Impact of Ofatumumab on Immune Responses Post-vaccination in RMS Patients: ALITHIOS Vaccination Sub-study Design

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Background

ALITHIOS study

- Ofatumumab, a fully human anti-CD20 monoclonal antibody, targets select B-cell subsets, allowing B-cell reconstitution and preserving pre-existing humoral immunity[1]
- Immunoglobulins (Ig) play an important role in adaptive/humoral immunity[2]
- Reduced serum IgG and/or IgM levels are known to occur with other anti-CD20 therapies in MS patients, resulting in an increased risk of infection[3-5]
- In the ASCLEPIOS phase 3 trials, no association was observed between decreased Ig levels and the risk of serious infections in ofatumumab-treated patients for up to 96 weeks[6]
- ALITHIOS (NCT03650114), an open-label, single-arm umbrella extension phase 3b trial was designed to assess the benefit-risk profile of ofatumumab (20 mg SC every 4 weeks) and its tolerability for up to 5 years in RMS patients[7]
  - The study enrolled 1703 RMS patients from the APLIOS, APOLITOS and ASCLEPIOS I/II trials who continued ofatumumab treatment
- A recent long-term safety analysis from ALITHIOS has evaluated IgM/IgG levels and their association with infection, for up to 3.5 years[8]

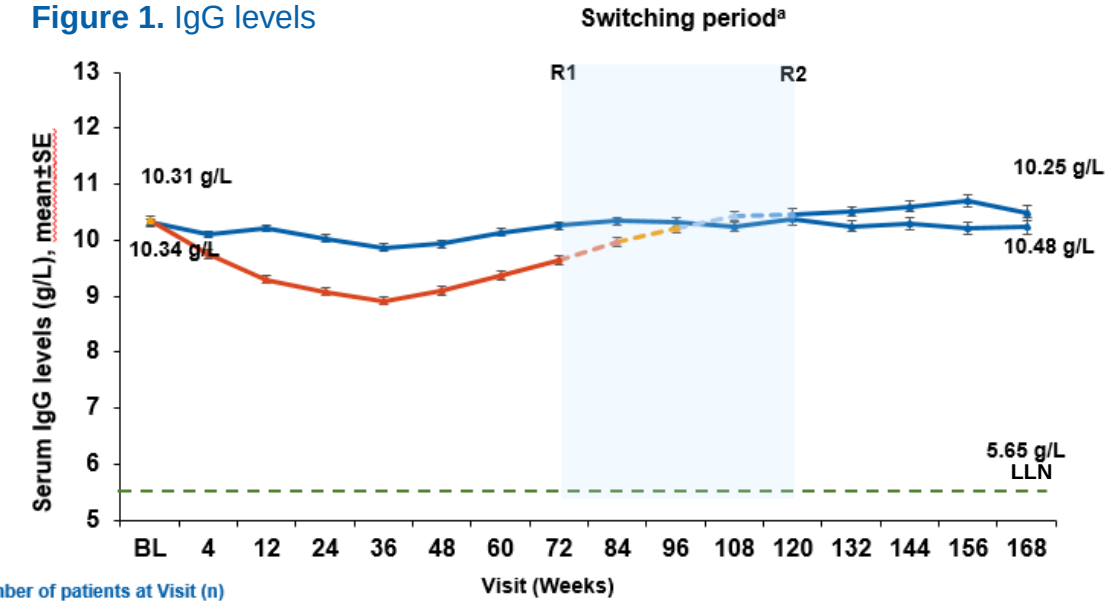
Ig, immunoglobulin; MS, multiple sclerosis; RMS, relapsing multiple sclerosis; SC, subcutaneous.

1. Dubey D, et al. *Neurol Neuroimmunol Neuroinflamm.* 2017;4(6) e405. 2. Furst DE. *Semin Arthritis Rheum.* 2009;39:18-29. 3. Kim S-H, et al. *JAMA Neurol*. 2013;70:1110-1117. 4. Tallantyre EC, et al. *J Neurol*. 2018;265:1115-1122. 5. Derfuss T, et al. *Mult Scler.* 2019;25(S2):3-130 (Presented at ECTRIMS 2019: OP65). 6. Wiendl H, et al. Presented at: the *MSVirtual*. 2020; P0236. 7. https://clinicaltrials.gov/ct2/show/NCT03650114 (accessed June 10, 2021). 8. Novartis data on file.

Background

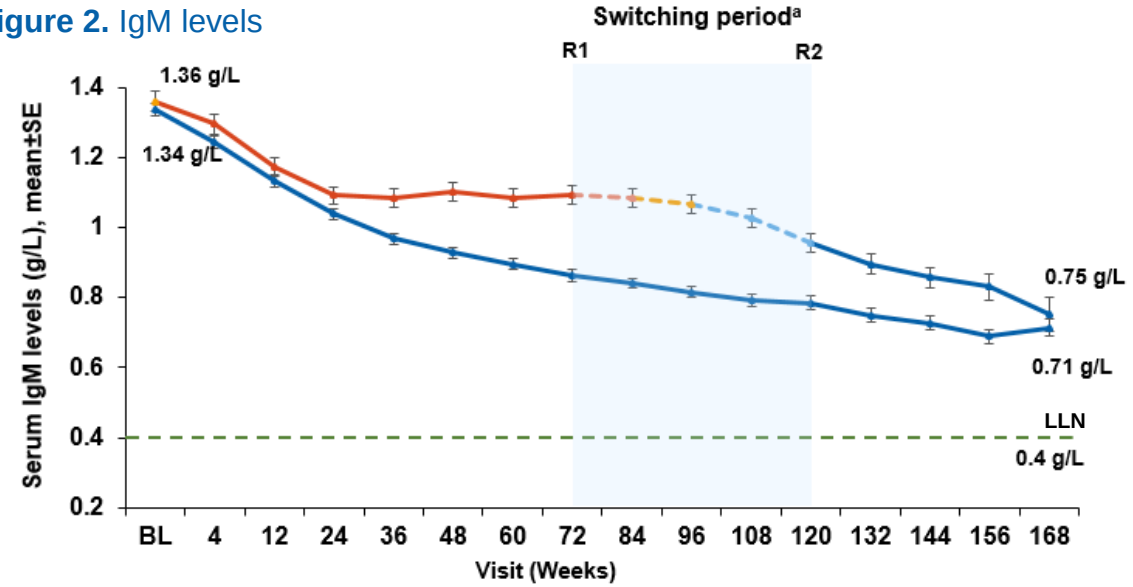
ALITHIOS: IgG/IgM levels in ofatumumab-treated RMS patients up to 3.5 years

Figure 1. IgG levels



Number of patients at Visit (n)	BL	4	12	24	36	48	60	72	84	96	108	120	132	144	156	168
Long-term OMB	1269	1233	1248	1219	1180	1132	1083	902	961	758	712	602	514	469	345	241
TER/OMB	675	672	673	666	672	669	666	670	635	634	635	567	499	447	350	215
Before/ After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 321	167/ 468	72/ 495	499	447	350	215

Figure 2. IgM levels



Number of patients at Visit (n)	BL	4	12	24	36	48	60	72	84	96	108	120	132	144	156	168
Long-term OMB	1271	1235	1250	1221	1182	1134	1088	906	965	768	715	603	515	477	350	248
TER/OMB	675	672	673	666	672	669	666	670	635	634	635	567	506	451	359	220
Before/ After switch	675	672	673	666	672	669	666	664/ 06	477/ 158	313/ 321	167/ 468	72/ 495	506	451	359	220

- The mean serum **IgG remained stable for up to 3.5 years** of ofatumumab treatment (*Figure 1*)
  - IgG levels remained similar to the baseline values in all quartiles[b] with low discontinuations (0.3%)
- The mean serum **IgM declined over time but remained above LLN for up to 3.5 years** (*Figure 2*)

Ig, immunoglobulin; LLN, lower limit of normal; SE, standard error; RMS, relapsing multiple sclerosis; TER/OMB, switched from teriflunomide to ofatumumab.

Long-term OMB, N=1292; TER/OMB, N=677. For all pooled analyses, a fixed value of LLN (using ALITHIOS study reference) was used: IgG: 5.65 g/L/IgM: 0.4 g/L. 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). [a]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 the first dose of TER till last dose of OMB plus 100 days/analysis cutoff date have been used. [b]Quartiles for IgG (g/L) Q1: 8.57, Q2: 10.07 and Q3: 11.51.
Novartis data on file.

Background

ALITHIOS: Association between IgM/IgG decrease and serious infections in ofatumumab-treated RMS patients up to 3.5 years

Patients with at least one serious infection within 1 month prior and until 1 month after any series of drops in IgM/IgG <LLN

	IgM				IgG				Overall	
	<LLN (N=454[a])		≥LLN (N=1512[b])		<LLN (N=30[a])		≥LLN (N=1936[b])		N=1969	
	n (%)	IR[c]	n (%)	IR[c]	n (%)	IR[c]	n (%)	IR[c]	n (%)	IR[c]
Patients with ≥1 serious infection	3 (0.7)	0.80	44 (2.9)	1.38	1 (3.3)	7.02	55 (2.8)	1.34	58 (2.9)	1.39
Herpes zoster (PT)	1 (0.2)	0.27	0	0	0	0	1 (0.1)	0.02	1 (0.1)	0.02
URTI (PT)	1 (0.2)	0.27	0	0	0	0	1 (0.1)	0.02	1 (0.1)	0.02
UTI (PT)	1 (0.2)	0.27	3 (0.2)	0.09	0	0	6 (0.3)	0.14	6 (0.3)	0.14
Escherichia UTI (PT)	0	0	1 (0.1)	0.03	NA	NA	NA	NA	1 (0.1)	0.02
Kidney infection (PT)	0	0	1 (0.1)	0.03	NA	NA	NA	NA	1 (0.1)	0.02
Pneumonia (PT)	0	0	8 (0.5)	0.25	1 (3.3)	7.02	8 (0.4)	0.19	9 (0.5)	0.21

- **The overall incidence of serious infections in ofatumumab-treated patients was low (1.39 IR per 100 patient-years) for up to 3.5 years**
  - There was no association between decreased IgG/IgM levels and risk of serious infections

Ig, immunoglobulin; IR, incidence rate; LLN, lower limit of normal; PT, preferred term; PY, patient-year.
[a]Number of patients with IgM/IgG <LLN at least once at any time during the post-baseline visits. [b]Number of patients with no occurrence of IgM/IgG <LLN at least once at any time during the post-baseline visit. [c]IR per 100 PY estimated via a Poisson regression model with only treatment as the factor and with the log-link and natural logarithm of time as the offset variable. For all pooled analyses, a fixed value of LLN (using ALITHIOS study reference) was used: IgM: 0.4 g/L; and IgG: 5.65 g/L.
Novartis data on file.

Background

ALITHIOS vaccination sub-study

- Considering the role of B cells in immune response, it is important to assess protective immune responses against clinically relevant vaccines in ofatumumab-treated patients
- To date, there are limited data on humoral response post vaccination in patients treated with ofatumumab

The open-label umbrella extension ALITHIOS vaccination sub-study *(NCT03650114)* will **investigate the effect of B-cell depletion by ofatumumab** on the elicitation of **acquired humoral immune responses post-vaccination** with the selected vaccines and KLH neo-antigen in patients with RMS

Objective

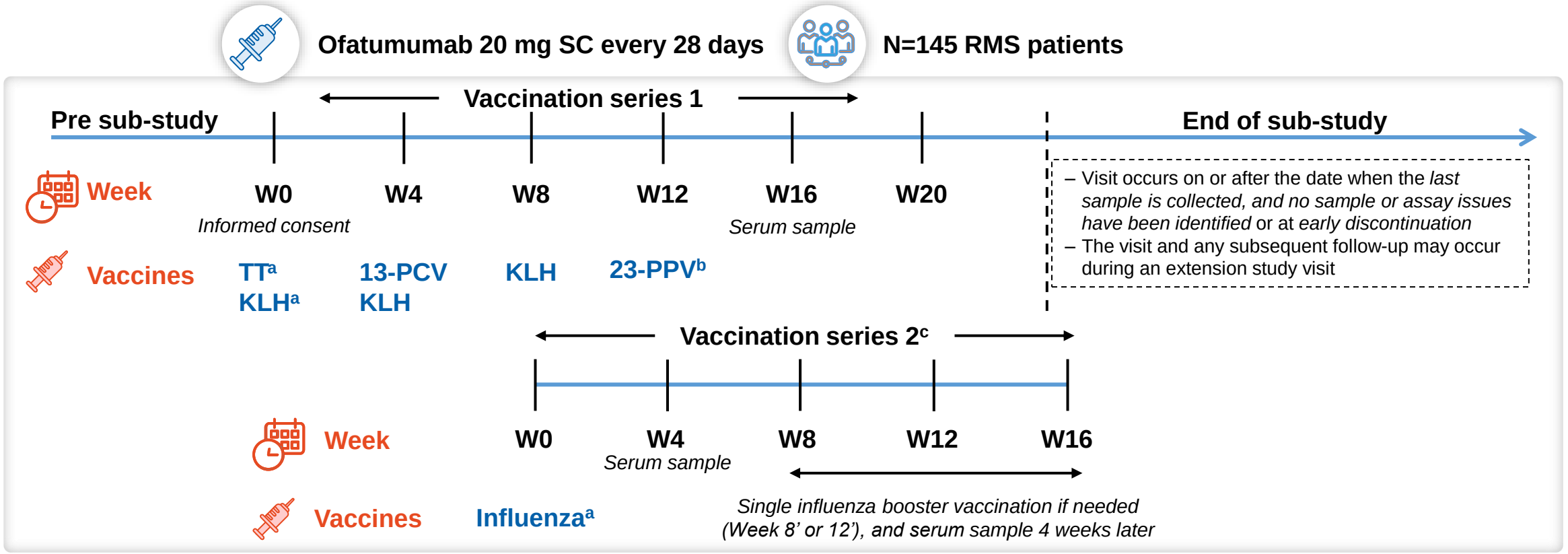
To present the design of ALITHIOS vaccination sub-study in patients with RMS treated with ofatumumab

KLH, keyhole limpet hemocyanin; RMS, relapsing multiple sclerosis.

Methods

ALITHIOS vaccination sub-study: Design

- This is a single-arm, vaccination sub-study embedded in the phase 3b ALITHIOS study. The vaccinations are administered in 2 series



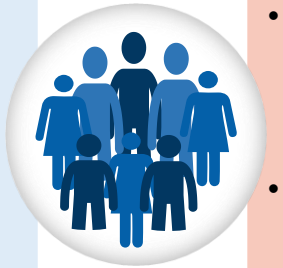
13-PCV, 13-valent pneumococcal conjugate vaccine; 23-PPV, 23-valent pneumococcal polysaccharide vaccine; KLH, keyhole limpet hemocyanin; RMS, relapsing multiple sclerosis; SC, subcutaneous; TT, tetanus toxoid; W, week.
[a]Subjects must receive continuous open-label ofatumumab treatment for a minimum of 12 weeks immediately preceding the first vaccination visit in each series. [b]Minimum interval of 8 weeks between 13-PCV and 23-PPV vaccinations.
[c]Vaccination series 2 for influenza must be coordinated to occur within the estimated start/end dates for the 2020-2021/2021-2022 influenza season for the study site where the subject is enrolled.

Methods

ALITHIOS vaccination sub-study: Patient population

Key inclusion criteria

- Received at **least 12 weeks of continuous open-label ofatumumab[a]** treatment immediately before study enrolment
- Received **at least one previous immunisation** against
  - Tetanus toxoid (TT)
  - Tetanus and diphtheria (DT/Td)
  - Tetanus, diphtheria, and acellular pertussis (DTaP/Tdap)
  - Tetanus, diphtheria, acellular pertussis, inactivated polio vaccine (Tdap-IPV), or
  - Other TT-containing vaccines



Key exclusion criteria

- **Known hypersensitivity to any component of any of the vaccines** in the vaccination sub-study
- **Low IgG/IgM levels** requiring an ofatumumab treatment interruption **within the 12 weeks** immediately before enrolment
- Any **major episode of infection requiring hospitalisation** or treatment with **intravenous antibiotics within 4 weeks or oral antibiotics within 2 weeks** before the first vaccination visit
- Before enrolment, history of immunisation with
  - any **TT-containing vaccine within 2 years**
  - any **13-PCV** or **23-PPV within 5 years**
  - **2020-2021 or 2021-2022 seasonal influenza vaccine**
  - other non-live vaccines within 4 weeks
- History of **previous exposure to KLH**
- Known **clinical diagnosis of influenza** infection during the **2020-2021 (or 2021-2022)** influenza season before enrolment

13-PCV, 13-valent pneumococcal conjugate vaccine; 23-PPV, 23-valent pneumococcal polysaccharide vaccine; Ig, immunoglobulin; KLH, keyhole limpet hemocyanin.
[a]Ofatumumab treatment not interrupted during the 12 weeks immediately prior to sub-study.
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Methods

ALITHIOS vaccination sub-study: Objectives

Primary objective

- To characterise the humoral immune response[a] to the TT vaccine *(8 weeks after immunisation)*

Secondary objectives

- To characterise the humoral immune response[a] to the:
  - TT vaccine *(4 weeks after immunisation)*
  - 13-PCV *(4 and 8 weeks after immunisation)*
  - 13-PCV including booster at 8 weeks later by 23-PPV *(4 and 8 weeks after immunisation)*
  - KLH neo-antigen *(4, 8 and 12 weeks after administration)*
  - 2020-2021/2021-2022 seasonal quadrivalent influenza vaccine *(4 weeks after immunisation)*

- Impact of ofatumumab exposure on immune response[a] to TT and influenza vaccination

[a]*Humoral immune response in patients with RMS is assessed by measuring antibody titres to vaccine antigens.*

13-PCV, 13-valent pneumococcal conjugate vaccine; 23-PPV, 23-valent pneumococcal polysaccharide vaccine; KLH, keyhole limpet hemocyanin; RMS, relapsing multiple sclerosis; TT, tetanus toxoid.

Methods

ALITHIOS vaccination sub-study: Sample size and statistical analysis

Sample size determination

- **Approximately 145 patients with RMS will be enrolled in the study**
  - Allowing for a 16% drop out rate, this will ensure at least 120 patients with available data for pre-immunisation tetanus antibody titres and post-immunisation tetanus antibody titres at 8 weeks after administration

Statistical analysis

- **The primary analysis will estimate the proportion of responders to the TT vaccine with a 95% CI based on a binominal distribution**
- Efficacy analysis: The geometric mean level of pre- and post-vaccination antibody titre levels will be reported. Efficacy analysis will be performed in the FAS
- Safety analysis: Recording of adverse events and vital signs will be performed in the safety analysis set, defined as patients who receive at least one dose of ofatumumab

CI, confidence interval; FAS, full analysis set; RMS, relapsing multiple sclerosis; TT, tetanus toxoid.

Conclusions

- Long-term findings of ofatumumab treatment over ~3.5 years were consistent with the 96-week phase 3 ASCLEPIOS trial data,[1] which showed that
  - the mean IgG levels remain similar to baseline values and mean IgM levels remain above the LLN throughout the study time period[2]
  - the overall incidence of infections was low, and no association was observed between decreased Ig levels and the risk of serious infections[2]
- FPFV for the vaccination sub-study was in September 2020, and the first interim results are expected in Q2 of 2022
- The vaccination sub-study will provide a better understanding of the effect of B-cell depletion by ofatumumab on immune responses post vaccination
- The results of the vaccination sub-study will help to guide physicians treating RMS patients with ofatumumab, with respect to primary and secondary immunisations

FPFV, first patient first visit; Ig, immunoglobulin; LLN, lower limit of normal; RMS, relapsing multiple sclerosis.

1. Wiendl H, et al. Presented at the *MSVirtual*. 2020; P0236. 2. Novartis data on file.

Thank you