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# Five-Year Safety of Ofatumumab in People Living With Relapsing Multiple Sclerosis

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## CONCLUSIONS

- **Extended treatment with ofatumumab for up to 5 years is well-tolerated in patients with RMS, with no new or increased safety risks identified**
- **EAIRs of AEs and SAEs remain consistent with observations in the double-blind Phase 3 ASCLEPIOS I/II trials**
- **EAIRs of serious infections remained stable with no increased risk over 5 years**
- **Most reported cases of COVID-19 were non-serious, and the majority of patients recovered**
- **Mean IgG levels remained stable while mean IgM levels decreased but remained above the lower limit of normal**
- **No increase in risk of malignancies up to 5 years was observed**
- **Combined with its sustained efficacy[7], these findings support the favorable benefit–risk profile for ofatumumab in RMS patients**

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## INTRODUCTION

- Ofatumumab, a fully human anti-CD20 monoclonal antibody with a 20-mg subcutaneous monthly dosing regimen, is approved for treating relapsing multiple sclerosis (RMS) in adults[1a]
- In the Phase 3 ASCLEPIOS I/II trials, ofatumumab treatment up to 30 months had a favorable safety profile and was generally well tolerated in RMS patients[2]
- Ofatumumab treatment up to 4 years[b] was well tolerated, with no new safety risks identified[3,4] and efficacy sustained over time[5]
- Longer-term safety and efficacy assessments are important to further understand ofatumumab's benefit–risk profile in RMS patients

[a]Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features[6]; [b]data cut-off: 25-Sep-2021

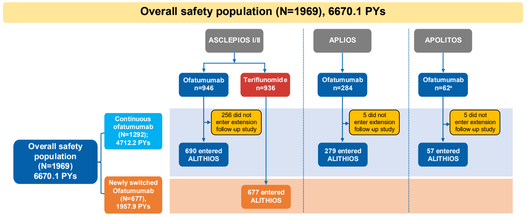
## OBJECTIVE

- To assess the longer-term safety and tolerability of ofatumumab treatment for up to 5 years (data cut-off: 25-Sep-2022) in patients with RMS

## METHODS

- In the overall safety population, 86.5% patients (1703/1969) completed the core studies and entered ALITHIOS **(Figure 1)**
- Of these, 83.1% patients (1416/1703) were still receiving ofatumumab treatment at the time of data cut-off (25-Sep-2022)

### Figure 1. Patient Population




[a]patients were either randomized to or switched to ofatumumab during the core study; PY, patient-years.

## RESULTS

- Baseline demographics and disease characteristics of RMS patient population are presented below (**Table 1**)

### Table 1. Baseline Demographics and Disease Characteristics

| | Continuous ofatumumab (N=1292) | Newly Switched Ofatumumab (N=677) | | Overall ofatumumab (N=1969) |
|---|---|---|---|---|
| | | Baseline from core study | Baseline from extension study | |
| **Age, years (mean±SD)** | 38.0±9.06 | 38.2±9.22 | 40.1±9.21 | 38.7±9.16 |
| **BMI, kg/m²** | 25.61±6.16 | 25.69±5.83 | 25.61±5.85 | 25.61±6.05 |
| **Female, n (%)** | 889 (68.8) | 456 (67.4) | 456 (67.4) | 1345 (68.3) |
| **Time since MS symptom onset, years (mean±SD)** | 8.48±7.33 | 8.06±7.21 | 9.94±7.23 | 8.98±7.33 |
| **Time since diagnosis, years (mean±SD)** | 5.87±6.31 | 5.45±6.00 | 7.33±6.01 | 6.37±6.25 |
| **EDSS score at baseline, (mean±SD)** | 2.90±1.33 | 2.77±1.32 | 2.82±1.46 | 2.88±1.38 |
| **IgG levels at baseline, g/L (mean±SD)** | 10.31± 2.24 | 10.35±2.09 | 10.23±2.14 | 10.28±2.21 |
| **IgM levels at baseline, g/L (mean±SD)** | 1.34± 0.65 | 1.36±0.74 | 1.14±0.67 | 1.27±0.66 |
| **Median duration of time at risk, years** | 3.8 | 3.2 | 3.2 | 3.3 |
| **Total time at risk, PYs** | 4712.2 | 1957.9 | 1957.9 | 6670.1 |

For OMB newly switched patients, their baseline values from extension study contribute to the overall ofatumumab baseline values. Baseline values are a typical of broad RMS population.

### Overall safety profile

- EAIR per 100 PYs of adverse events (AEs) and serious adverse events (SAEs) over 5 years of ofatumumab treatment remained consistent during the ASCLEPIOS I/II trials and ALITHIOS (**Table 2**)
- No new safety signals were identified
- The most common AEs were infections (COVID-19 [30.3%], nasopharyngitis [19%], upper respiratory tract infection (URTI) [12.8%] and urinary tract infection (UTI) [12.7%])
  - Most (90.3%) infections resolved without discontinuing ofatumumab treatment

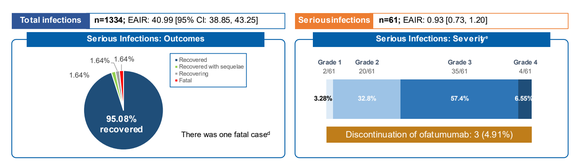
### Table 2. Overall Safety Profile Over 5 Years of Treatment

| Adverse event | Core, ASCLEPIOS | | | | Core + extension, Overall OMB, (N=1969) | |
|---|---|---|---|---|---|---|
| | OMB; n (%) | OMB; EAIR (95% CI) | TER; n (%) | TER; EAIR (95% CI) | n (%) | EAIR (95% CI) |
| **Patients with at least one AE** | 791 (83.61) | 188.55 [175.86, 202.16] | 788 (84.2) | 188.92 [176.18, 202.58] | 1771 (89.9) | 124.65 [118.97, 130.59] |
| **Patients with at least one SAE** | 83 (8.77) | 5.56 [4.48, 6.89] | 73 (7.8) | 4.94 [3.93, 6.21] | 289 (14.7) | 4.68 [4.17, 5.26] |
| **AEs leading to OMB discontinuation** | 54 (5.70) | -- | 49 (5.2) | -- | 139[a] (7.1) | -- |
| **Infections and infestations** | 488 (51.58) | 51.14 [46.80, 55.88] | 493 (52.7) | 52.59 [48.14, 57.44] | 1334 (67.75) | 40.99 [38.85, 43.25] |
| **Serious infections** | 24 (2.54) | 1.55 [1.04, 2.31] | 17 (1.8) | 1.12 [0.69, 1.80] | 106 (5.38) | 1.63 [1.35, 1.97] |
| **Serious infections (excluding COVID-19)** | 24 (2.54) | 1.55 [1.04, 2.31] | 17 (1.8) | 1.12 [0.69, 1.80] | 61 (3.09) | 0.93 [0.73, 1.20] |
| **Serious COVID-19 infections** | 0 | 0 | 0 | 0 | 50 (2.53) | 0.75 [0.57, 1.00] |
| **Injection-related systemic reactions** | 195 (20.61) | 15.49 [13.46, 17.83] | 143 (15.3) | 10.90 [9.25, 12.84] | 508 (25.79) | 10.06 [9.22, 10.98] |
| **Injection-site reactions** | 103 (10.88) | 7.21 [5.94, 8.74] | 52 (5.55) | 3.54 [2.70, 4.65] | 243 (12.34) | 4.08 [3.60, 4.63] |
| **Malignancies** | 5 (0.53) | 0.32 [0.13, 0.77] | 4 (0.4)[c] | 0.26 [0.10, 0.69] | 21 (1.06) | 0.32 [0.21, 0.48] |
| **Deaths** | 0 | -- | 1[d] | -- | 9[b] (0.46) | -- |

[a]AEs related to reduced IgM levels is the most common reason for treatment discontinuation (n=71 [3.6%]); [b]PT for these 9 cases include: sudden death (n=1), completed suicide (n=1), COVID-19 and COVID-19 pneumonia (n=2), COVID-19 (n=2), intestinal metastasis (n=1), pneumonia and septic shock (n=1); pneumothorax (n=1); [c]One case of basal cell carcinoma was not listed as a serious AE; [d]death was due to aortic dissection.

### Serious infections (Excluding COVID-19)

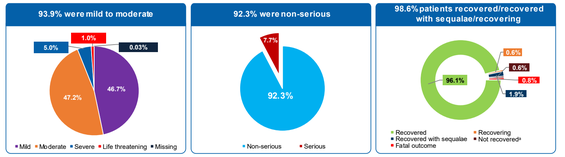
- The overall EAIR per 100 PYs of serious infections (excluding COVID-19) was consistent with the ASCLEPIOS I/II trials (EAIR: 1.55) and no increased risk was observed over 5 years of ofatumumab treatment; most common serious infections (excluding COVID-19) included appendicitis[a] (n=13) and pneumonia[b] (n=9)
- One case of serious opportunistic infection (Pneumocystis jirovecii pneumonia[c]) was reported; the final diagnosis was not confirmed by an external expert and the clinical course was not suggestive of Pneumocystis jirovecii pneumonia




[a]all cases recovered and majority of them were not related to ofatumumab treatment; [b]Majority (77.77%) cases recovered; [c]Patient was suspected to have serious, Grade 2 *Pneumocystis jirovecii* pneumonia and was assessed by independent, external expert. No action was taken on ofatumumab therapy and patient recovered; [c]one fatal case was due to pneumonia and septic shock [n=1]; [a]severity grading is done by the investigator based on CTCAE version 5.0.

### COVID-19 outcomes

- As of 25-Sep-2022, 38% (648/1703) of ofatumumab-treated patients entering ALITHIOS reported COVID-19 (confirmed [n=603]; suspected [n=45])
- 93.9% of cases were mild or moderate in severity and 92.3% were non-serious
- 98.6% of patients treated with ofatumumab recovered, recovered with sequalae or were recovering from COVID-19



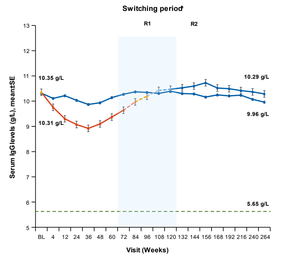

- Most patients (87.5%) had no interruption in ofatumumab treatment and only 5 patients discontinued treatment due to COVID-19 or COVID-19 pneumonia
- At the data cutoff, 167/704 (23.7%) patients had confirmed COVID-19 after being fully vaccinated; mostly were mild to moderate and most recovered
- Five (0.8%) patients had fatal outcomes[b] (3 patients were unvaccinated; 2 patients were fully vaccinated[c])
- Only 3.8% (n=64) patients had a COVID-19 reinfection

[a]at the time of data cutoff; [b]5 fatal cases consisted of the following: COVID-19 [n=2], COVID-19 pneumonia [n=1], COVID-19 and COVID-19 pneumonia [n=1], COVID-19 pneumonia and pneumothorax [n=1]; [c]Fully vaccinated means at least 14 days after completing the primary vaccine series, may or may not be after booster. These 2 fatal cases are before booster, one case had multiple risk factors for severe COVID-19 and the other case which was complicated by a bilateral pneumothorax).

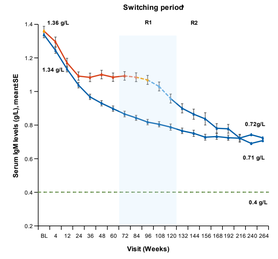
### Mean Ig levels

- The majority of patients had Ig levels above lower limit of normal (LLN) (98% in IgG and 69.4% in IgM) **(Figure 2A, Figure 2B)**
- Treatment interruption/discontinuation[a] was reported in 3 (0.2%)/4 (0.2%) patients due to low IgG; and 202 (10.3%)/71 (3.6%) patients due to low IgM
- Sensitivity analyses confirmed that interruption/discontinuation of ofatumumab due to low IgG/IgM did not impact overall IgG/IgM pattern

### Figure 2A: Mean IgG Levels




### Figure 2B: Mean IgM Levels

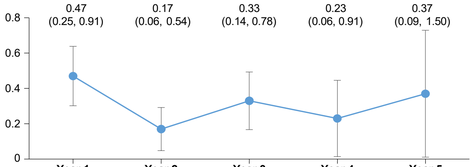



[a]Treatment interruption PT due to low IgM include blood immunoglobulin M decreased, immunoglobulins decreased, hypogammaglobulinemia and hypoglobulinemia while for discontinuation includes blood immunoglobulin M decreased, immunoglobulins decreased, blood immunoglobulin M abnormal and hypogammaglobulinemia while treatment interruption PT due to low IgG include blood immunoglobulin G decreased and for discontinuation include immunoglobulins decreased, blood immunoglobulin G abnormal, blood immunoglobulin G decreased.

### Malignancy

- EAIRs for malignancies did not increase over time in the overall ofatumumab population **(Figure 3)**
- Cumulatively (core+extension), malignancies were reported in 21 patients[a] (1.07%) with EAIRs of 0.32 (95% CI: 0.21, 0.48)
- Median onset time since the first dose of ofatumumab was 565 days (191-1747 days)

### Figure 3: EAIR of malignancy by year in overall safety population




| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Patients (N)** | 1969 | 1812 | 1618 | 1381 | 615 |
| **PY** | 1901 | 1719 | 1531 | 877 | 535 |
| **No. of events** | 9 | 3 | 5 | 2 | 2 |

[a]21 malignancies includes breast and nipple neoplasms malignant (n=9); colorectal neoplasms malignant (n=1); metastases to specified sites (n=1); esophageal neoplasms malignant (n=1); neoplasms malignant site unspecified NEC (n=1); non-Hodgkin's lymphomas NEC (n=1); ovarian neoplasms malignant (excl germ cell) (n=1); renal neoplasms malignant (n=2); skin melanomas (excl ocular) (n=1); skin neoplasms malignant and unspecified (excl melanoma) (n=4).

**ABBREVIATIONS:** AE, adverse event; BMI, body mass index; EAIR, Exposure-adjusted incidence rates per 100 PY; EDSS, Expanded Disability Status Scale; Ig, immunoglobulin; MS, multiple sclerosis; OMB, ofatumumab; PT, preferred term; PYs, patient-years; RMS, relapsing multiple sclerosis; SAE, serious adverse event; SD, standard deviation.

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**REFERENCES:** 1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed February 17, 2022). 2. Hauser SL, et al. N Engl J Med 2020;383:546–57. 3. Hauser SL, et al. Mult Scler. 2022; 28 (10): 1576-1590. 4. Sacca F, et al. Oral presentation presented at EAN 2022; 5. Kappos L, et al; Poster presented at EAN 2022. 6. Kesimpta (ofatumumab). Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/kesimpta-epar-product-information_en.pdf Accessed March 8, 2023.7. Kappos L, et al. ePresentation at EAN 2023.

**Definitions:** EAIR, exposure-adjusted incidence rate per 100 patient years; Exposure-adjusted incidence rates per 100 PYs are defined as the number of patients with a particular event during 100 years of exposure to a treatment, estimated by Poisson regression where patients were censored at time of first event OMB. Switching period refers to the patients started with teriflunomide and not applicable to the patients with ofatumumab in core period; For TER/OMB group, data from 1st dose of TER until last dose of OMB plus 100 days/ analyses cut-off date have been used; R1: The first patient with first treatment-emergent assessment in OMB period after switching to OMB (72 weeks); R2: The last patient with last treatment-emergent assessment in TER period before switching to OMB (120 weeks); For all pooled analyses, a fixed value of LLN (using ALITHIOS study reference) was used: IgG: 5.65 g/L and IgM: 0.4 g/L; Per core and extension study protocols, investigators were required to interrupt study treatment if IgM levels fell below 10% LLN or IgG levels fell below 20% LLN. The requirement to interrupt treatment due to low IgM or IgG levels was removed with protocol amendment 2 for study COMB157G2399 and is left to the discretion of the investigator

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