Longer-Term Effects of Ofatumumab on Clinical and MRI Outcomes in Patients With Relapsing Multiple Sclerosis

DMT20

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Background

- Early initiation of high-efficacy therapies for the treatment of relapsing multiple sclerosis (RMS) has been shown to improve longer-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 longer-term efficacy and safety of ofatumumab is important to further understand its benefit-risk profile in patients with RMS
  - The longer-term safety of ofatumumab is being discussed separately at this congress in the platform presentation DMT04 and poster DMT33

Objective

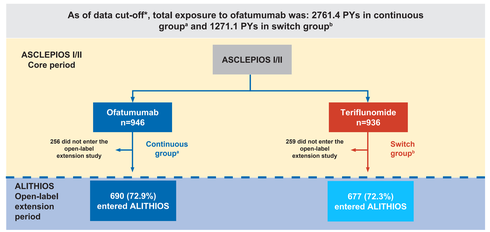
- To assess the longer-term efficacy of ofatumumab treatment for up to 4 years (data cut-off: 25-Sep-2021) in patients with RMS in the ongoing ALITHIOS open-label extension study

Methods

Study design and patient population

- This analysis included cumulative data from patients randomized to ofatumumab/teriflunomide in the ASCLEPIOS I/II trials (core study) and the ongoing, open-label, ALITHIOS extension study
- 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 (**Figure 1**)

Figure 1. Patient disposition



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.

- The main reasons for discontinuing treatment were the occurrence of adverse events (AEs) (4.0%) and patient/guardian decision (4.0%)
- Patients were analyzed in two treatment groups:
  - **Continuous group (OMB-OMB):** Patients randomized to ofatumumab in the core (ASCLEPIOS I/II)
  - **Switch group (TER-OMB):** Patients randomized to teriflunomide in the core study were switched to ofatumumab in ALITHIOS

Key efficacy assessments:

- Annualized relapse rate (ARR)
- 3- and 6-month Confirmed Disability Worsening (3mCDW, 6mCDW)
  - Confirmed disability worsening is an increase from baseline in Expanded Disability Status Scale (EDSS) score sustained for at least 3 or 6 months
- Brain MRI outcomes
  - Mean number of Gadolinium (Gd)-enhancing T1 lesions per scan
  - Number of new or enlarging T2 (neT2) lesions per year
- ARR and MRI outcomes were analyzed
  - between the groups (defined as comparison of the cumulative outcomes between the continuous and switch groups) and
  - within the groups (defined as comparison of the core and extension periods within the continuous and switch groups)

Results

Baseline characteristics

- At baseline, mean age of patients was approximately 38 years in the ofatumumab continuous and switch groups; majority of patients were women (>65%) (**Table 1**)
- The mean EDSS at baseline was approximately 2.9 for both the continuous and switch groups
- The total exposure to ofatumumab was: 2761.4 PYs in continuous group and 1271.1 PYs in switch group

Table 1. Baseline demographics and clinical characteristics

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	39.0 ± 9.22	40.1 ± 9.21
Female, n (%)	637 (67.3)	636 (67.9)	456 (67.4)
BMI in 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

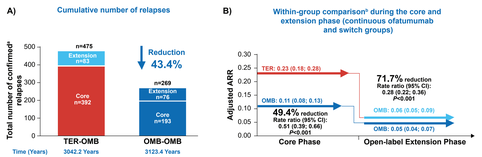
[a]Values are represented as mean±SD unless specified otherwise. [b]Treatment naive patients are those who have not received a prior multiple sclerosis disease modifying therapy; [c]not applicable since all patients have been pre-treated with teriflunomide; [d]The baseline from the extension study in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

Annualized relapse rate (ARR)

- The between-group analysis over a period of up to 4 years shows that earlier initiation of ofatumumab was associated with a reduction in the cumulative number of relapses by 43.4% (**Figure 2A**)
- 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 (**Figure 2A**)
- The within group analysis showed that continuous use of ofatumumab was associated with a significant reduction in ARR by 49.4% with longer-term treatment, while switch from teriflunomide to ofatumumab resulted in a pronounced reduction in ARR (71.7%) (**Figure 2B**)
- The significant reduction in ARR observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies was numerically maintained over the longer-term treatment

Figure 2. A) Between group comparison - Cumulative number of relapses B) Within-group comparison during the core and extension phase



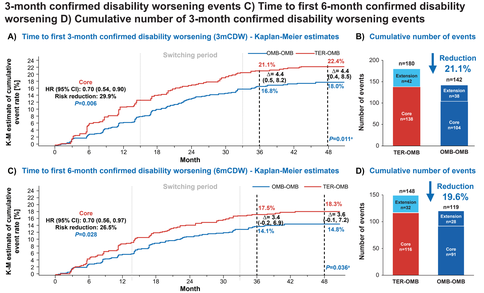
[a]Confirmed relapses are those accompanied by a clinically relevant change in the EDSS; [b]Obtained from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, number of relapses in previous year, baseline 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; EDSS, Expanded Disability Status Scale; Gd, gadolinium; OMB, ofatumumab; OMB-OMB, continuous ofatumumab; TER, teriflunomide; TER-OMB, switch from teriflunomide to ofatumumab

3- and 6-month confirmed disability worsening

- As shown by the delta at months 36 and 48 in **Figure 3A and 3C**, and the difference in the Cumulative number of events (**Figure 3B and 3D**) 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

Figure 3. A) Time to first 3-month confirmed disability worsening B) Cumulative number of 3-month confirmed disability worsening events C) Time to first 6-month confirmed disability worsening D) Cumulative number of 3-month confirmed disability worsening events



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). *P value represented here is P value for Log-Rank test.

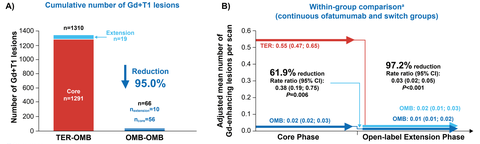
3mCDW, 3-month confirmed disability worsening; 6mCDW, 6-month confirmed disability worsening; CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier, OMB-OMB, continuous ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab

MRI lesion activity

Mean number of Gd+T1 lesions per scan

- The between-group analysis over a period of up to 4 years shows that earlier initiation of ofatumumab was associated with a reduction in the cumulative number of Gd+ T1 lesions by 95% (**Figure 4 A**)
- The number of Gd+ T1 lesions per scan in the continuous ofatumumab group remained low for up to 4 years after treatment initiation (**Figure 4A**)
- The with-in group analysis showed that continuous use of ofatumumab was associated with a reduction in the mean number of lesions per scan by 61.9% with longer-term treatment, while switch from teriflunomide to ofatumumab resulted in an almost complete suppression of Gd+ T1 lesion activity (97.2%) (**Figure 4B**)
- A significant reduction in the Gd+ T1 lesion activity observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies was numerically maintained over longer-term

Figure 4. A) Between group comparison - Cumulative number of Gd+ T1 lesions B) Within-group comparison during the core and extension phase for mean number of Gd+T1 lesions



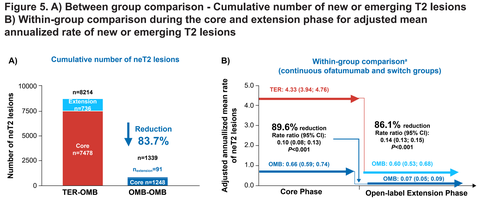
[a]Estimated from fitting a piecewise negative binomial model for the time period core phase and extension phase with log-link, adjusted for treatment and region as factors, baseline number of T1 Gd-enhancing lesions and patient's age at baseline as covariates. The natural log of the number of scans 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.

Number of neT2 lesions per year

- Similar to Gd+T1 lesions, tThe between-group analysis over a period of up to 4 years shows that earlier initiation of ofatumumab was associated with a reduction in the cumulative number of neT2 lesions by 83.7% (**Figure 5A**)
- 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 (**Figure 5A**)
- The within-group analysis showed that continuous use of ofatumumab was associated with a reduction in the neT2 lesions by 89.6% with longer-term treatment, while switch from teriflunomide to ofatumumab resulted in a pronounced reduction in the number of neT2 lesions (86.1%) (**Figure 5B**)
- A significant reduction in the neT2 lesion activity observed for ofatumumab versus teriflunomide in the core ASCLEPIOS I/II studies was numerically maintained over longer-term

Figure 5. A) Between group comparison - Cumulative number of new or emerging T2 lesions B) Within-group comparison during the core and extension phase for adjusted mean annualized rate of new or emerging T2 lesions



[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.

Conclusions

- Longer-term, continuous ofatumumab treatment up to 4 years showed sustained efficacy by reducing relapses, MRI lesions, and risk of disability worsening
- 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

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Acknowledgments

The authors acknowledge the following Novartis employees: **Venkateswarlu Bonala and Saimithra Thammera** for medical writing assistance and coordinating author reviews, and **Saketh Vellanki** for creative design assistance. The final responsibility for the content lies with the authors.

Disclosures

The study was supported by Novartis Pharma AG, Switzerland.

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.

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.

Wendy Su, Ronald Zielman, Ayan Das Gupta, Jing Xi, Dee Stoneman are employees of Novartis.

Jeffrey A. Cohen received personal compensation for consulting for Biogen, Bristol-Myers Squibb, Convelo, Gerrentech, Janssen, NervGen, Novartis, and PSI; speaking for H3 Communications; and serving as an Editor of Multiple Sclerosis Journal.

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

Poster presented at the annual meeting of the Consortium of Multiple Sclerosis Centers, June 1–4, 2022.

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