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 personal compensation for participating on advisory boards, trial steering committees and data and safety monitoring committees, as well as for scientific talks and project support from: Almirall, Bayer, BAT, Biogen, Celgene, Sanofi Genzyme, Merck, Novartis, Roche, Vitaccess, and Teva.

Benedict Rauser and **Marie Groth** are employees of the Novartis Pharma GmbH, Nuremberg, Germany.

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Background

- SARS-CoV-2 mRNA vaccines are a key factor fighting the COVID-19 pandemic across the globe. However, to date limited data is available on the efficacy of vaccination in patients with secondary progressive multiple sclerosis (SPMS) on disease-modifying therapies (DMTs) both over time and after booster vaccination[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 but also the T-cell response especially in a therapy such as siponimod.

- **With this data on SARS-CoV-2 vaccinations in siponimod treated SPMS patients we aim to offer a 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.

Objectives

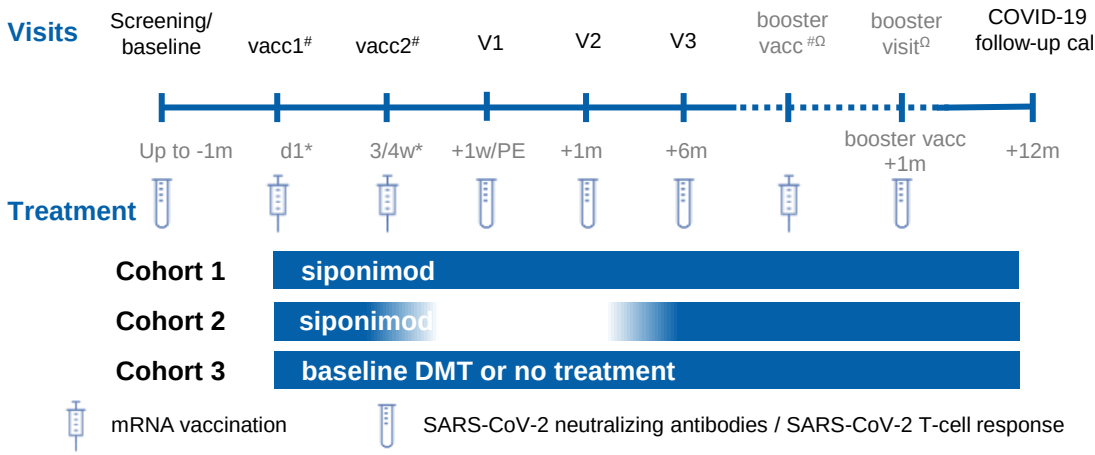
- **With this study, we are aiming to characterize the immune response in siponimod treated SPMS patients after initial and booster SARS-CoV-2 mRNA vaccination.**

- Moreover, we would like to understand the longitudinal cellular and humoral immune responses to SARS-CoV-2 mRNA vaccines depending on the timing of vaccination and SPMS treatment.

Methods

- AMA-VACC[4] is a clinical open-label, three-cohort, prospective study with 41 MS patients enrolled at 10 sites in Germany.
- (SP)MS patients 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 if there was no sign of an acute (PCR) or previous (IgG or IgA) SARS-CoV-2 infection.
- Participants received SARS-CoV-2 mRNA vaccinations as part of clinical routine, independently of this study (**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



Cohort 1
(n = 17 SPMS patients)
vaccination **during ongoing** siponimod treatment±

Cohort 2
(n = 4 SPMS patients)
vaccination during siponimod **treatment interruption**

Cohort 3
(n = 20 MS patients)
vaccination **while** on **first-line DMT** or **no current treatment**

*# 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.*

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

Demographics and baseline information

- Patient characteristics at screening for this first interim analysis are depicted in **Table 1**.
  - 17, 4, and 20 patients were recruited into cohort 1, 2, and 3, respectively.
  - Mean interruption period of siponimod treatment in cohort 2 was 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.

Table 1: Patient characteristics

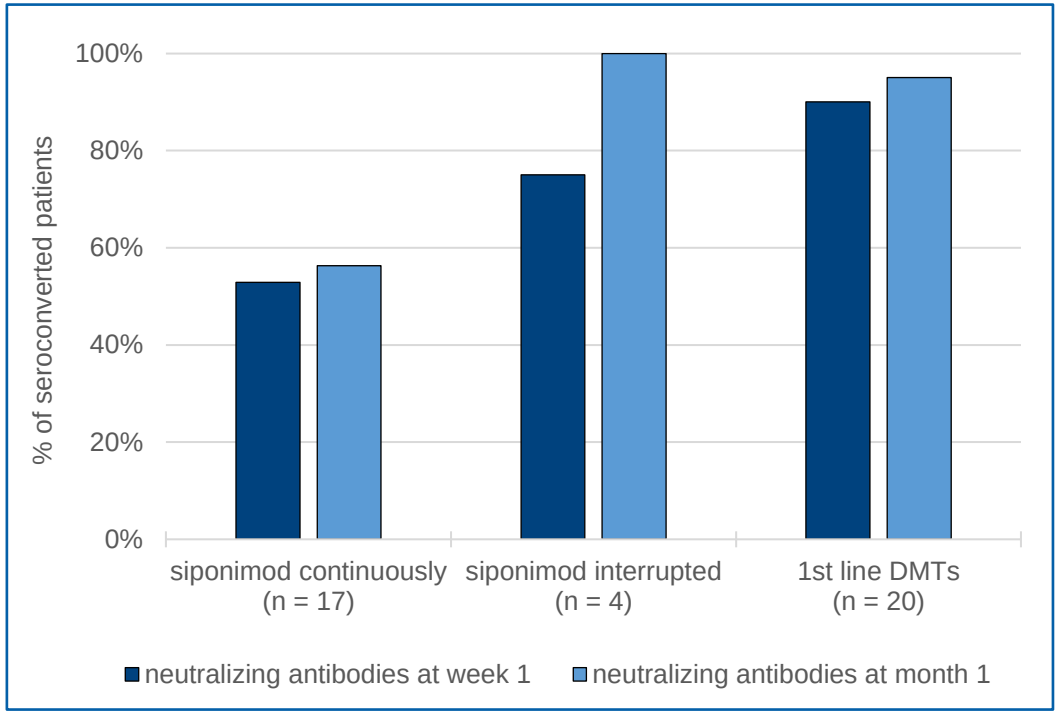
Variable*	Cohort 1 – siponimod continuously	Cohort 2 – siponimod interrupted for vaccination	Cohort 3 – first line DMT / no current treatment
N	17	4	20
Age, years	56 [42; 66]	56 [53; 58]	51 [22; 71]
Sex, female, n (%)	13 (76.5)	3 (75.0)	16 (80.0)
MS diagnosis, n (%)			
SPMS, active SPMS	17 (100.0)	4 (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]

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

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 here 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.
- Although 100% of patients with siponimod treatment interruption showed NAb at some point, the very small number of patients in that cohort (n=4) limits the meaningfulness of this value and should not be the basis for rushed treatment decisions.
- 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 2: Development of SARS-CoV-2 neutralizing antibodies

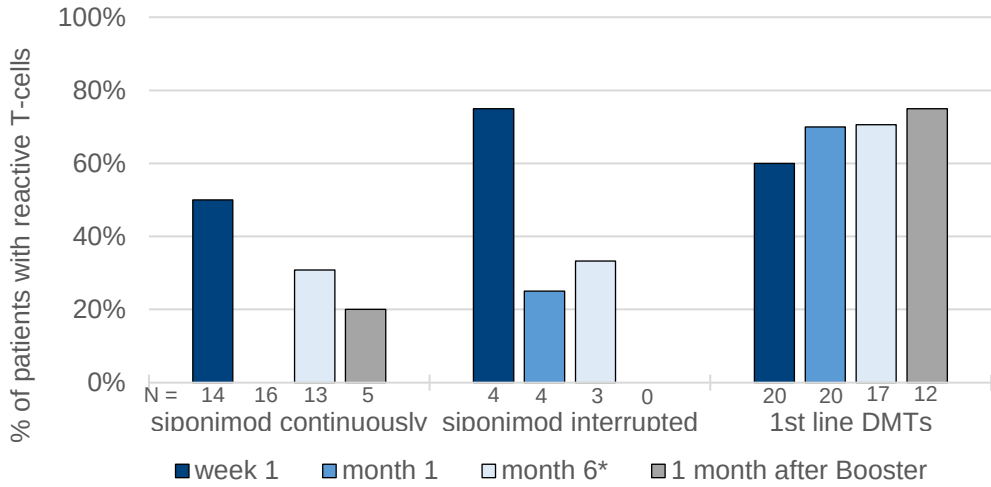


5. Collier, D.A., Ferreira, I.A.T.M., Kotagiri, P. et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature 596, 417–422 (2021). **6.** Bates, T.A., Leier, H.C., Lyski, Z.L. et al. Neutralization of SARS-CoV-2 variants by convalescent and BNT162b2 vaccinated serum. Nat Commun 12, 5135 (2021). https://doi.org/10.1038/s41467-021-25479-6.

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 3**).
- 1 week after vaccination, **50% of patients continuously treated with siponimod**, 75% of patients interrupting their siponimod treatment, and 60% of patients with first line DMTs 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 2**) 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 3: SARS-CoV-2 specific T-cell response



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.*

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

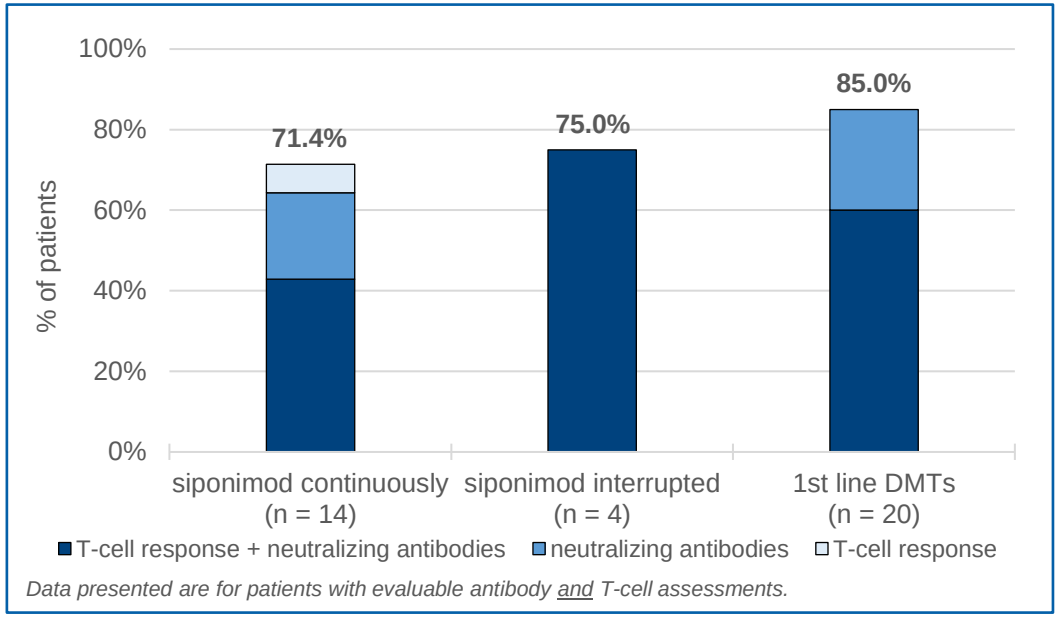
	siponimod continuously	siponimod interrupted	1st line DMTs
Week 1	27.81 (17.8-69.4)	83.70 (73.9-86.9)	71.10 (70.9-71.3)
Month 1	18.14 (6.9-52.2)	76.44 (68.6-83.5)	74.67 (50.7-88.8)
Month 6	11.96 (0.9-61.6)	68.82 (62.2-75.4)	77.12 (45.0-89.2)

shown: median (min-max)

Combined immune response

- **Figure 4** depicts that not all patients react to vaccinations the same way –patients were either positive for humoral or cellular response or both.
- Taken together, **> 70% of patients with continuous siponimod treatment developed an immune response** (i. e. humoral or cellular response or both) towards SARS-CoV-2 mRNA vaccines as soon as 1 week after full vaccination.

Figure 4: Combined immune response



Data presented are for patients with evaluable antibody and T-cell assessments.

Safety

- Until the cut-off date of this interim analysis, one relapse occurred during the study (cohort 1, > 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.

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. In younger patients, even higher immune response rates might be possible[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].

- The proportion of siponimod treated patients with **neutralizing antibodies increases until 1 month after the 2nd SARS-CoV-2 mRNA vaccine** while detection of T-cell response in peaks early after full vaccination.

- Our results are in line with previous publications that **recommend SARS-CoV-2 vaccination** for patients currently receiving DMTs[14].

- Analyses of later time points (including one month after booster vaccinations) will be required to draw conclusions regarding the maintenance of immune response as well as the effectiveness of booster vaccines in siponimod treated patients.

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.** Centozone et al. (2021) *J Neurol.* 12;1-8