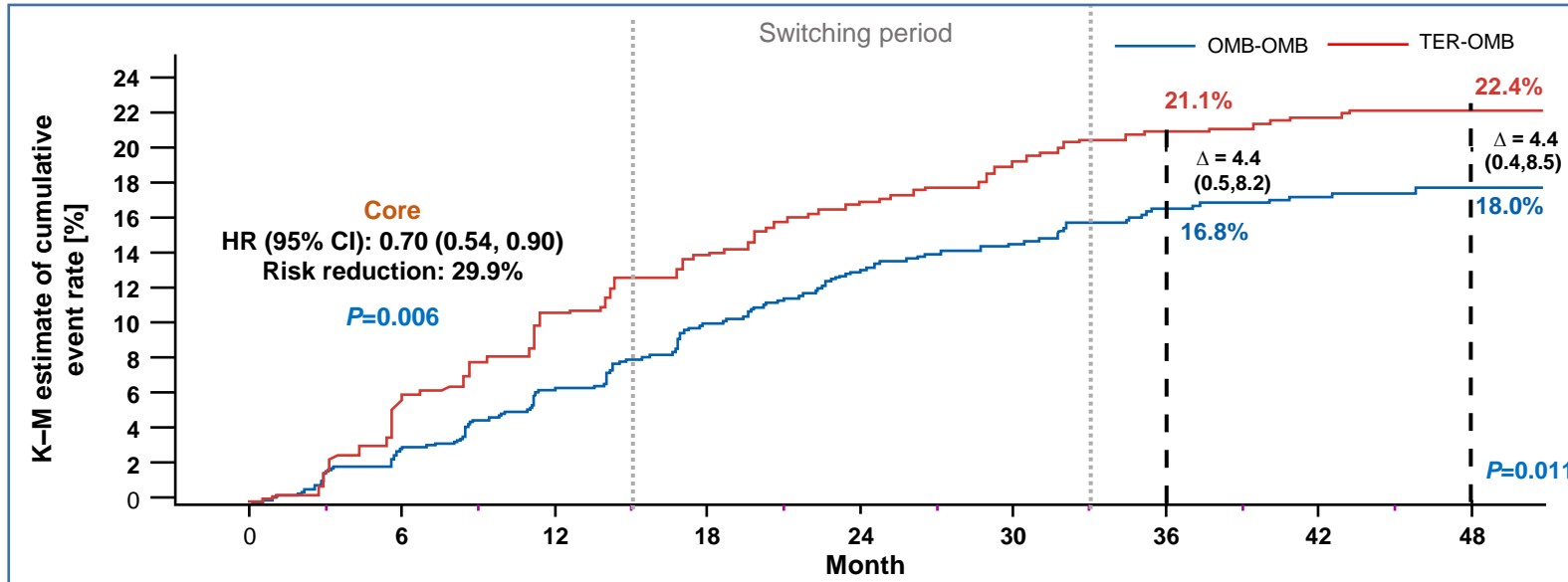
Cumulative number of events
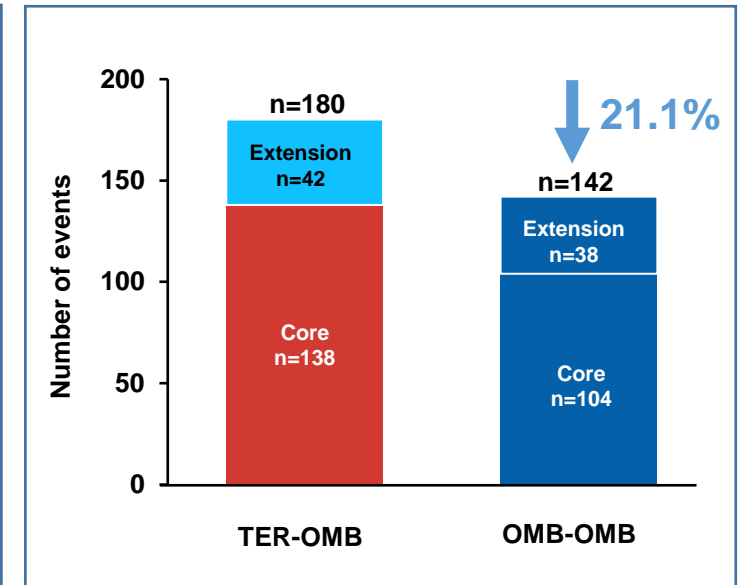
- **As shown by the delta at months 36 and 48, and the difference in the cumulative number of events over a period of up to 4 years, earlier treatment with ofatumumab was associated with an efficacy benefit that is lost and cannot be recovered in those initially randomized to teriflunomide**
- **After switching from teriflunomide to ofatumumab, the risk of subsequent 3mCDW events was similar in both treatment arms**

Cut-off for core and extension periods refer to the first dose of ofatumumab in extension. Δ, Difference in KM estimates (TER-OMB minus OMB-OMB). [a]P value represented here is P value for Log-Rank test.
3mCDW, 3-month confirmed disability worsening; CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier, OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab.
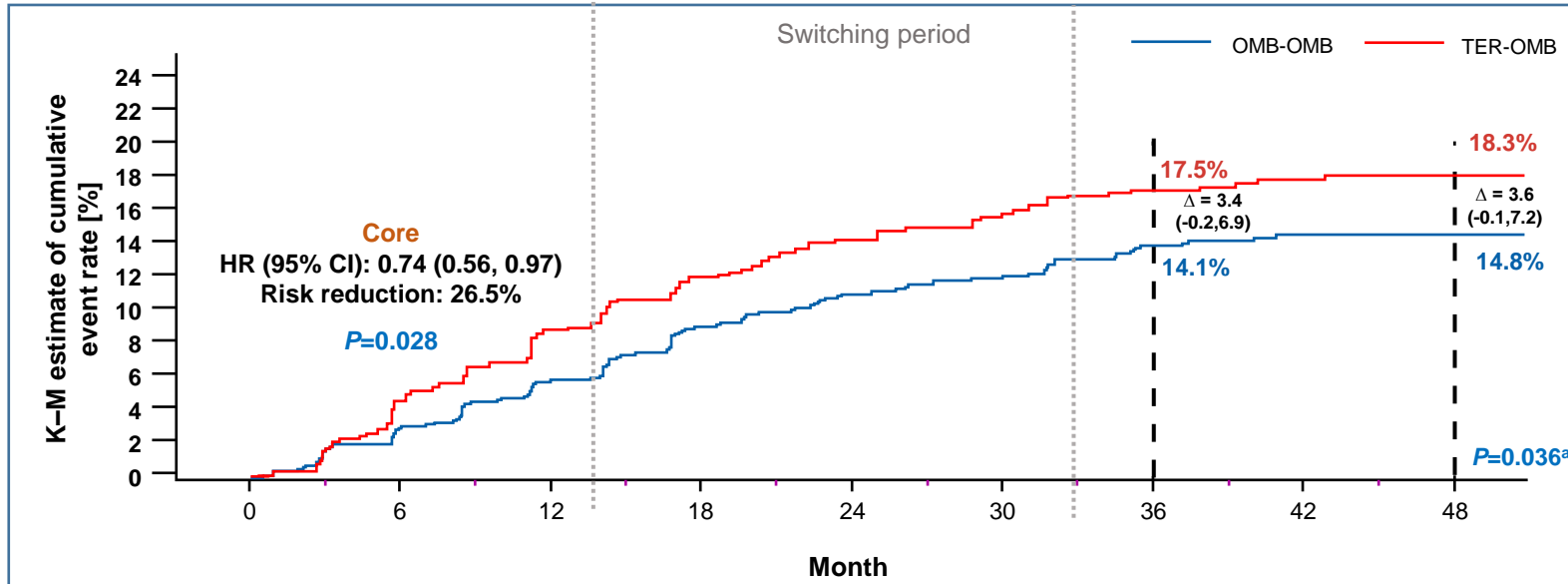
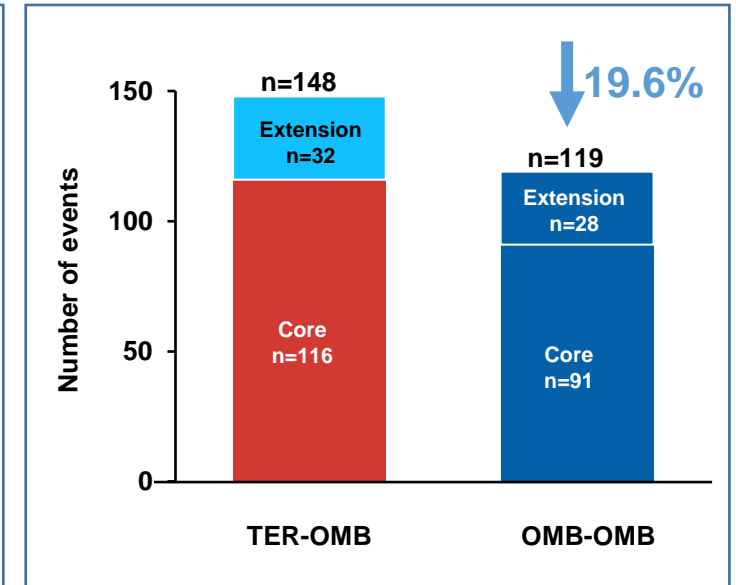Background   Objectives   Methods   Results   Conclusions

Time to first 6-month confirmed disability worsening (6mCDW) - Kaplan-Meier estimates
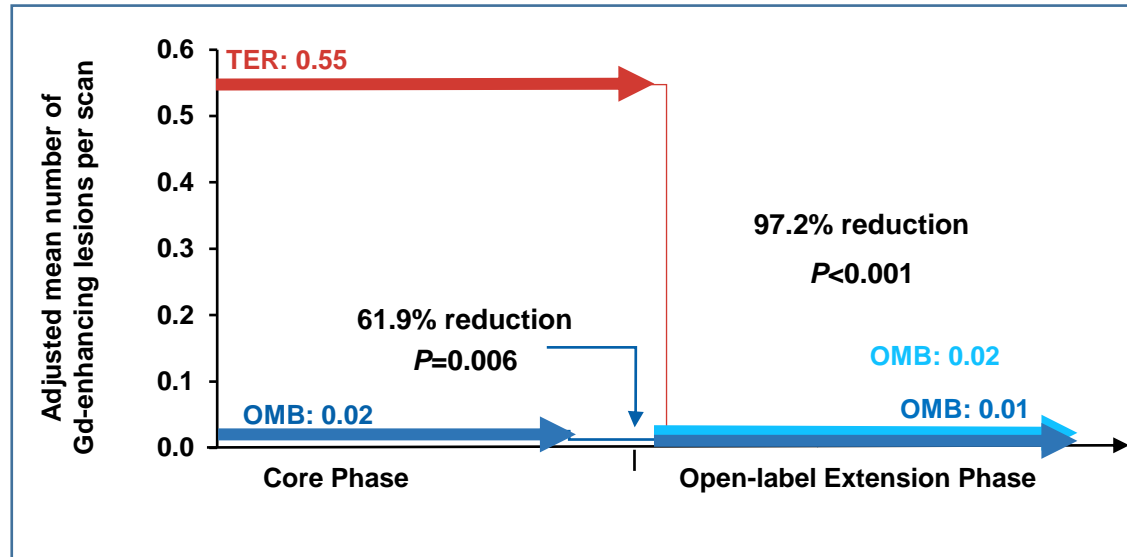
Cumulative number of events

- **Again, the deltas at 36 and 48 months, and the difference in the cumulative number of events over a period of up to 4 years, show that earlier treatment with ofatumumab was associated with an efficacy benefit that is lost and cannot be recovered in those initially randomized to teriflunomide**
- **As seen with 3mCDW, the risk of subsequent 6mCDW events after switching from teriflunomide to ofatumumab was similar in both treatment arms**
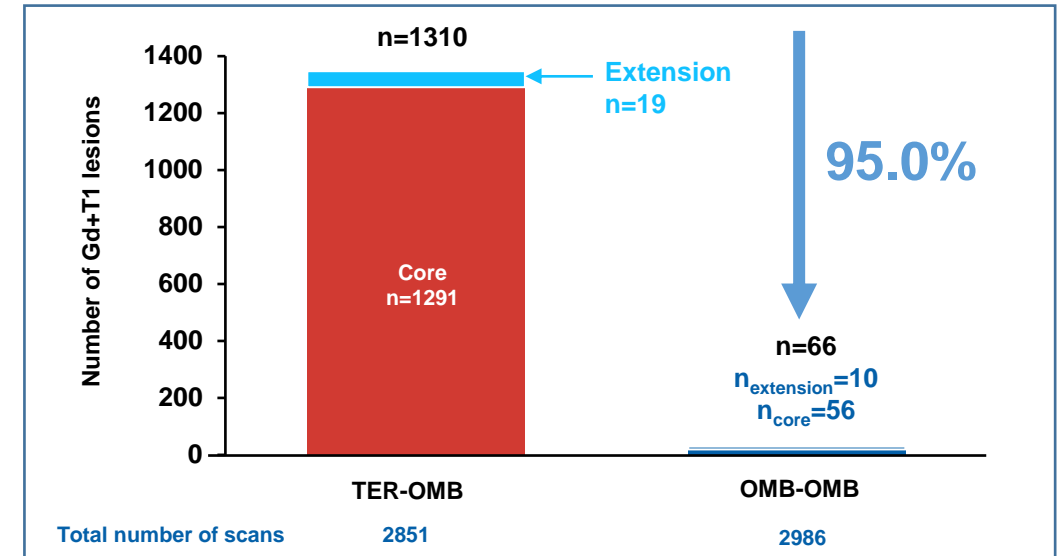
Cut-off for core and extension periods refer to the first dose of ofatumumab in extension. Δ, Difference in KM estimates (TER-OMB minus OMB-OMB). [a]P value represented here is P value for Log-Rank test.
OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab. 6mCDW, 6-month confirmed disability worsening; CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier.

Background | Objectives | Methods | Results | Conclusions

9

Within-group comparison during the core and extension phase

- Adjusted mean number of Gd-enhancing lesions per scan (y-axis, 0.0–0.6)
- TER: 0.55
- OMB: 0.02
- 61.9% reduction, *P*=0.006
- 97.2% reduction, *P*<0.001
- OMB: 0.02
- OMB: 0.01
- Core Phase
- Open-label Extension Phase

Between-group comparison Cumulative number of Gd+T1 lesions

- Number of Gd+T1 lesions (y-axis, 0–1400)
- n=1310
  - Extension n=19
  - Core n=1291
- 95.0%
- n=66
  - $n_{extension}=10$
  - $n_{core}=56$
- TER-OMB
- OMB-OMB
- Total number of scans: 2851 (TER-OMB), 2986 (OMB-OMB)

- **Between-group analysis over a period of up to 4 years show the extent of the cumulative benefit on acute inflammatory activity with the earlier initiation of ofatumumab**
- **The number of Gd+ T1 lesions per scan in the continuous ofatumumab group remained low for up to 4 years after treatment initiation**
- **Switching from teriflunomide to ofatumumab resulted in an almost complete suppression of Gd+ T1 lesion activity**

All P values are nominal P values; additional details including the confidence intervals are presented in the backup slides.

Gd+, gadolinium-enhancing; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.
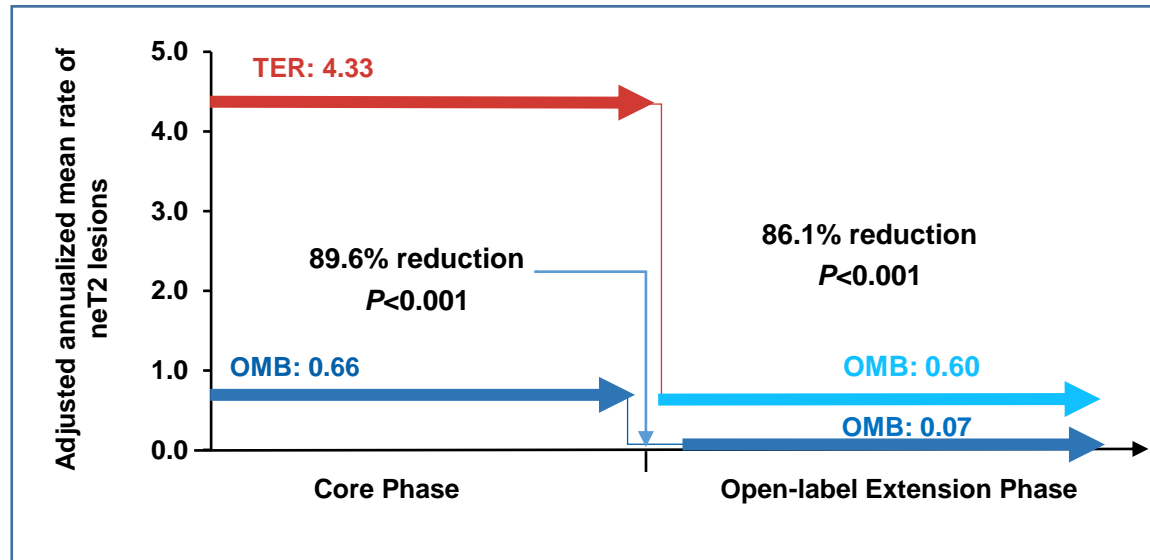
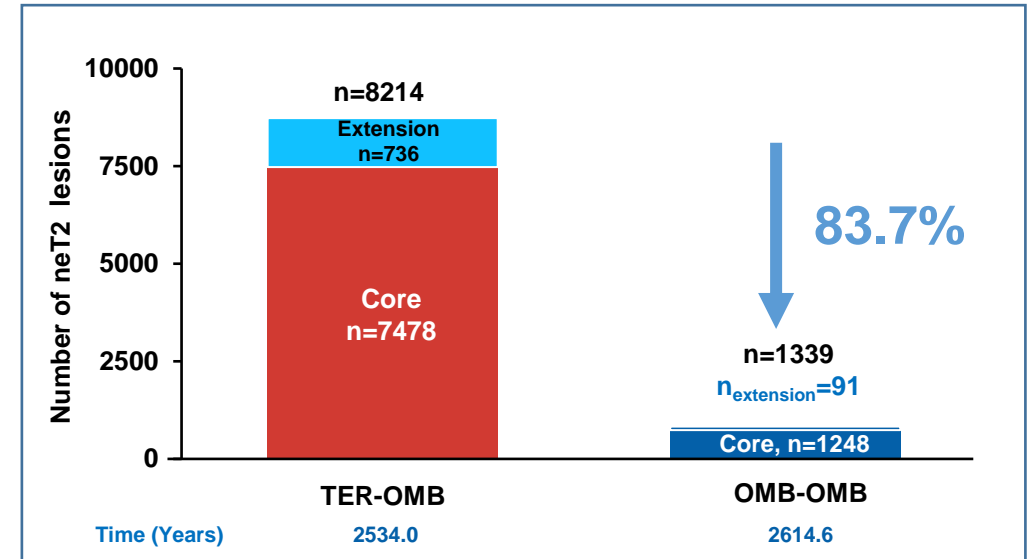| Background | Objectives | Methods | Results | Conclusions |

Within-group comparison during the core and extension phase

Between-group comparison Cumulative number of neT2 lesions

- As for Gd+ T1 lesions, the between-group analysis over a period of up to 4 years show the extent of the cumulative benefit on neT2 lesions with the earlier initiation of ofatumumab
- The number of neT2 lesions in the continuous ofatumumab group remained low for up to 4 years after treatment initiation; a near complete suppression was observed during the extension phase
- Switching from teriflunomide to ofatumumab resulted in a pronounced reduction in the number of neT2 lesions

All P values are nominal P values; additional details including the confidence intervals are presented in the backup slides.

Gd+, gadolinium-enhancing; neT2, new or emerging T2; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

Background | Objectives | Methods | Results | Conclusions

- Long-term, continuous ofatumumab treatment up to 4 years showed **sustained efficacy on relapses, MRI lesions, and risk of disability worsening**

    o The **low rate of relapses and MRI lesions observed in the core phase were at least sustained, if not further reduced, during the extension phase**, showing continued efficacy on these outcomes with up to 4 years of treatment

- Patients **switching from teriflunomide to ofatumumab** in the extension phase demonstrated **pronounced reductions in relapses and MRI lesions**

- **Sustained differences in relapses, MRI lesion activity, and the risk of disability worsening** observed in the **continuous versus the switch group** highlight the value of **earlier initiation of high-efficacy therapy, ofatumumab** compared to a lower efficacy therapy

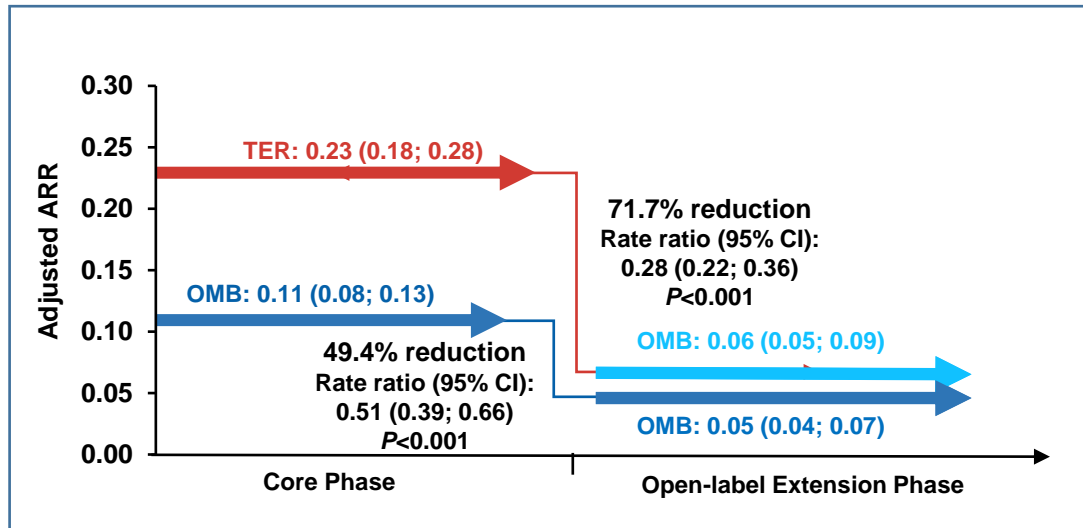HET, high efficacy therapy; MRI, magnetic resonance imaging.
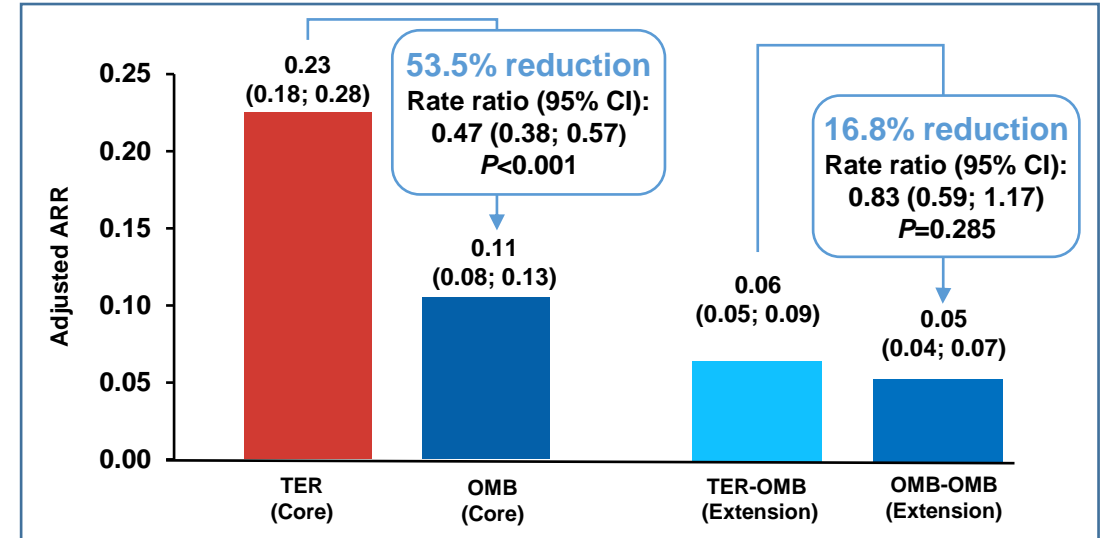
Backup Slides

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Within-group comparison[b] during the core and extension phase
(continuous ofatumumab and switch groups)

Between-group comparison[b] during the core and extension phase
(continuous ofatumumab vs switch group)

- **Continuous use of ofatumumab was associated with a further reduction in ARR with long-term treatment by 49.4%**
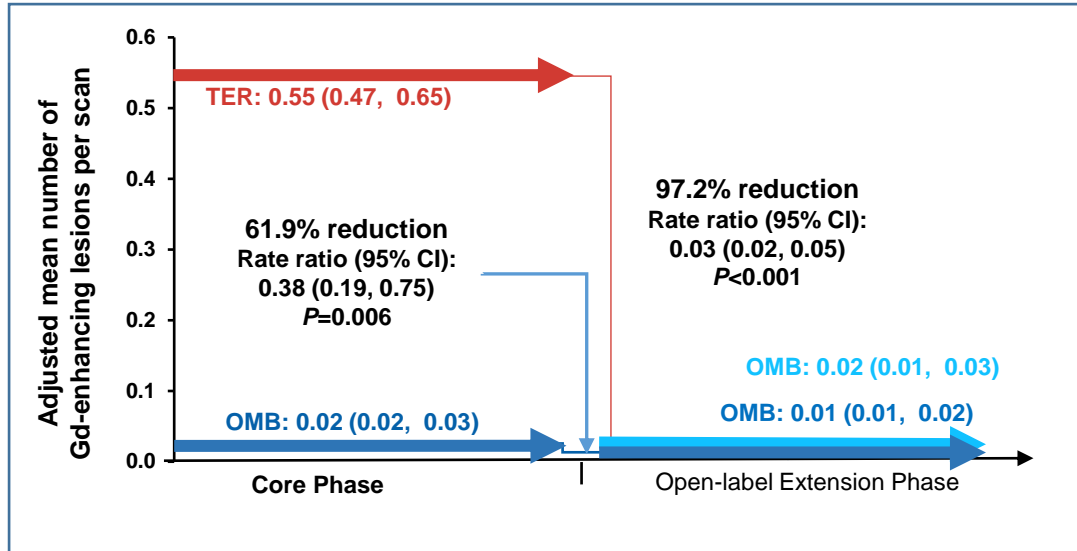
- **The significant reduction in ARR observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies was numerically maintained over long-term**

[a]Confirmed relapses are those accompanied by a clinically relevant change in the EDSS; [b]Obtained from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing lesions and the patient's age at baseline as covariates. The natural log of the time-in-study (in years) by period is used as offset to annualize the relapse rate in each period. Baseline variables are from the core study baseline. All P values are nominal P values.

ARR, annualized relapse rate, CI, confidence interval; Gd, gadolinium; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.
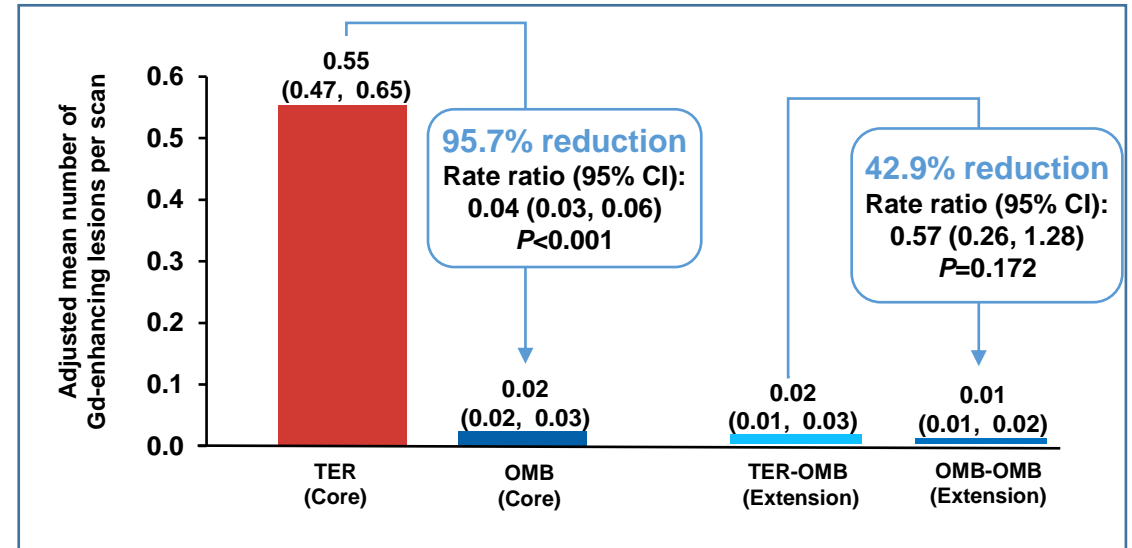
Background | Objectives | Methods | Results | Conclusions

Within group comparison[a]
(Continuous ofatumumab and switch groups)

Between group comparison[a]
(Continuous ofatumumab vs switch group)

- **Continuous use of ofatumumab was associated with a further reduction in the mean number of Gd+ T1 lesions with long-term treatment by 61.9%**
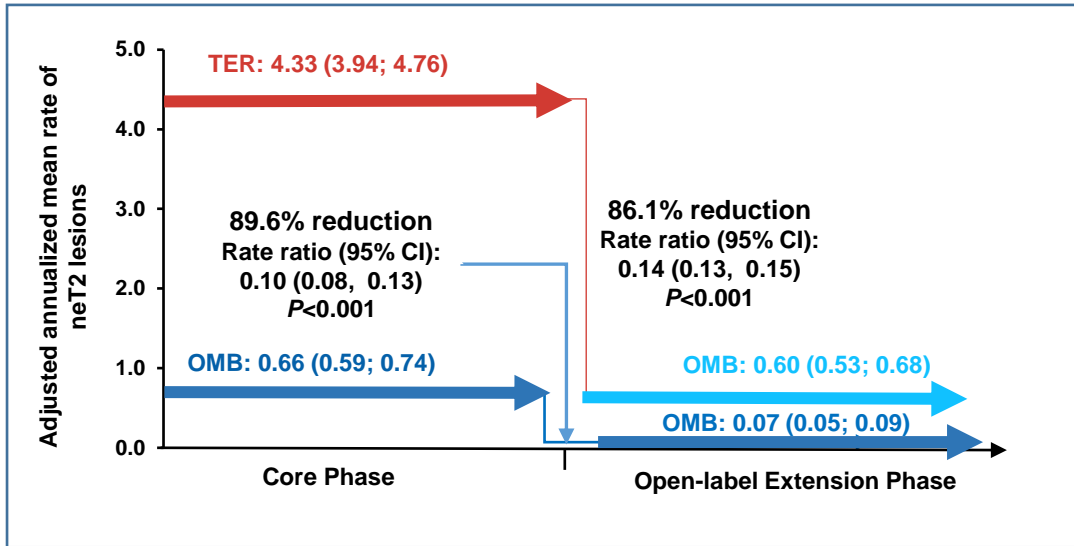
- **A significant reduction in the mean number of Gd+ T1 lesions observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies was numerically maintained over long-term**

[a]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, baseline number of T1 Gd-enhancing lesions and patient's age at baseline as covariates. The natural log of the number of scans with evaluable Gd-enhancing lesion counts by period is used as offset to obtain the lesion rate per scan in each period. Baseline variables are from the core study baseline.

All P values are nominal P values. CI, confidence interval; Gd, gadolinium; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.
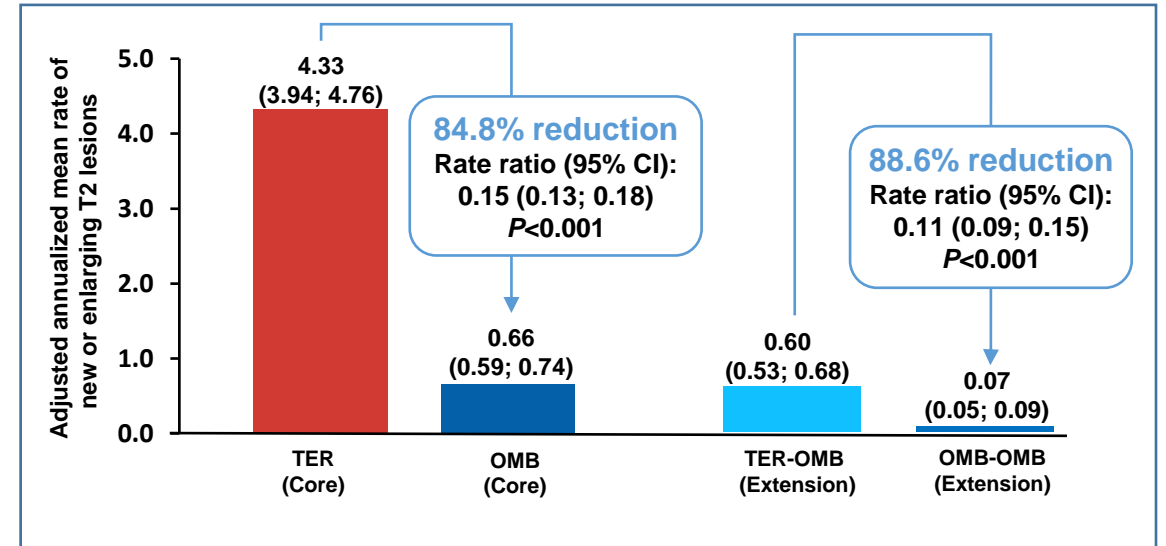
Background Objectives Methods Results Conclusions

12

Within group comparison[a]
(Continuous ofatumumab and switch groups)

Between group comparison[a]
(Continuous ofatumumab vs switch group)

- **Continuous use of ofatumumab was associated with a further reduction in the mean rate of neT2 lesions with long-term treatment by 89.6%**

- **The significant reduction in the mean rate of neT2 lesions observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies was maintained over long-term**

[a]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment as factor, baseline volume of T2 lesions and patient's age at baseline as covariates. The natural log of the time-in-study (in years) by period is used as offset to annualize the lesion rate in each period. Baseline variables are from the core study baseline. All P values are nominal P values.

CI, confidence interval; neT2, new or enlarging T2; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab.

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