AMA-VACC: Clinical trial assessing the immune response to SARS-CoV-2 mRNA vaccines in siponimod treated patients with secondary progressive multiple sclerosis

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Disclosures

Tjalf Ziemssen has received research support, consulting fee, and honoraria for lectures from Alexion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, Teva.

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Introduction

- SARS-CoV-2 mRNA vaccines are a key factor in the fight against the COVID-19 pandemic across the globe. Although evidence on the effect of SARS-COV-2 vaccinations in multiple sclerosis patients receiving immunomodulating treatment is growing, immune response of SPMS patients treated with S1PR modulators has not been systematically analyzed.[1,2]
- Siponimod is a highly selective $S1P_1$ and $S1P_5$ receptor modulator authorized by the EMA for the treatment of SPMS with active disease. One key mode of action for siponimod is the retention of lymphocytes in the lymph nodes[3].
- As both humoral and cellular immune responses play an important role in vaccinations, it is essential to investigate not only the antibody response but also the effect on T-cells especially in a therapy such as siponimod.

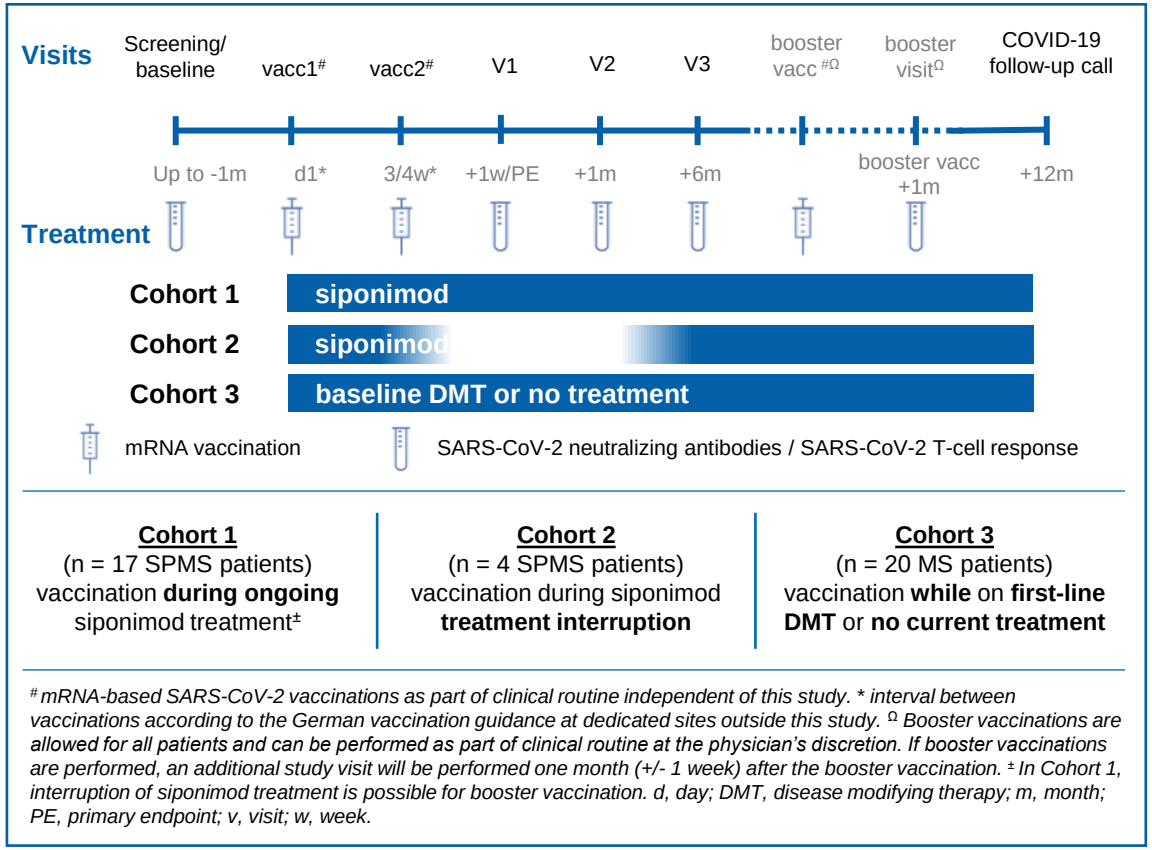
With this study, we are aiming to characterize the immune response in siponimod treated SPMS patients after initial and booster SARS-CoV-2 mRNA vaccination and offer guidance to treating physicians and patients for the coordination of MS treatment and vaccination.

1. Negahdaripour et al. (2021) Int Immunopharmacol 99:108021. **2.** Bigaut et al. (2021) Neurol Neuroimmunol Neuroinflamm. 8(5):e1055. **3.** Behrangi et al. (2019) Cells. 7;8(1):24.

Methods

- AMA-VACC is a clinical three-cohort, prospective, open-label study with 41 MS patients enrolled at 10 sites in Germany.
- (SP)MS patients without previous or acute SARS-CoV-2 infection currently treated with siponimod or a first line DMT (glatirameracetate, dimethylfumarate, interferons, teriflunomide) or no current therapy as part of clinical routine were eligible to participate.
- Participants received SARS-CoV-2 mRNA vaccinations independently of this study as part of clinical routine (**Figure 1**).
- **Neutralizing antibodies** were analyzed utilizing the cPassTMSARS-CoV-2 Neutralization Antibody Detection Kit from GenScriptUSA Inc(L00847).
- **SARS-CoV-2 reactive T-cells** were detected with the CoV-iSpot Interferon-γ + Interleukin-2 (ELSP 7010 strip format) from GenID®GmbH. Each ELISpot assay was performed with $2x10^5$ PBMCs (peripheral blood mononuclear cells).

Figure 1: Study design



SPMS = Secondary Progressive Multiple Sclerosis

Demographics and baseline information

- Patient characteristics at screening are depicted in **Table 1**.
  - 17, 4, and 20 patients were recruited into cohort 1, 2, and 3, respectively.
  - In cohort 2, siponimod treatment was interrupted for 15.3 (7-25) days before 1st vaccination until 29.7 (28-33) days after 2nd vaccination.
  - Participants were of advanced age (51-56 years) with a long MS history (9-17 years). Age and MS history were both considerably longer in the siponimod cohorts (cohorts 1 and 2).
  - At baseline, all patients were tested negative for a previous or acute SARS-CoV-2 infection by assessing IgA (≤ 0.8 Index) and IgG (≤ 50 AU/ml) levels and a PCR test.

Variable*	Cohort 1 – siponimod continuously	Cohort 2 – siponimod interrupted for vaccination	Cohort 3 – first line DMT / no current treatment
N	17	4	20
Age, years	56 [42; 66]	56 [53; 58]	51 [22; 71]
Sex, female, n (%)	13 (76.5)	3 (75.0)	16 (80.0)
MS diagnosis, n (%)			
SPMS, active SPMS	17 (100.0)	4 (100.0)	2 (10.0)
RRMS, active RRMS	-	-	12 (60.0)
MS, not specified	-	-	6 (30.0)
Time since first MS diagnosis, years	15.06 [5.4; 30.9]	17.60 [3.4; 25.0]	9.13 [3.2; 37.9]
MS treatment, n (%)			
Siponimod	17 (100.0)	4 (100.0)	-
Glatirameracetate	-		6 (30.0)
Interferon	-		3 (15.0)
Teriflunomide	-		7 (35.0)
No current therapy	-		4 (20.0)
Time on current treatment, years	0.63 [0.1; 0.9]	0.34 [0.2; 0.5]	4.33 [2.8; 22.1]
Vaccination, n (%)			
1st (BioNTech | Moderna)	16 (94.1) | 1 (5.9)	4 (100.0) | -	19 (95.0) | 1 (5.0)
2nd (BioNTech | Moderna)	16 (94.1) | 1 (5.9)	4 (100.0) | -	19 (95.0) | 1 (5.0)
Vaccination time interval (days)			
1st to 2nd vaccination	41.0 [21; 42]	36.5 [21; 42]	42.0 [21; 47]
2nd vaccination to Visit 1	7.0 [6; 10]	6.0 [6; 10]	7.0 [6; 10]

DMT = Disease modifying treatment

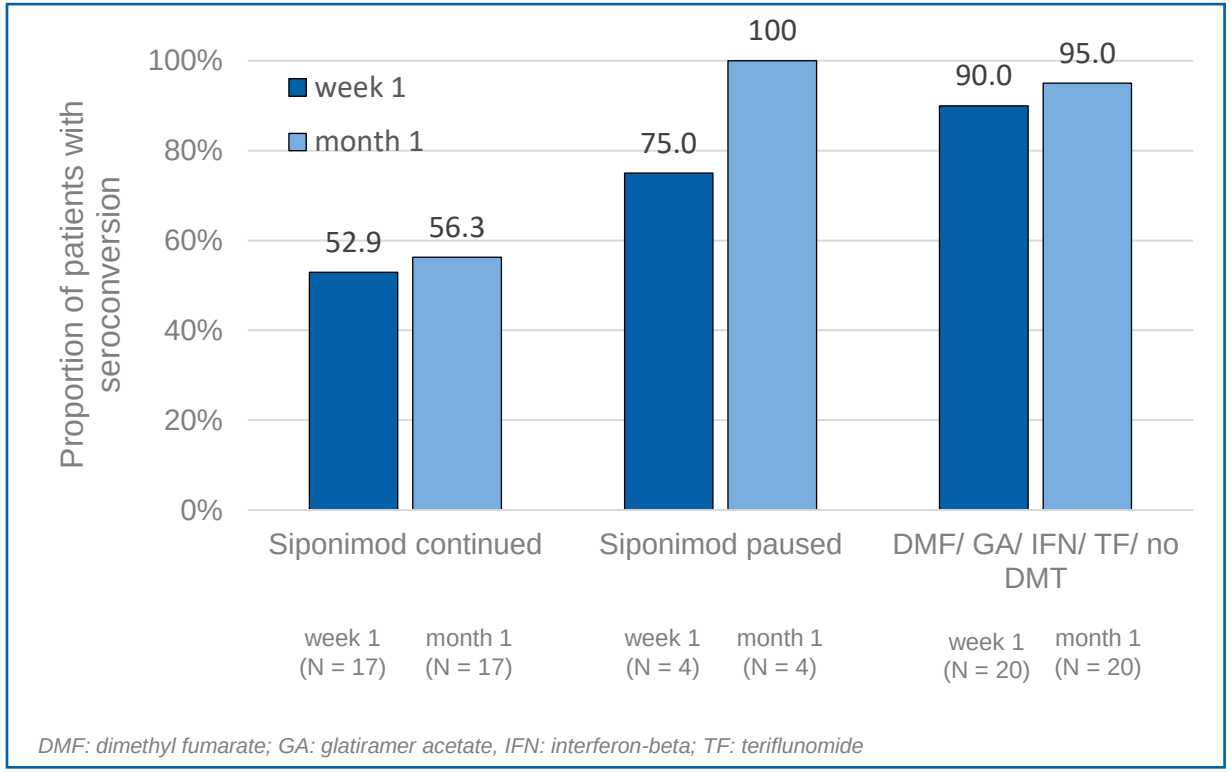
* if not indicated otherwise, data are presented as median [min; max]

Results

Development of SARS-CoV-2 neutralizing antibodies

- Neutralizing antibodies (NAb) represent only **a subset of all specific antibodies** and are considered a **more stringent** correlate of protective immunity. Total anti-SARS-CoV-2 IgGs were not measured yet but might further contribute to immunity.
- NAb could be detected some point (at either one week or one month or both time points) in **65% of continuously treated siponimod patients** and 95% of patients on first line DMTs.
- Limited results from the very small-sized cohort 2 (n=4) are insufficient to support an interruption of siponimod.
- Note: Participants in cohort 1 and 2 were older and had a longer MS history than cohort 3. Based on recently published data, especially **higher age** is negatively correlated with SARS-CoV-2 neutralizing antibody titers after vaccination and can therefore be considered as **confounding factor** in this analysis[5,6].

Figure 1: Development of SARS-CoV-2 neutralizing antibodies



DMF: dimethyl fumarate; GA: glatiramer acetate, IFN: interferon-beta; TF: teriflunomide

5. Collier, D.A., Ferreira, I.A.T.M., Kotagiri, P. et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature 596, 417–422 (2021). 6. Bates, T.A., Leier, H.C., Lyski, Z.L. et al. Neutralization of SARS-CoV-2 variants by convalescent and BNT162b2 vaccinated serum. Nat Commun 12, 5135 (2021).

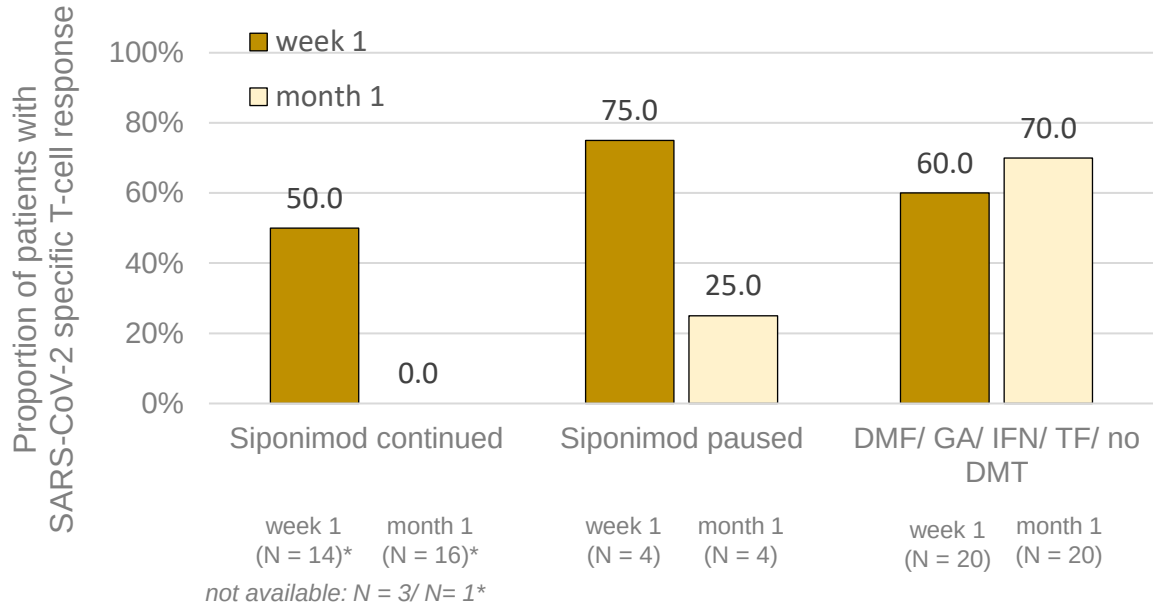
Results

N = the number of patients whose T cell response could be measured at the respective time points.
**Of all patients with reactive T-cells at the 6-months visit (light blue), 50% (2/4) in cohort 1, 100% (1/1) in cohort 2, and 44% (4/9) in cohort 3 had already received a booster within the previous month.*

SARS-CoV-2 specific T-cell response

- SARS-CoV-2 specific T-cell response was assessed by EliSpot measuring the release of Interleukin-2 (IL-2) or interferon gamma (IFN-γ) by isolated peripheral blood mononuclear cells (PBMCs) upon antigen stimulation (**Figure 2**).
- 1 week after vaccination, **50% of patients continuously treated with siponimod** mounted a SARS-CoV-2 specific T-cell response.
- T-cell response in siponimod treated patients peaked early after vaccination while it remained stable in the control group. Nevertheless, the development of neutralizing antibodies (**Figure 1**) suggests functional T-cell-B-cell interaction in all patients.
- Note: Siponimod treatment reduces the proportion of CD3+ T-lymphocytes in the blood (**Table 2**), which leads to a lower absolute number of plated T-cells in ELISpot assays and thus a lower number of cells that could theoretically be stimulated to release IFN-γ or IL-2.

Figure 2: SARS-CoV-2 specific T-cell response (IFN-γ and/or IL-2)



*DMF: dimethyl fumarate; GA: glatiramer acetate, IFN: interferon-beta; TF: teriflunomide. *For 3 patients at week 1 and 1 patient at month 1 T-cell response could not be assessed due to insufficient cell counts.*

Table 2: Proportion of CD3+ T-lymphocytes of total PBMCs

	siponimod continuously	siponimod interrupted	1st line DMTs
Week 1	27.81 (17.8-69.4)	83.70 (73.9-86.9)	71.10 (70.9-71.3)
Month 1	18.14 (6.9-52.2)	76.44 (68.6-83.5)	74.67 (50.7-88.8)
Month 6	11.96 (0.9-61.6)	68.82 (62.2-75.4)	77.12 (45.0-89.2)

shown: median (min-max)

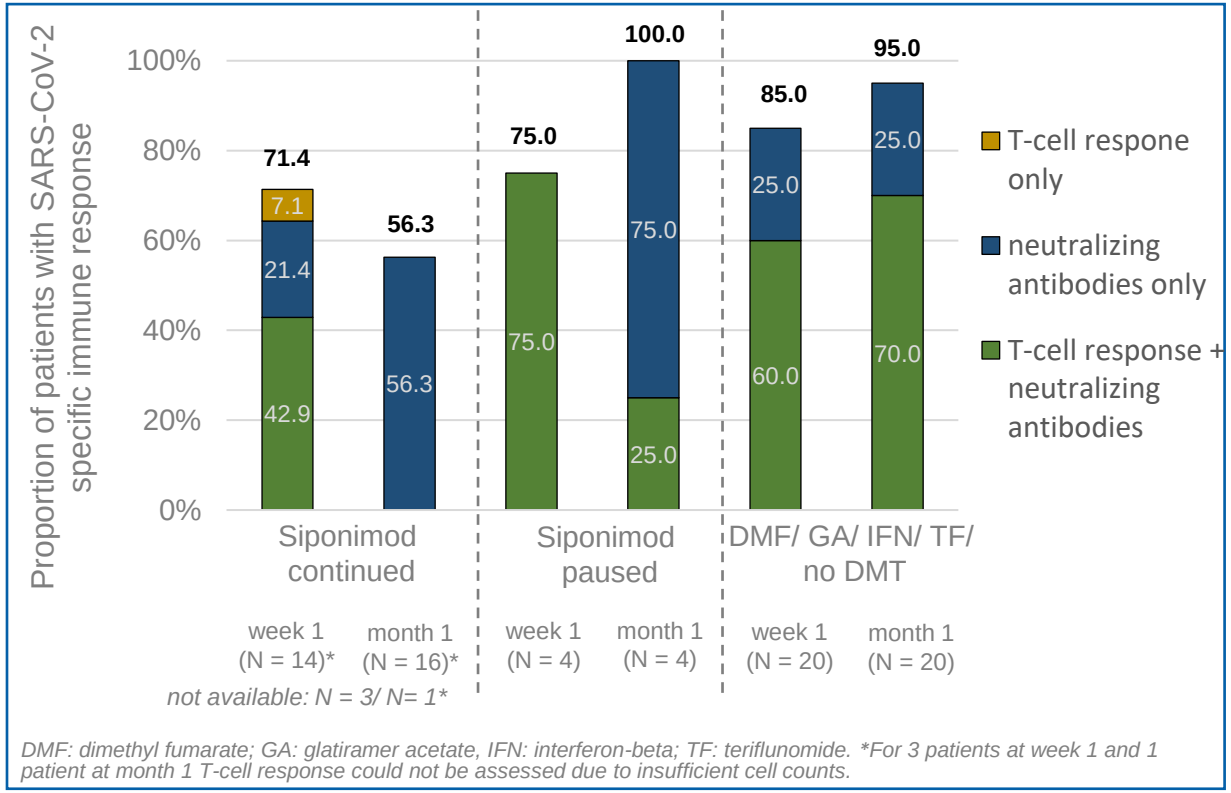
Results

Combined immune response

- > 70% of patients with continuous siponimod treatment developed an immune response towards SARS-CoV-2 mRNA vaccines as soon as 1 week after full vaccination (**Figure 3**).

- Varying immune responses could be observed- patients were either positive for humoral or cellular response or both.

Figure 3: Combined immune response



*DMF: dimethyl fumarate; GA: glatiramer acetate, IFN: interferon-beta; TF: teriflunomide. *For 3 patients at week 1 and 1 patient at month 1 T-cell response could not be assessed due to insufficient cell counts.*

Results

Safety

- Until the cut-off date of this interim analysis, one relapse occurred during the study
  - cohort 1 (siponimod continued)
  - > 5 months after the last vaccination

- No COVID-19 infection was reported, and no adverse events led to permanent discontinuation of study medication until the cut-off date. Overall, safety results agreed with previous safety data, both for MS DMTs and vaccines.

DMT = Disease Modifying Treatment, MS = Multiple Sclerosis

Conclusions

- In this analyzed patient population of advanced age, **more than 2 out of 3 patients with SPMS on siponimod develop an immune response to SARS-CoV-2 mRNA vaccines** as soon as one week after full vaccination.
- It can be hypothesized that immune response rates in earlier diagnosed and thus younger SPMS patients might be even higher[9,10].

- Siponimod patients can mount **humoral and cellular immune responses**, and both need to be considered when assessing vaccination efficacy as already pointed out by others[11].
- This finding supports the hypothesis that both types of immune responses must be functional in patients treated with S1P modulators as the majority of patients recovers unremarkably from COVID-19[12,13].

- In line with previous publications recommending SARS-CoV-2 vaccination for patients currently receiving DMTs,[12, 14] the presented results **support vaccination of siponimod-treated patients**. The interim analysis data is, however, insufficient to support an interruption of treatment for the purpose of vaccination.

- Antibody titers, the effect of booster vaccinations, the maintenance of the immune response, and COVID-19 occurrence and severity in siponimod-treated patients will be reported in the final analysis.

9. Collier et al. (2021) Nature 596, 417–422, 10. 417–422 Müller et al. (2021) Clin. Infect. Dis. 73(11):2065-2072, 11. Woopen et al. (2021) Front. Immunol. 12:701752. 12. Giovannoni et al. (2021) Mult. Scler. Relat. Disord., 53:Article 103155, 13. Sullivan et al. (2021) Neuroimmunol Neuroinflamm. Nov 30;9(1):e1092., 14. Centonze et al. (2021) J Neurol. 12;1-8