# Effect of Longer-term Ofatumumab Treatment on Disability Worsening and Brain Volume Change

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# Disclosures

**Heinz Wiendl** has received honoraria for acting as a member of scientific advisory boards for Biogen, Evgen, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Roche Pharma AG, and Sanofi-Aventis, as well as speaker honoraria and travel support from Alexion, Biogen, Cognomed, F. Hoffmann-La Roche Ltd., Gemeinnützige Hertie-Stiftung, Merck Serono, Novartis, Roche Pharma AG, Genzyme, Teva, and WebMD Global. Heinz Wiendl is acting as a paid consultant for AbbVie, Actelion, Biogen, IGES, Johnson & Johnson, Novartis, Roche, Sanofi-Aventis, and the Swiss Multiple Sclerosis Society. His research is funded by the German Ministry for Education and Research (BMBF), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, the European Union, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster and RE Children's Foundation, Biogen, GlaxoSmithKline GmbH, Roche Pharma AG, and Sanofi-Genzyme.

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**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.

**Ronald Zielman, Ayan Das Gupta, Amin Azmon, Jing Xi, Gina Mavrikis Cox** are employees of Novartis

**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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# Introduction

Ofatumumab is the first fully human anti-CD20 monoclonal antibody with a 20 mg s.c. monthly dosing regimen in 0.4ml, approved for the treatment of RMS in adults in the US[1] and other countries[a]

Data from the ASCLEPIOS I/II trials and the open-label ALITHIOS extension with up to 4 years treatment with ofatumumab showed:

- Significantly delayed disability accrual compared with teriflunomide[2]
- Sustained efficacy by reducing relapses and MRI lesions[2,3,4]
- 93% of patients receiving continuous ofatumumab achieved no evidence of disease activity (NEDA-3)* [5]

Relapse-associated disability worsening (RAW) and progression independent of relapse activity (PIRA)[6,7] both contribute to confirmed disability worsening (CDW) in patients with relapsing multiple sclerosis (RMS)[8]

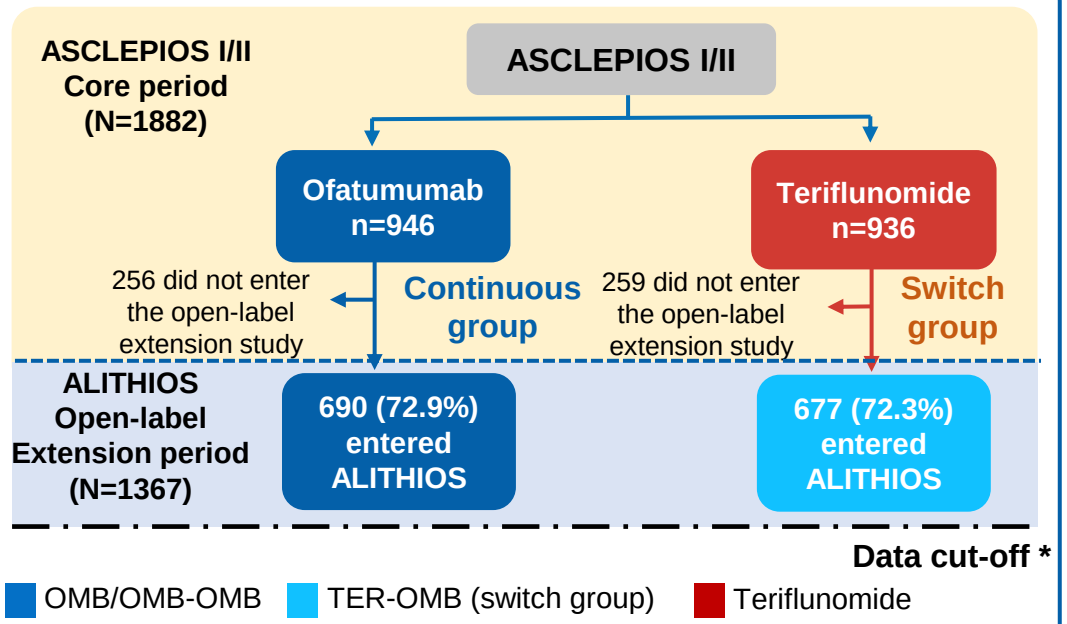
The ASCLEPIOS I and II trials had a flexible duration of up to 2.3 years of individual exposure to randomized study treatment (either teriflunomide or ofatumumab); after this initial core period all patients switched to open-label ofatumumab; MRI, magnetic resonance imaging; s.c., subcutaneous.
*NEDA-3 is defined as no 6-month confirmed disability worsening, no confirmed MS relapse, no new or enlarging T2 lesions compared to baseline and no T1 gadolinium-enhancing lesions.

[a]Kesimpta® (ofatumumab) has now been approved in many countries including US, Canada, Switzerland, Singapore, Australia, Japan and the EU.

1. KESIMPTA® (ofatumumab) Prescribing information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed March 22, 2023); 2. Hauser et al. N Engl J Med. 2020; 383:546-557; 3. Kappos et al. ERP161 Poster Presented at EAN 2022; 4. Hauser SL, et al. ePoster #004 presented at AAN 2022. 5. Kuhle et al. P1198 poster presented at ECTRIMS 2022; 6. Kappos et al. Mult Scler 2018; 24: 963–973; 7. Kappos et al. Clinical Trials. JAMA Neurol 2020; 77: 1132–1140; 8. Lublin F, et al. Brain 2022;145,9:3147-3161

# Methods

**Objective:** To assess longer-term effects (up to 5 years of treatment) of continuous ofatumumab treatment on disability outcomes (CDW, PIRA, RAW) and brain volume change compared with delayed ofatumumab treatment (after switching from teriflunomide)




| Demographics and clinical characteristics[a] | Ofatumumab continuous (N=946) | | Switch from teriflunomide to ofatumumab (N=936) | |
|---|---|---|---|---|
| | Baseline of core study (N=946) | Baseline of extension study (N=690) | Baseline of core study (N=936) | Baseline of extension study[d] (N=677) |
| Age, years | 38.4±9.04 | 38.1±8.69 | 38.0±9.22 | 40.1±9.21 |
| Female, n (%) | 637 (67.3) | 483 ( 70.0) | 636 (67.9) | 456 (67.4) |
| BMI, kg/m$^2$ | 25.86±6.22 | 25.73±6.00 | 25.93±6.02 | 25.61±5.85 |
| Treatment-naive patients[b], n (%) | 386 (40.8) | Not applicable[c] | 363 (38.8) | Not applicable[c] |
| EDSS score at baseline | 2.93±1.35 | 2.80±1.49 | 2.90±1.36 | 2.81±1.46 |
| Number of relapses in the 12 months prior to screening, n (%) | 1.2±0.69 | 0.1±0.35 | 1.3±0.71 | 0.2±0.49 |
| Number of Gd+ T1 lesions | 1.7±4.51 | 0.0±0.21 | 1.3±3.43 | 0.8±2.37 |
| Total volume of T2 lesions, cm$^3$ | 13.72±13.79 | Not available | 12.55±13.81 | Not available |

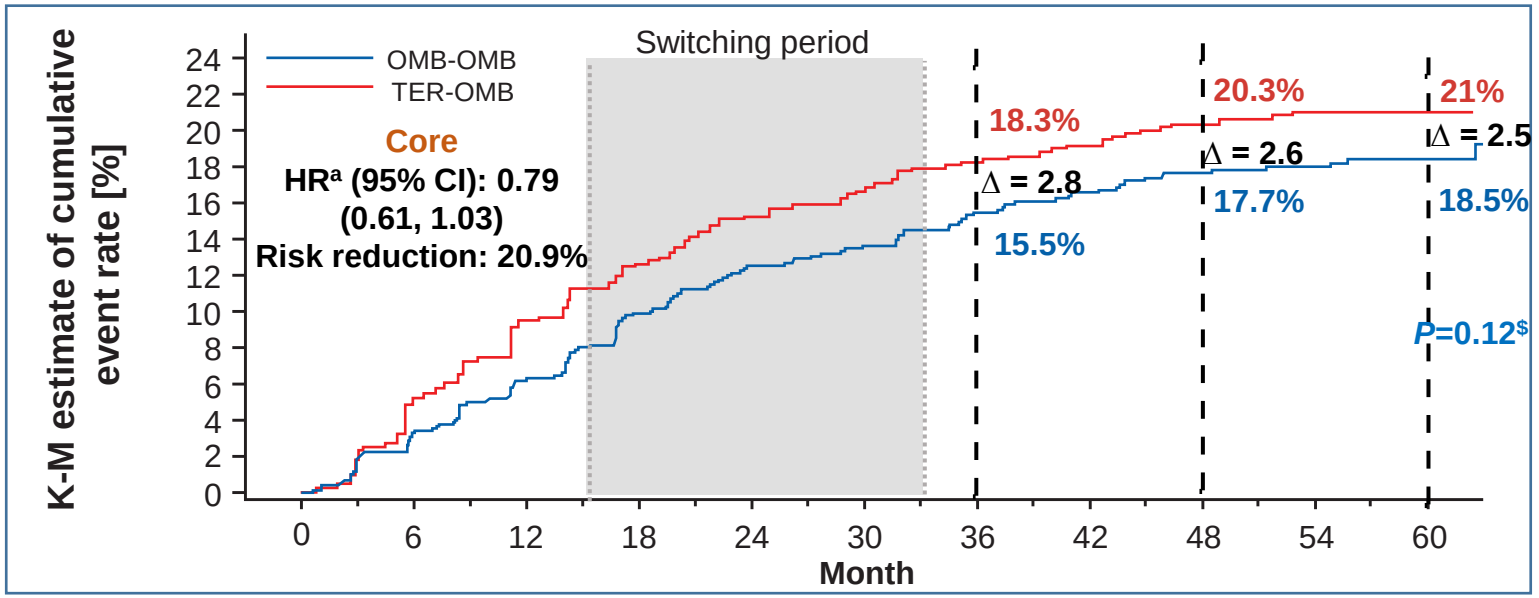
## Key assessments

- 6-month confirmed disability worsening (6m-CDW)
  - 6-month confirmed relapse associated worsening (6m-RAW)
  - 6-month confirmed progression independent of relapse activity (6m-PIRA)
  - 6-month confirmed and sustained progression independent of relapse activity (6m-sPIRA)
- Brain volume change (BVC) MRI outcomes
  - Annual rate of brain volume change (ABVC) over the study duration (Core & Extension)
  - Percentage brain volume change (PBVC) at each year

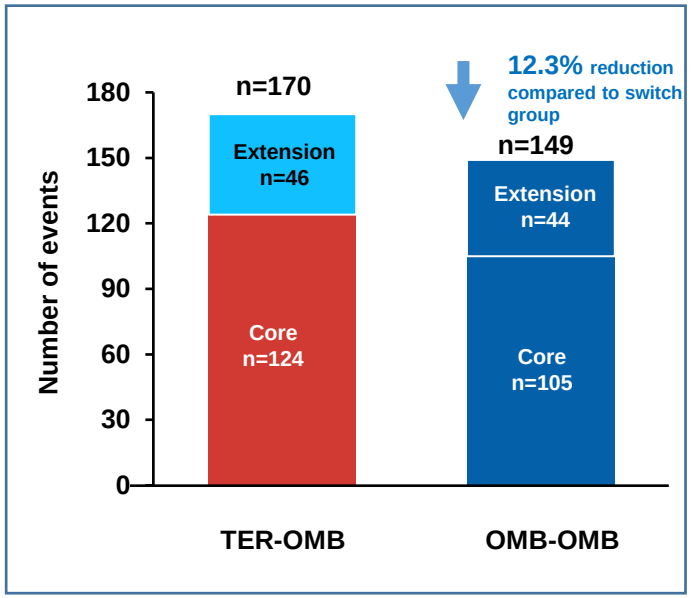
[a]Values are represented as mean±SD unless specified otherwise; [b]Treatment naive patients are those who have not received a prior multiple sclerosis disease modifying therapy; [c]not applicable since all patients have been pre-treated with either ofatumumab or teriflunomide in the core period; [d]the baseline from the extension study in the ofatumumab continuous and the ofatumumab switch from teriflunomide groups reflect the relative treatment effects during the double-blind treatment phase in the ASCLEPIOS I/II studies, *Data cut-off: 25-Sep-2022.
6m-CDW, 6-month CDW; BMI, body mass index; CDW, confirmed disability worsening; EDSS, expanded disability status scale; Gd+, gadolinium enhanced; HR, hazard ratio; K-M, Kaplan-Meier; OMB/OMB-OMB, patients randomized to ofatumumab in the Core period and continuing ofatumumab in ALITHIOS; PIRA, progression independent of relapse activity; RAW, relapse associated worsening; TER-OMB, patients randomized to teriflunomide during the Core and switched to ofatumumab during ALITHIOS.

# 6-month Confirmed Disability Worsening

**Time to first 6-month confirmed disability worsening (6mCDW) - Kaplan-Meier estimates**




**Cumulative number of first events**

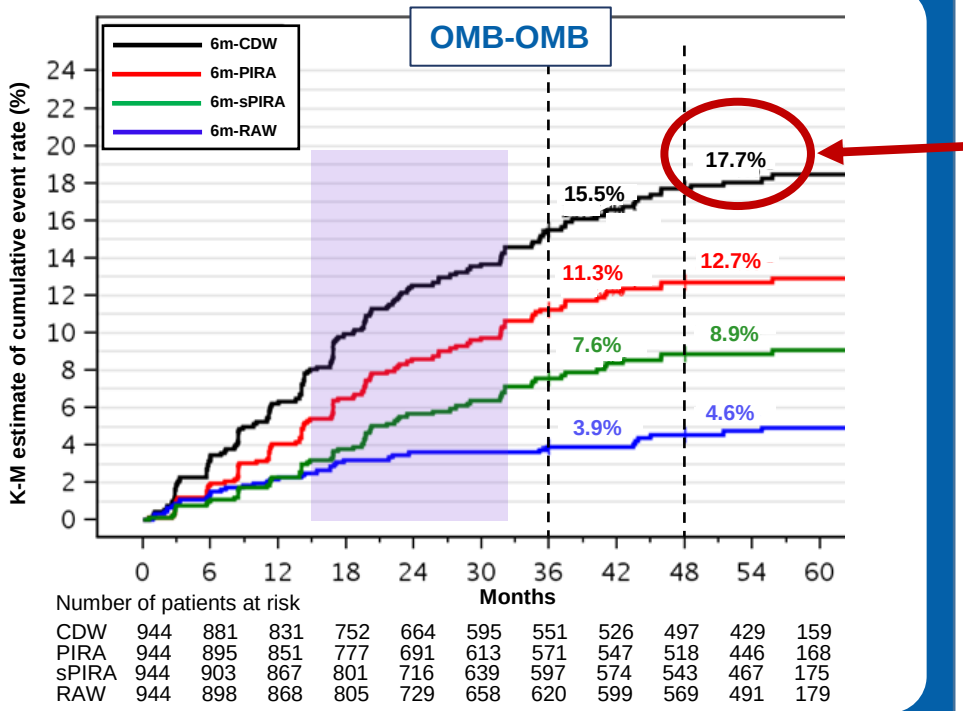


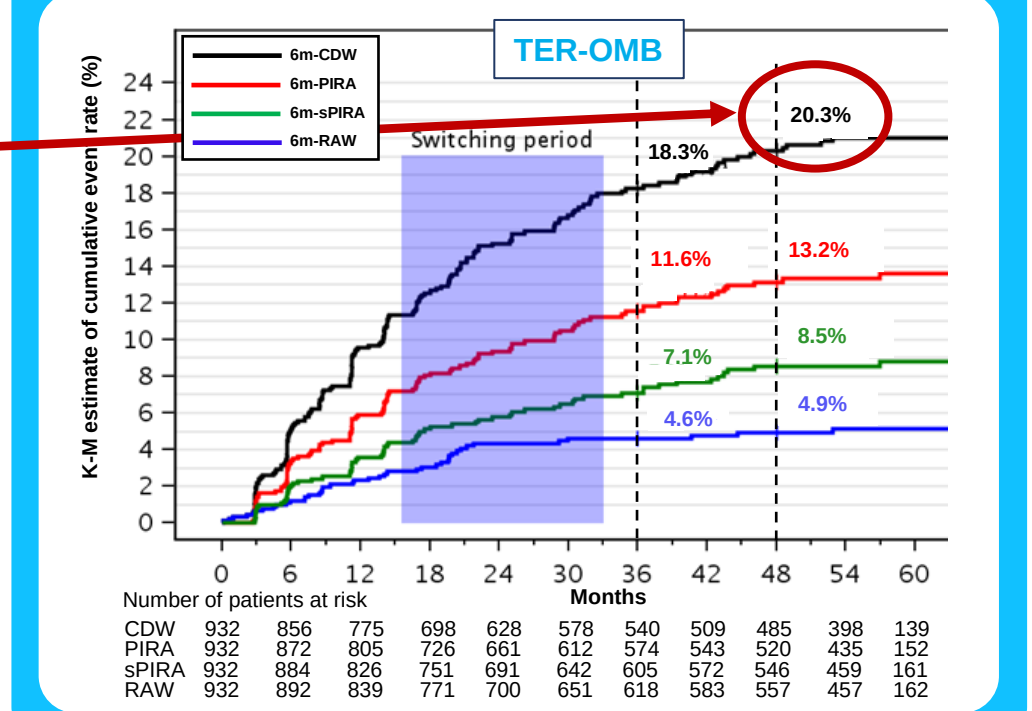

- **The deltas at 48 and 60 months, and the difference in the cumulative number of events over a period of up to 5 years, show that earlier treatment with ofatumumab was associated with an efficacy benefit that is lost and cannot be recovered in those initially randomized to teriflunomide; similar patterns were identified for the 3m-CDW**
- **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 K-M estimates (TER-OMB minus OMB-OMB). [a]HR determined by Cox regression model; [b]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.

# Results: Kaplan-Meier estimates of 6m-CDW, 6m-PIRA, 6m-sPIRA, and 6m-RAW up to 5 years

## Fewer disability events over 5 years with early initiation of ofatumumab




- **RMS patients treated with disease modifying therapies accumulate disability primarily via PIRA**
- **Overall, fewer CDW, PIRA and RAW events were observed in patients receiving continuous ofatumumab versus those initially randomized to teriflunomide and switched to ofatumumab; similar patterns were identified for the 3m-CDW**
- **Ofatumumab's high anti-inflammatory efficacy is evident with flattening of the 6m-RAW curve in the TER-OMB switch group in the extension period**

6m-CDW, 6-month CDW; 6m-PIRA, 6-month confirmed PIRA; 6m-RAW, 6-month confirmed RAW; 6m-sPIRA, 6-month confirmed and sustained PIRA; CDW, confirmed disability worsening; K-M, Kaplan-Meier; OMB-OMB, patients randomized to ofatumumab in the Core period and continuing ofatumumab in ALITHIOS; PIRA, progression independent of relapse activity; RAW, relapse associated worsening; RMS, relapsing multiple sclerosis; sPIRA, sustained progression independent of relapse activity; TER-OMB, patients randomized to teriflunomide during the Core and switched to ofatumumab during ALITHIOS.

# Results: Brain Volume Change

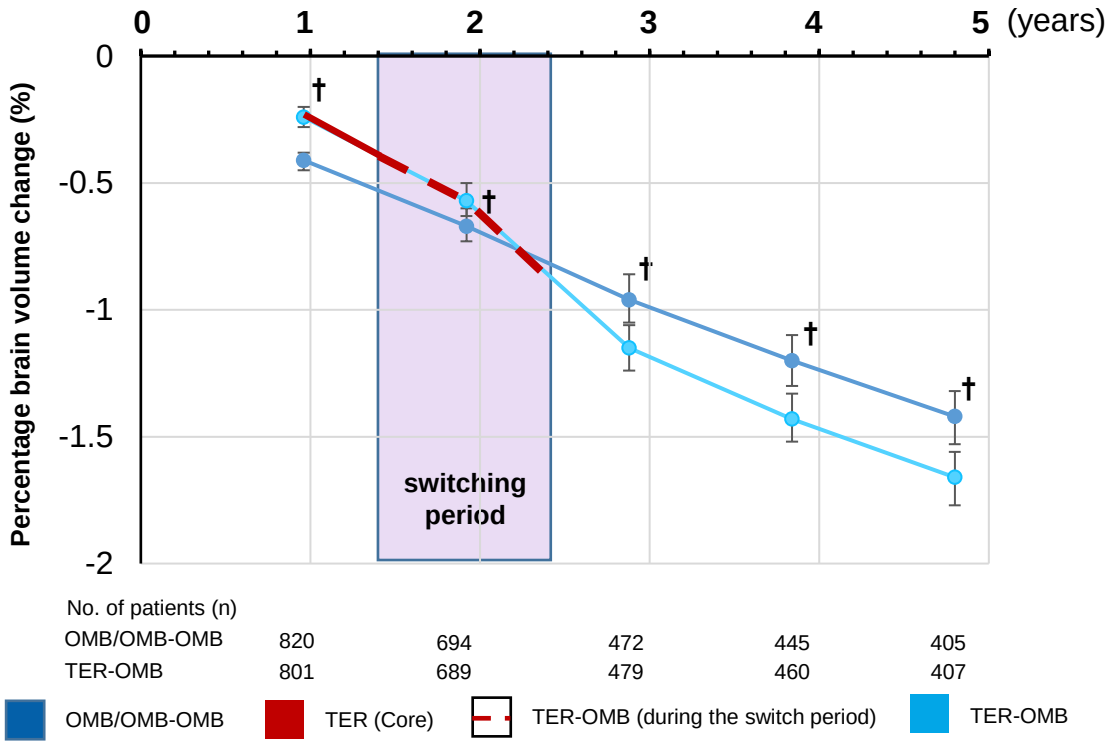
- **PBVC remained low (<1.5% loss) up to 5 years with continuous ofatumumab treatment#**
- Overall, **annual BVC** remained low in patients receiving continuous ofatumumab with -0.27% BVC per year during the Extension

| Annual rate of brain volume change | | | | |
|---|---|---|---|---|
| **Group** | **Core (%)** | **P-value*** | **Extension (%)** | **P-value*** |
| OMB-OMB | -0.34 | 0.115 | -0.27 | 0.666 |
| TER-OMB | -0.42 | | -0.28 | |

- ABVC differences between OMB-OMB vs TER-OMB in the core and extension shows the benefit of early initiation and prolonged benefit of ofatumumab for up to 5 years
- Initially, a steeper decline was observed with TER-OMB vs OMB-OMB during the Core while the annual BVC rate became similar to OMB-OMB during the Extension indicating a slowing of BVC following switch to ofatumumab and demonstrating the impact of ofatumumab on limiting brain volume loss

*Between-group comparison for ABVC

## PBVC up to 5 years




†Statistically significant between-group comparison at each year for PBVC
# The initial difference between groups in brain volume in the first year and during the switch period may be due to the strong effect of ofatumumab on lesions and lesion-related edema (pseudo-atrophy).
Note: PBVC estimates are obtained from a mixed model for repeated measure

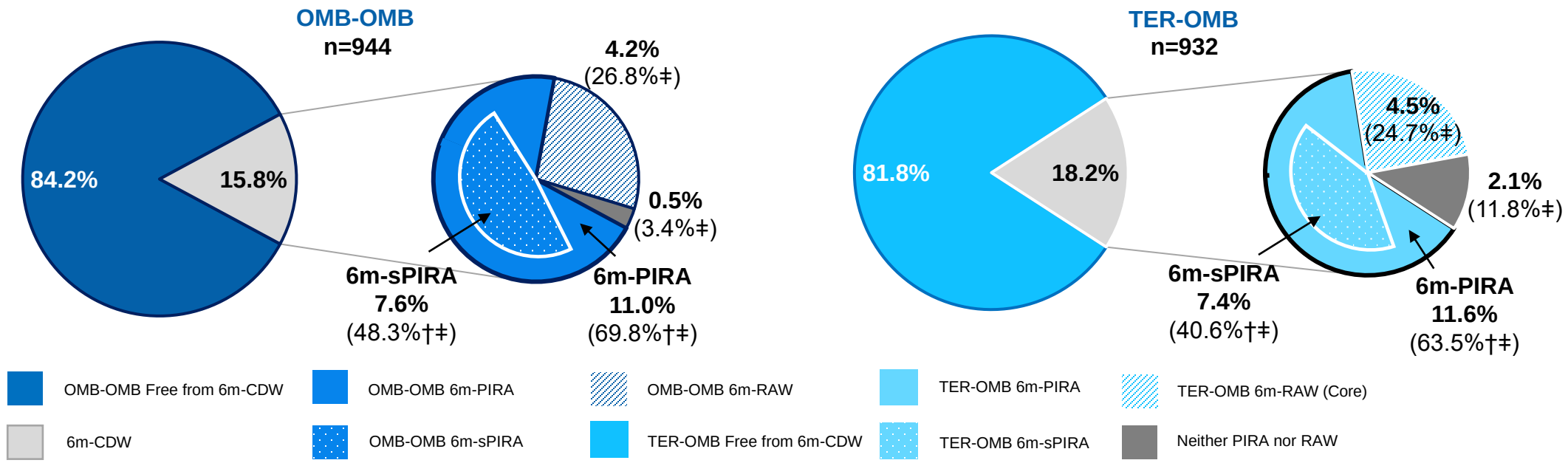
ABVC, annual rate of brain volume change estimated from all the post-baseline MRI scans; BVC, brain volume change; OMB/OMB-OMB, patients treated with ofatumumab during the Core period (OMB) and continued with ofatumumab (OMB-OMB) during the Extension period; PBVC, percentage brain volume change; TER-OMB, patients randomised to teriflunomide during the Core period and switched to ofatumumab during the Extension period (ALITHIOS); n, total number of patients included in the analysis.

Note, ABVC estimates detail the average amount of change per annum and are reported for the core and extension periods; PBVC estimates detail the change in brain volume relative to baseline measures.

# Conclusions

- Low rates of disability worsening are observed, with >80% free of 6m-CDW after 5 years on ofatumumab
- There were fewer disability events (both PIRA and RAW) with earlier initiation of ofatumumab compared with the switch group
- The 5-year PBVC remained low, with less than <1.5% loss with earlier initiation of ofatumumab
- Initially, a steeper decline in brain volume was observed with the switch group vs earlier initiation of ofatumumab, however after switch to ofatumumab, the annual rate of BVC became similar to the early ofatumumab group, indicating a slowing of brain volume loss
- Overall, these data support the early use of ofatumumab in patients with RMS

# Backup Slide
# Proportion of 6m-CDW: 6m-PIRA, 6m-sPIRA, 6m-RAW (Overall)




Primary pie chart details the proportion free from 6m-CDW and proportion of 6m-CDW events; Expanded pie chart details the proportion of 6m-CDW events, 6m-PIRA, 6m-sPIRA and 6m-RAW shown as a proportion of total number of 6m-CDW events; Neither refers to events not attributed to 6m-PIRA or 6m-RAW; n, number of patients

†The inset patterned segments represent the proportion classified as sustained 6m-PIRA and form subsegment of the PIRA segments; ‡Values in brackets are the proportion of events relative to all 6m-CDW

- **6m-PIRA was the main contributor to overall 6m-CDW**
- **6m-sPIRA meaningfully contributed to the overall proportion of 6m-CDW and represented a greater proportion of 6m-CDW events than 6m-RAW**

6m-CDW, 6-month CDW; CDW, confirmed disability worsening; 6m-PIRA, 6-month confirmed PIRA; 6m-RAW, 6-month confirmed RAW; 6m-sPIRA, 6-month confirmed sustained PIRA; OMB-OMB, patients randomized to ofatumumab in the Core period and continuing ofatumumab in ALITHIOS; PIRA, progression independent of relapse activity; RAW, relapse associated worsening; sPIRA, sustained progression independent of relapse activity; TER-OMB, patients randomized to teriflunomide during the Core and switched to ofatumumab during ALITHIOS; TER, patients randomized to teriflunomide during the core ASCLEPIOS I/II trials.

Note: 6m-CDW overall proportion is represented by total number of 6m-PIRA, 6m-RAW and 'Neither' events; Neither 6m-PIRA nor 6m-RAW describes 6m-CDW events that do not meet the criteria for 6m-PIRA or 6m-RAW.

# Backup slide
# Statistical models

**Statistical models applied**

- The average rate of brain volume change per annum (Annualised brain volume change, ABVC) estimates were obtained from a random coefficient model which is a mixed model extension in a hierarchical data setup so that subject level random effect can be included in the model. Model parameters: Treatment group, time period (core phase vs. extension phase) and region as factors, time, baseline number of Gd-enhanced lesions, baseline T2 volume, and baseline normalized brain volume as continuous covariates; three-way interaction (treatment group x time period x time) and all its associated two-way interactions
- PBVC estimates were obtained from a mixed model for repeated measures, a model that specifies no patient level random effects, but instead assumes that the residual errors of repeated measures over time are correlated. Model parameters: treatment and visit window as interacting factors, region as a factor and age, baseline number of Gd-enhanced lesions, baseline T2 volume, and baseline normalized brain volume as continuous covariates

ABVC, annual rate of brain volume change estimated from all the post-baseline MRI scans; BVC, brain volume change;  PBVC, percentage brain volume change).