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.

Tobias Bopp has received consulting fee and honoraria for lectures from AstraZeneca, Biogen, Celgene, Janssen-Cilag, Merck, Novartis, Pathios Therapeutics, Roche, Sanofi, Teva.

Marie Groth and **Veronika Eva Winkelmann** are employees of the Novartis Pharma GmbH, Nuremberg, Germany.

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Background

- 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.

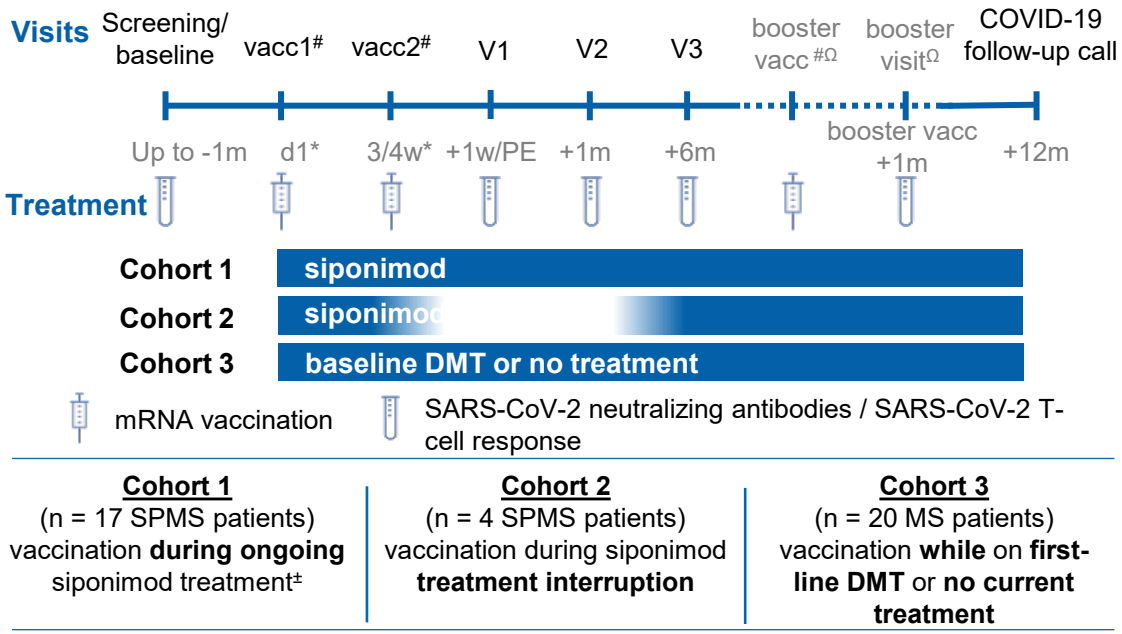
1. Negahdaripour et al. (2021) Int Immunopharmacol 99:108021. **2.** Bigaut et al. (2021) Neurol Neuroimmunol Neuroinflamm. 8(5):e1055. **3.** Behrangi et al. (2019) Cells. 7;8(1):24..

Objective

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.

Methods

- AMA-VACC[4] is a clinical three-cohort, prospective, open-label study with 41 MS patients enrolled at 10 sites in Germany.
  - **Cohort 1:** SPMS patients receiving Siponimod without interruption during SARS-CoV-2 mRNA vaccination (continuous Siponimod)
  - **Cohort 2:** SPMS patients receiving Siponimod with interruption during SARS-CoV-2 mRNA vaccination
  - **Cohort 3**: MS patients receiving first-line DMT (glatirameracetate, dimethlyfumarate, interferons, teriflunomide) or no treatment during SARS-CoV-2 mRNA booster vaccination during first-line treatment or no treatment
- Participants received SARS-CoV-2 mRNA vaccinations independently of this study as part of clinical routine (Fig 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 IFN-γ + IL-2 (ELSP 7010 strip format) from GenID®GmbH. Each ELISpot assay was performed with $2x10^5$ PBMCs (peripheral blood mononuclear cells).



*# mRNA-based SARS-CoV-2 vaccinations as part of clinical routine independent of this study. * interval between vaccinations according to the German vaccination guidance at dedicated sites outside this study. Ω Booster vaccinations are allowed for all patients and can be performed as part of clinical routine at the physician's discretion. If booster vaccinations are performed, an additional study visit will be performed one month (+/- 1 week) after the booster vaccination. ± In Cohort 1, interruption of siponimod treatment is possible for booster vaccination. d, day; DMT, disease modifying therapy; m, month; PE, primary endpoint; v, visit; w, week.*

Figure 1: Study design

4. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-005752-38/DE.

SPMS = Secondary Progressive Multiple Sclerosis; MS = Multiple Sclerosis; IL-2 Interleukin-2; IFN-γ interferon gamma; PBMCs peripheral blood mononuclear cells .

Results

Demographics and baseline information

- Patient characteristics (at screening) and vaccination characteristics are depicted in **Tab 1**.
  - 17, 4, and 20 patients were recruited into cohort 1, 2, and 3, respectively.
  - In cohort 2, siponimod treatment was interrupted for a median of 77.0 days (9.5).
  - 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 both siponimod cohorts
  - 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 – 1st line DMT / no DMT
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, yr	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, yr	0.69 [0.1; 0.9]	0.39 [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)
Booster (BioNTech | Moderna | no booster documented)*	11 (64.7) | 5 (29.4) | 1 (5.9)	2 (50.0) | 2 (50.0) | -	11 (55.0) | 7 (35.0.9) | 2 (10.0)
Vaccination time interval			
1st to 2nd vaccination (days)	41.0 [21; 42]	36.5 [21; 42]	42.0 [21; 47]
2nd vaccination to booster(months)	5.74 [4.95; 7.41]	5.74 [5.38; 6.89]	5.82 [5.18; 6.52]

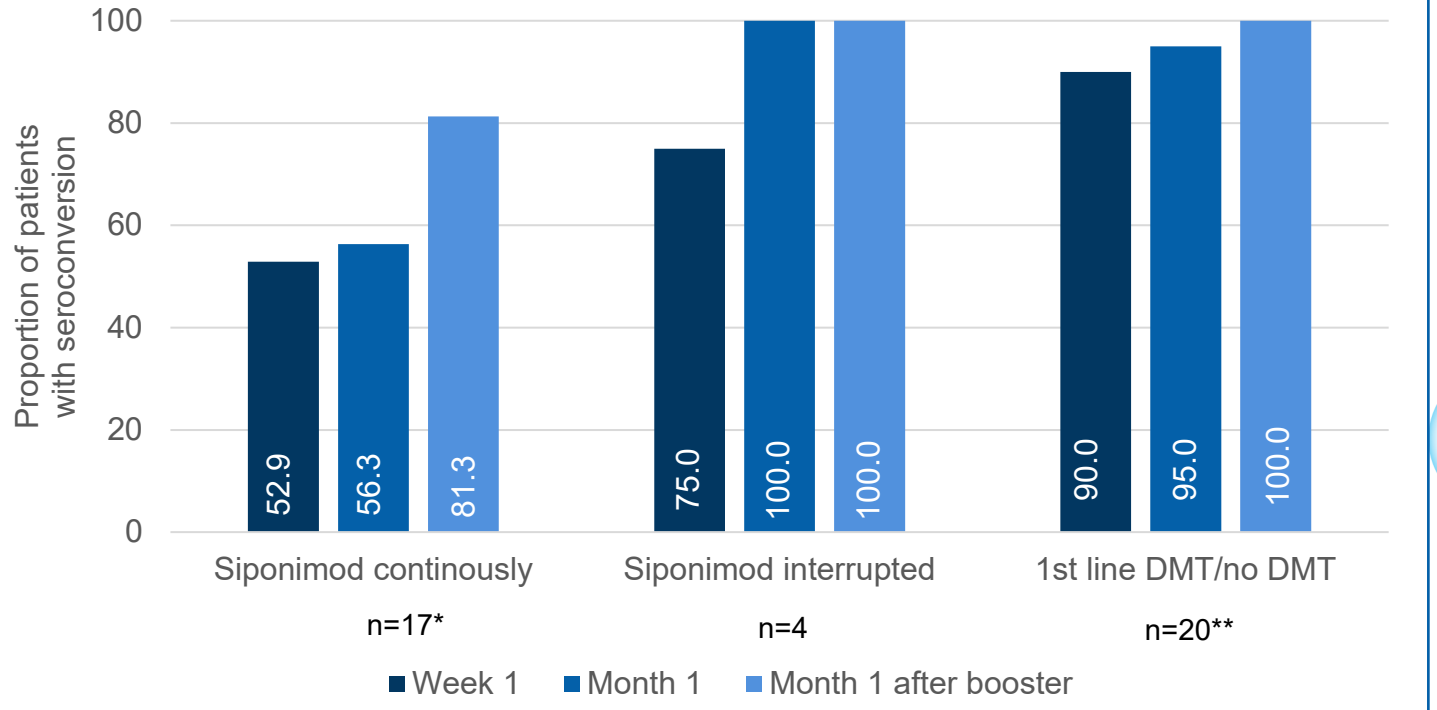
° if not indicated otherwise, data are presented as median [min; max];
* No cross-vaccination was documented for 26 of 38 booster vaccinations

Table 1: Patient characteristics (at screening) and vaccination characteristics

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 one month after booster vaccination in **81.3% of continuously treated siponimod patients** and 100% of patients on 1st line DMTs (**Fig 2**).
- 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].



1st line DMT: Dimethylfumarat, Glatirameracetat, Interferon-beta, Teriflunomid;
**1 sample missing for Month 1 & Month 1 after booster; ** 2 patients did not receive a booster vaccination*

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

5. Collier et al. (2021) Nature 596, 417–422. **6.** Bates et al. (2021) Nat Commun 12, 5135.

Results

SARS-CoV-2 specific T-cell response

- SARS-CoV-2 specific T-cell response was assessed by EliSpot (release of IL-2 or IFN-γ by isolated PBMCs upon antigen stimulation (**Fig 3**).
- 1 month after booster vaccination, **28.6% 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 and increased only slightly after booster vaccination, while it steadily increased in the control group. Nevertheless, the development of neutralizing antibodies (**Fig 2**) suggests functional T-cell-B-cell interaction in all patients.
- Note: Siponimod treatment reduces the proportion of CD3+ T-lymphocytes in the blood (**Tab 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.

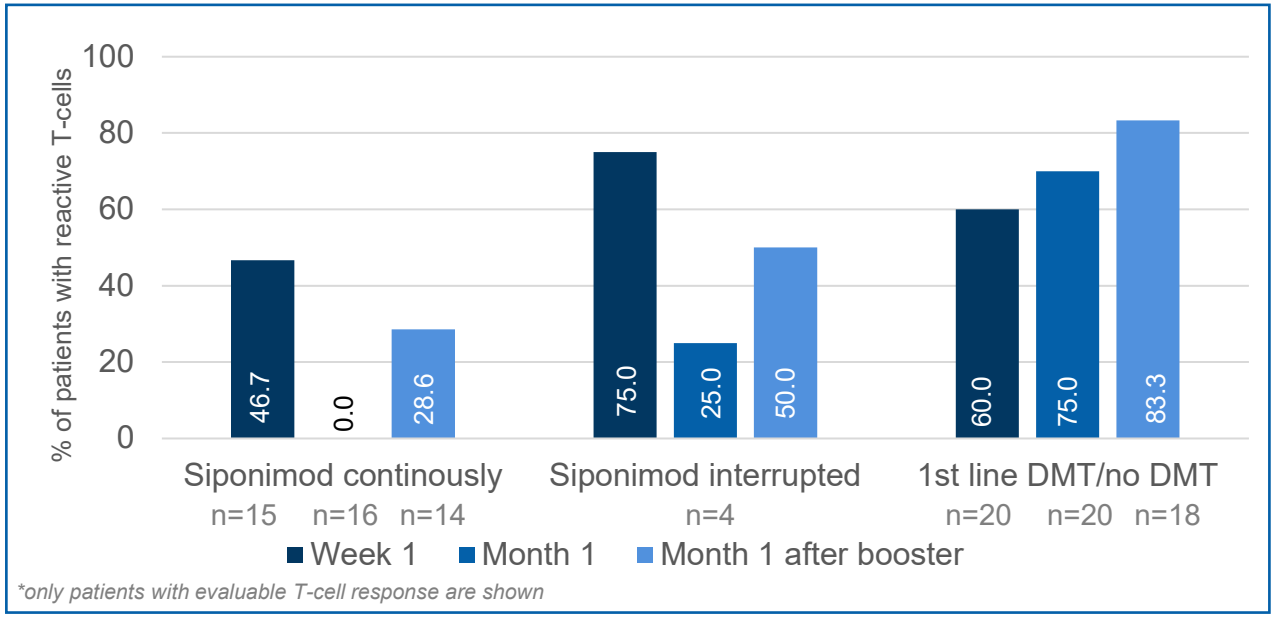


Figure 3: SARS-CoV-2 specific T-cell response

	siponimod continuously	siponimod interrupted	1st line DMTs
Week 1	27.81 (17.8-69.4)	83.7 (73.9-86.9)	71.1 (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 1 after booster	21.93 (0.9-61.6)	67.02 (62.6-81.9)	79.36 (61.2-91.9)

shown: median (min-max)

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

IL-2 Interleukin-2; IFN-γ interferon gamma; PBMCs peripheral blood mononuclear cells .

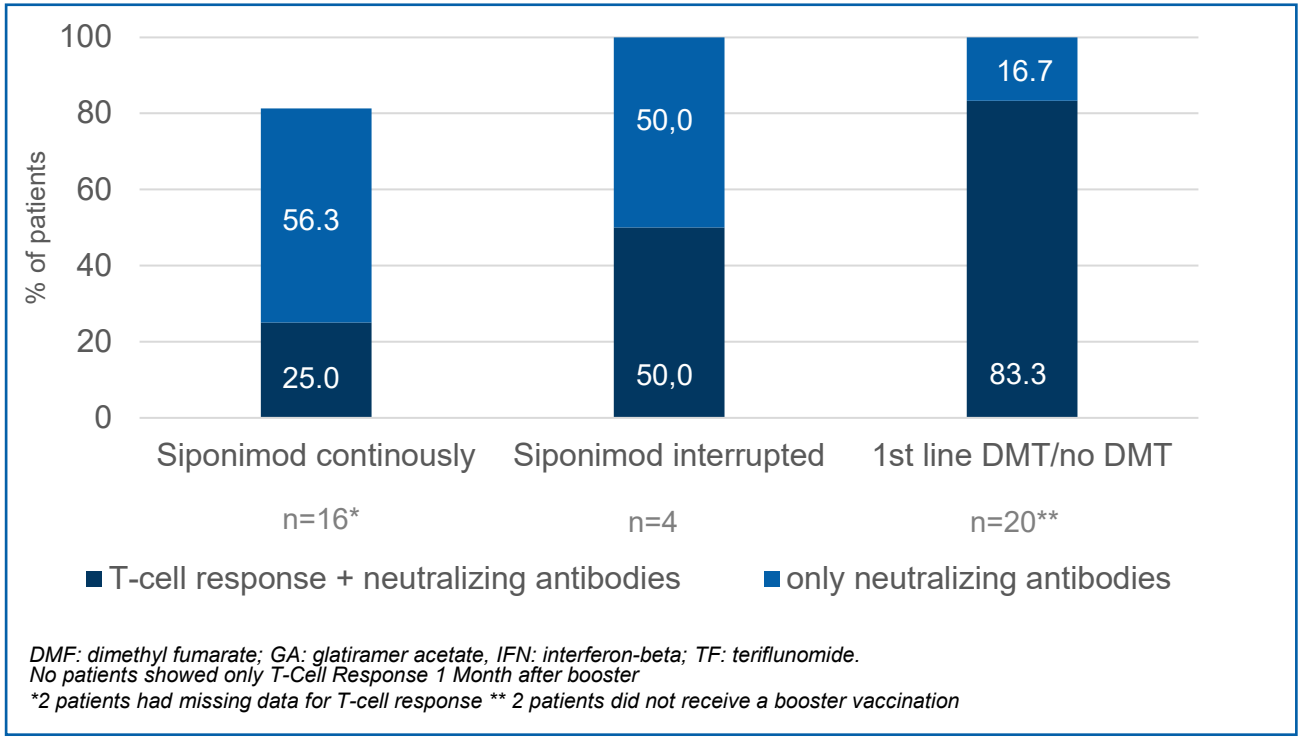
Results

Combined immune response after booster vaccination

- **Fig 4** depicts that not all patients react to vaccinations the same way –patients were either positive for humoral or cellular response or both. Cellular response alone was not observed 1 month after booster vaccination in any cohort
- Taken together, **> 80% of patients with continuous siponimod treatment developed an immune response** towards SARS-CoV-2 mRNA vaccines 1 month after booster vaccination.

Safety

- Until the cut-off date of the interim analysis, three relapses occurred during the study
- Nine COVID-19 infections were reported. All infections were mild or moderate 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.



DMF: dimethyl fumarate; GA: glatiramer acetate, IFN: interferon-beta; TF: teriflunomide.
No patients showed only T-Cell Response 1 Month after booster
**2 patients had missing data for T-cell response ** 2 patients did not receive a booster vaccination*

Figure 4: Combined immune response 1 month after booster vaccination

Conclusions

- In this analyzed patient population of advanced age, **> 80 % patients with SPMS on continuous Siponimod treatment** showed an immune response to SARS-CoV-2 mRNA vaccines one month after booster vaccination.
- 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 [7]. 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 recover unremarkably from COVID-19 [8,9].
- In line with previous publications recommending SARS-CoV-2 vaccination for patients currently receiving DMTs[8, 10], the presented results support initial and booster vaccination of siponimod-treated patients.
- The observed increase in neutralizing antibodies as well as T-Cell response after booster vaccination support administration of booster vaccines in MS patients treated with Siponimod and first line DMTs. It can be hypothesized that immune response rates in earlier diagnosed and younger SPMS patients might be even higher [11,12].

7. Woopen et al. (2021) Front. Immunol. 12:701752.8**.** Giovannoni et al. (2021) Mult. Scler. Relat. Disord., 53:Article 103155, **9.** Sullivan et al. (2021) Neuroimmunol Neuroinflamm. Nov 30;9(1):e1092., **10.** Centonze et al. (2021) J Neurol. 12;1-8 **11.** Collier et al. (2021) Nature 596, 417–422, 7**.** 417–422 **12.**Müller et al. (2021) Clin. Infect. Dis. 73(11):2065-2072,