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# COVID-19 outcomes and vaccination to SARS-CoV-2 in Siponimod treated patients: clinical trial and real-world evidence

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## CONCLUSIONS

1. **The response to SARS-CoV-2 mRNA vaccination was studied in the AMA-VACC clinical trial. According to the non-interventional AMASIA study, most patients receive mRNA vaccines in the real-world scenario, highlighting the importance of the AMA-VACC results.**
2. **Over 80% of SPMS patients on siponimod developed an immune response to SARS-CoV-2 mRNA vaccination following a booster dose approximately 6 months after the second initial vaccination.**
3. **Compared to the clinical trial AMA-VACC, fewer vaccinations were reported in the AMASIA study. However, the pattern of COVID-19 (breakthrough) infections was similar between the participants in the two studies, although fewer vaccinations were reported in the observational study AMASIA.**
4. **Most COVID-19 infections were mild and moderate and occurred during the Omicron waves, in line with what was observed for the general population.**
5. **Overall, observed COVID-19 infections, severity and duration of infection as well as SARS-CoV-2 vaccination characteristics are comparable to trends obsvered in the general population. The observation of this analysis support vaccination and booster vaccination of siponimod-treated patients.**

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## INTRODUCTION

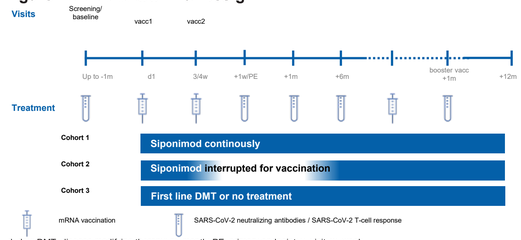
- Treatment with immunomodulators may increase the risk of infection. During the SARS-CoV-2 pandemic and once vaccines became available, the question arose whether or not patients with multiple sclerosis (MS) would mount a sufficient immune response.
- Although evidence on the effect of SARS-COV-2 vaccinations 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]
- **For this analysis, we compared (1) infection dynamics of COVID-19 in MS patients treated with Siponimod and (2) coordination of SARS-CoV-2 vaccination in a clinical trial (AMA-VACC) vs. a real-world setting (AMASIA).**

## METHODS

- AMA-VACC is a clinical three-cohort, prospective, open-label trial 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, beta-interferons, teriflunomide) or no current therapy as part of clinical routine were eligible to participate (Fig. 1).
- Participants received SARS-CoV-2 mRNA vaccinations independently of this study as part of clinical routine.
- Neutralizing antibodies and SARS-CoV-2 reactive T-cells were analyzed with specific tests*.

***Neutralizing antibodies** were analyzed utilizing the cPassTMSARS-CoV-2 Neutralization Antibody Detection Kit from GenScriptUSA Inc (L00847).

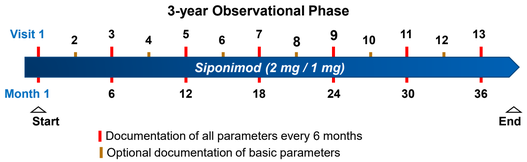
### Figure 1. AMA-VACC Trial Design




d, day; DMT, disease modifying therapy; m, month; PE, primary endpoint; v, visit; w, week.

- AMASIA is a non-interventional study which will provide real-world evidence on the long-term effectiveness and safety of siponimod as well as its impact on quality of life (Fig. 2).
- 679 Siponimod-treated SPMS patients were enrolled in the study and are documented for 2 - 3 years. In this interim analysis 670 patients were included in the analysis.
- SARS-CoV-2 infections and/or vaccinations could be routinely documented by the physicians as adverse event or concomitant treatment.

### Figure 2. AMASIA Study Design




## RESULTS

### Demographics and baseline information

- Patients from the real-world study AMASIA were comparable to patients included in the clinical trial AMA-VACC in terms of age, sex ratio, diagnosis and time since first MS diagnosis.
- AMA-VACC Cohort 3 (patients treated with first line DMT or receiving no current treatment) were slightly younger and had a shorter disease history. However, time on current treatment was longer than compared to Cohort 1 or 2 of the AMA-VACC trial as well as compared to the AMASIA real-world population.
- In the further analyses, cohort 3 is neglected because only cohorts 1 and 2 can be compared with the AMASIA study due to receiving the same treatment, Siponimod.

### Table 1. Baseline Characteristics

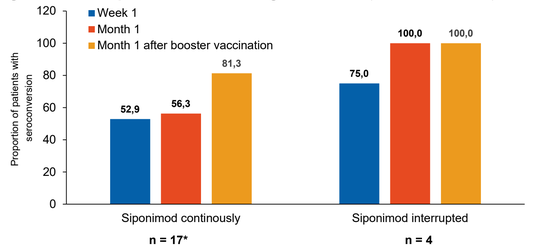
| Study and Variables* | Clinical Trial AMA-VACC: Cohort 1 – siponimod continuously | Clinical Trial AMA-VACC: Cohort 2 – siponimod interrupted for vaccination | Clinical Trial AMA-VACC: Cohort 3 – first line DMT / no current treatment | Real world study AMASIA |
|---|---|---|---|---|
| **N** | 17 | 4 | 20 | 670° |
| **Age, years** | 56 [42; 66] | 56 [53; 58] | 51 [22; 71] | 55 [27; 78] |
| **Sex, female, n (%)** | 13 (76.5) | 3 (75.0) | 16 (80.0) | 459 (68.5) |
| **MS diagnosis, n (%)** | 17 (100.0) | 4 (100.0) | 2 (10.0) | 670 (100.0) |
| SPMS, active SPMS | - | - | 12 (60.0) | - |
| RRMS, active RRMS | - | - | 6 (30.0) | - |
| MS, not specified | - | - | - | - |
| **Time since first MS diagnosis, years** | 15.06 [5.4; 30.9] | 17.60 [3.4; 25.0] | 9.13 [3.2; 37.9] | 17.3 [0.1; 47.1] |
| **MS treatment, n (%)** | | | | |
| Siponimod | 17 (100.0) | 4 (100.0) | - | 670 (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] | 1.0 [0.0; 2.4] |

* if not indicated otherwise, data are presented as median [min; max]
° *3 patients participating in the AMASIA trial switched to the AMA-VACC trial for the duration of AMA-VACC, their data is recorded for both datasets*

### Vaccination Characteristics and Development of SARS-CoV-2 neutralizing antibodies

- Administration regimes of SARS-CoV-2 vaccines are detailed in Tab 2. All patients in the AMA-VACC trial received mRNA vaccination, (Tab. 2) as well as most AMASIA patients. However, vaccination of any kind was only documented for around 30% for participants of the observational AMASIA study. Booster vaccinations were given approximately 6 months after the second initial vaccination.
- In the AMA-VACC trial, neutralizing antibodies could be detected 1 month after booster vaccination in 81% of continuously treated siponimod patients (Fig. 3)[3].

### Figure 3. Development of neutralizing antibodies (AMA-VACC trial)




* 1 sample missing for Month 1 & Month 1 after booster vaccination

### COVID-19 Infection Characteristics and Dynamics

- Characteristics of documented COVID-19 infections are shown in Tab. 3. The median duration of infection was similar between both trials and most patients experienced full recovery.
- Similar to the general population[3] most COVID-19 cases in both trials occurred during the Omicron Waves[4] (Fig.4). As all patients in the AMA-VACC trial received their vaccination in the trial, the shown COVID-19 infections are considered breakthrough infections.

### Table 2. Vaccination Characteristics

| Study and Variables* | Clinical Trial AMA-VACC: Cohort 1 – siponimod continuously | Clinical Trial AMA-VACC: Cohort 2 – siponimod interrupted for vaccination | Real world study AMASIA |
|---|---|---|---|
| **N** | 17 | 4 | 670° |
| **Vaccination, n (%)** 1st (BioNTech \| Moderna \| other \| unknown ) | 16 (94.1) \| 1 (5.9) \| - \| - | 4 (100.0) \| - \| - \| - | 161 (24.0) \| 14 (2.1) \| 52 (7.8) \| 452 (66.1) |
| 2nd (BioNTech \| Moderna \| other \| unknown) | 16 (94.1) \| 1 (5.9) \| - \| - | 4 (100.0) \| - \| - \| - | 144 (21.5) \| 12 (1.8) \| 24 (3.6) \| 499 (73.1) |
| Booster (BioNTech \| Moderna \| other \| no booster documented) | 11 (64.7) \| 5 (29.4) \| 1 (5.9) \| - | 2 (50.0)\| 2(50.0) \| - \| - | 67 (10.0) \| 20 (3.0) \| 11 (1.6) \| 581 (85.4) |
| Additional booster vaccinations | na | na | 4th Booster: 20 (2.9) 5th Booster: 3 (0.4) |
| **Vaccination time interval** 1st to 2nd vaccination (days) | 41.0 [21; 42] | 36.5 [21; 42] | 43 [13; 86] |
| 2nd vaccination to booster (months) | 5.74 [4.95; 7.41] | 6.44 [5.38; 6.89] | 6.2 [1.6; 18.1] |

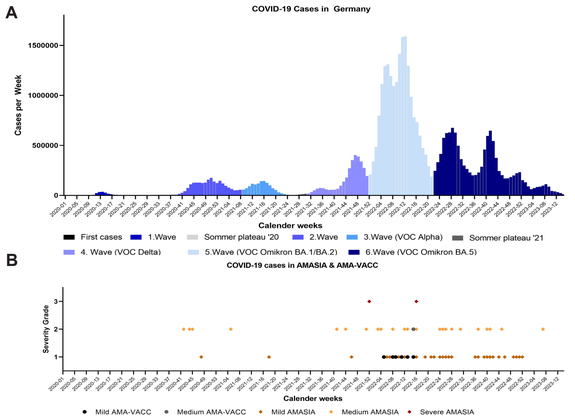
* if not indicated otherwise, data are presented as median [min; max]
° *3 patients participating in the AMASIA trial switched to the AMA-VACC trial for the duration of AMA-VACC, their data is recorded for both datasets.*

### Table 3. COVID-19 infection characteristics

| Study and Variables* | Clinical Trial AMA-VACC: Cohort 1 – siponimod continuously | Clinical Trial AMA-VACC: Cohort 2 – siponimod interrupted for vaccination | Real world study AMASIA |
|---|---|---|---|
| **N** | 17 | 4 | 670° |
| **COVID-19 cases, n** | 4 | 0 | 93^ |
| **Median duration of infection, days** | 12 [10;17] | na | 14 [1; 86] |
| **CTCAE grade** (mild \| medium \| severe ) | 3 \| 1 \| 0 | na | 58 \| 32 \| 2 |
| **Fully recovered, n** | 4 | na | 87** |

na = not applicable; * if not indicated otherwise, data are presented as median [min; max]; ° 3 patients participating in the AMASIA trial switched to the AMA-VACC trial for the duration of AMA-VACC, their data is recorded for both datasets; ^ For 5 patients more than one infection was documented; ** For 6 cases no outcome of COVID-19 infection was documented.

### Figure 4. COVID-19 Infection dynamics




A) COVID-19 Cases shown per calender week reported in Germany from the EDCC database, different waves and variants of concern are color-coded B) COVID-19 cases in the AMASIA and AMA-VACC shown per calender week and severity according to CTCAE grading (1-5, 1 mild, 2 medium, 3 severe, 4 life-threatening, 5 death). Only patients for which a start date of infection was documented are shown here. If only month of infection was given, patients are depicted for the calender week which included the 15th.

**REFERENCES:**
**1.** Negahdaripour et al. (2021) Int Immunopharmacol 99:108021. **2.** Bigaut et al. (2021) Neurol Neuroimmunol Neuroinflamm. 8(5):e1055. **3.** Ziemssen et al, AAN 2023 P12.004 **4.** Data on 14-day notification rate of new COVID-19 cases and deaths (europa.eu) (last accessed on April 7th 2023) **5.** Tolksdorf K, Loenenbach A, Buda S: Dritte Aktualisierung der „Retrospektiven Phaseneinteilung der COVID-19-Pandemie in Deutschland" Epid Bull 2022;38:3-6

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