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DMT27

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

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CONCLUSIONS

1. With up to 5 years treatment with ofatumumab, >80% of patients remained free of 6m-CDW
2. Fewer disability events including PIRA and RAW, were experienced by patients who received ofatumumab continuously versus those initially randomized to teriflunomide
3. PBVC remained low (<1.5% loss) over 5 years in patients continuously on ofatumumab
   - Early ofatumumab initiation resulted in statistically significantly lower levels of PBVC versus later switch from teriflunomide to ofatumumab at year 5
4. Overall, these data support the early use of ofatumumab in patients with RMS

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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*
- 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 magnetic resonance imaging (MRI) lesions[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]

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)

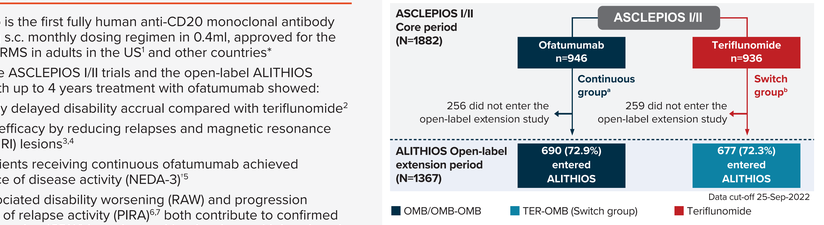
KEY ASSESSMENTS

- 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
- Refer to Table 1 for Patient demographics and clincal characteristics

RESULTS

- 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 5 years cumulatively (**Figure 1**)
- Of these, 1145/1367 (83.8%) patients were still receiving ofatumumab treatment at the time of data cut-off (25-Sep-2022)
- Overall, fewer CDW, PIRA and RAW events were observed in patients receiving continuous ofatumumab versus those initially randomized to teriflunomide and switched to ofatumumab (**Figures 2 & 3**); similar patterns were identified for the 3m-CDW
- RMS patients treated with disease modifying therapies accumulate disability primarily via PIRA (**Figure 3**)
- 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 (**Figure 3**)

Figure 1. Participant disposition



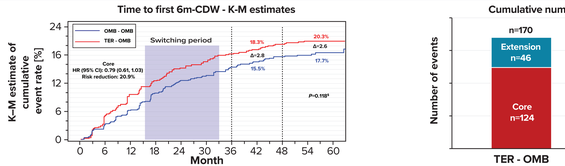
All percentages are calculated based on the number of patients in full analysis set in the corresponding column. Dotted line represents the first dose of ofatumumab in extension period.
Core period is period before the dotted line.

Only patients from the ASCLEPIOS I/II studies are included in the analyses presented here; *randomized to ofatumumab in the core; †switch group refers to the patients who were randomized to teriflunomide in the core and switched to ofatumumab during the extension period.

The 259 patients who took teriflunomide in the core period but did not enter the extension study are included in the switch group.

Note: Patients in ASCLEPIOS I/II had a flexible trial duration with individual patient's exposure of up to 2.3 years; Hauser et al. N Engl J Med. 2020; 383:546-557, supplementary figure S2

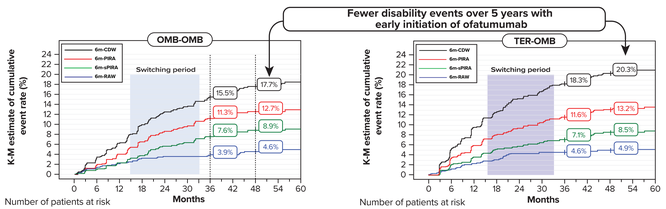
Figure 2. 6m-CDW



*p-value from log-rank test on difference between the cumulative K-M curves of the two treatment groups

6m-CDW, 6-month CDW; CDW, confirmed disability worsening; K-M, Kaplan-Meier; OMB-OMB, patients randomized to ofatumumab in the Core period and continuing ofatumumab in ALITHIOS; TER-OMB, patients randomized to teriflunomide during the Core and switched to ofatumumab during ALITHIOS.

Figure 3. Kaplan-Meier estimates of 6m-CDW, 6m-PIRA, 6m-sPIRA, and 6m-RAW up to 5 years



Number of patients at risk

CDW	944	881	831	752	664	595	551	526	497	429	159
PIRA	944	895	851	777	691	613	571	547	518	446	168
RAW	944	898	868	805	729	658	620	599	569	491	179
sPIRA	944	903	867	801	716	639	597	574	543	467	175

CDW	932	856	775	698	628	578	540	509	485	398	139
PIRA	932	872	805	726	661	612	574	543	520	435	152
RAW	932	892	839	771	700	651	618	583	557	457	162
sPIRA	932	884	826	751	691	642	605	572	546	459	161

6m-CDW, 6-month CDW; 6m-PIRA, 6-month confirmed PIRA; 6m-RAW, 6-month confirmed RAW; 6m-sPIRA, 6-month confirmed 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.

Table 1. Baseline demographics and clinical characteristics

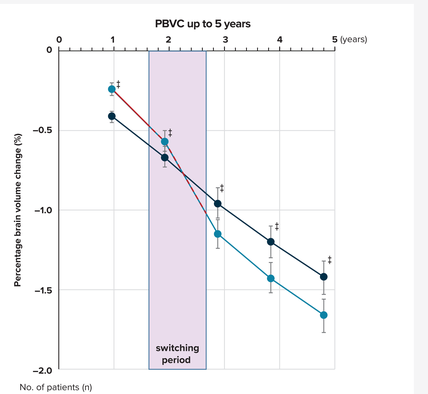
Demographics and clinical characteristics[a]	Ofatumumab continuous (N=946)		Switch from teriflunomide to ofatumumab (N=936)	
	Baseline of core study (N=946)	Baseline of extension study (N=690)	Baseline of core study (N=936)	Baseline of extension study[d] (N=677)
Age, years	38.4±9.04	38.1±8.69	38.0±9.22	40.1±9.21
Female, n (%)	637 (67.3)	483 (70.0)	636 (67.9)	456 (67.4)
BMI, kg/m²	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 last 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, cm³	13.72±13.79	Not available	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 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.

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

- Patients receiving continuous ofatumumab had a lower number of cumulative events versus the switch group

Figure 4. PBVC up to 5 years



No. of patients (n)

OMB/OMB-OMB	820	694	472	445	405
TER/TER-OMB	801	689	479	460	407

OMB/OMB-OMB; TER (Core); TER-OMB (during the switch period); TER-OMB

‡Statistically significant between-group comparison at each year for PBVC

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, all estimates are obtained from a mixed model for repeated measured with treatment and visit window as interacting factors, region as a factor and with age, baseline number of Gd-enhanced lesions, baseline T2 volume, and baseline normalized brain volume as continuous covariates.

- PBVC remained low (<1.5% loss) up to 5 years with continuous ofatumumab treatment[#] (**Figure 4**)
- Overall, ABVC remained low in patients receiving continuous ofatumumab with –0.27% BVC per year during Extension

Table 2. Annual Brain Volume Change

Group	Core (%)	P-value[ΠΠ]	Extension (%)	P-value[ΠΠ]
OMB/OMB-OMB	–0.34	0.115	–0.27	0.666
TER-OMB	–0.42		–0.28	

[ΠΠ]Between-group comparison for ABVC

  - A steeper decline was observed with TER-OMB vs OMB-OMB during Core while the annual rate became similar to OMB-OMB during Extension indicating a slowing of BVC following switch to ofatumumab

[#]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, all ABVC estimates are obtained from a random coefficient model with treatment, time period (core vs. extension) and region as factors, time, baseline number of Gd-enhanced lesions, baseline T2 volume, and baseline normalized brain volume as continuous covariates, the three-way interaction (treatment group x time period x time) and all its associated two-way interactions.

REFERENCES: 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: 963–739; **7.** Kappos et al. Clinical Trials. *JAMA Neurol* 2020; 77: 1132–40; **8.** Lublin F, et al. *Brain* 2022;145,9:3147-3161.

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

†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.

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