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Sponsor

Novartis

Generic Drug Name

Siponimod

Trial Indication(s)

Secondary Progressive Multiple Sclerosis

Protocol Number

CBAF312ADE03

Protocol Title

An open-label multicenter study to assess response to SARS-CoV-2 modRNA vaccines in participants with secondary progressive multiple sclerosis treated with Mayzent (siponimod)

Clinical Trial Phase

Phase 4

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: April 19, 2021 (Actual)

Primary Completion Date: September 06, 2021 (Actual)
Study Completion Date: August 15, 2022 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a three cohort, multicenter, open-label, study of 60 planned (optionally up to 90) multiple sclerosis (MS) patients who were on treatment with siponimod or a first-line disease modifying therapy (DMT) or without MS treatment planning to undergo a SARS-CoV-2 modRNA vaccination as part of clinical routine.

- The first cohort enrolled participants who did not interrupt their siponimod therapy for the purpose of a SARS-CoV-2 modRNA vaccination.
- The second cohort enrolled participants who interrupted their siponimod therapy for the purpose of a SARS-CoV-2 modRNA vaccination for approximately 2-3 months
- The third cohort enrolled participants who received modRNA vaccination while on treatment with the following first-line DMTs (dimethylfumarate, glatirameracetate, interferons, teriflunomide) or no current treatment in clinical routine.

The study consists of a screening period, vaccination period and investigational period. During the screening period of up to one month eligibility and SARS-CoV-2 antibodies at baseline were assessed. The 3-4 week vaccination period started with first dose of modRNA vaccine on Day 1 and ended with second dose of modRNA vaccine 3-4 weeks after first dose depending on EU SmPC.

The investigational period lasted 12 months, during which blood samples for primary and secondary endpoint analyses were drawn at 1 week (Visit 1), 1 Month (Visit 2) and 6 months (Visit 3) after completion of vaccination (i.e. second dose of vaccine). 12 months after completion of vaccination a COVID-19 follow-up call was scheduled.

As patients were treated according to clinical routine, the start of treatment was defined as the date the informed consent was signed.

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Centers

Germany(10)

Objectives:

The primary objective was to estimate the proportion of participants (concomitantly treated with siponimod, on siponimod treatment break or being on DMT/no treatment according to clinical routine) achieving seroconversion (i.e., having SARS-CoV-2 serum functional antibodies) after receiving a modRNA vaccination.

Secondary objectives were:

- Describe SARS-CoV-2 serum functional antibody levels over time in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in participants currently not on a DMT
- Describe the T cell response to modRNA vaccines over time in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in participants currently not on a DMT
- Number of adverse events and serious adverse events including confirmed cases of COVID-19 in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in participants currently not on a DMT and number of adverse events causing study discontinuation

Test Product (s), Dose(s), and Mode(s) of Administration

Oral tablets of siponimod (1 or 2 mg) or other disease-modifying therapy (DMT) of various modes of administration

Intramuscular injection of BNT162 vaccine via 2 doses administered 3 weeks apart.
Intramuscular injection of mRNA-1273 vaccine via 2 doses administered 1 month apart.

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Statistical Methods

For all analysis sets, participants were analyzed according to the study treatment(s) received.

The safety analysis set (SAF) included all participants that received any study drug.

The efficacy analysis set (EAS) included all participants who had a valid primary endpoint (i. e. determination of functional antibodies to SARS-CoV-2 at Visit 1 / Week 1). All participants received their second dose of study vaccine.

The primary endpoint was the proportion of participants achieving seroconversion as defined by detection of SARS-CoV-2 serum functional antibodies one week after second dose of vaccine.

Secondary endpoints were analyzed descriptively: semiquantitative SARS-CoV-2 serum functional antibody titer, qualitative and quantitative results of IFNg and IL-2, combined response in qualitative INFγ or IL-2, cell viability (CD3 lymphocytes, CD4 and CD8 cells).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Secondary Progressive Multiple Sclerosis (SPMS) diagnosis or with
Relapsing Remitting Multiple Sclerosis (RRMS) at risk to develop SPMS (at the discretion of the treating physician)
- on stable MS treatment (Siponimod, dimethylfumarate, glatirameracetate, interferon, teriflunomode) or no current treatment
- no recent treatment changes

Exclusion Criteria:
- prior or current COVID-19 disease
- SARS-CoV-2 antibodies at screening
Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	Siponimod - continuous	Siponimod- interrupted	DMT or no MS treatment	Total
Arm/Group Description	Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	Siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) with treatment interruption (for approx. 2-3 months) for the purpose of a SARS-CoV-2 mRNA vaccination	Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination	
Started	17	4	20	41
Completed	17	4	20	41
Not Completed	0	0	0	0

Baseline Characteristics

	Siponimod - continuous	Siponimod- interrupted	DMT or no MS treatment	Total
Arm/Group Description	Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	Siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) with treatment interruption (for approx. 2-3 months) for the purpose of a SARS-CoV-2 mRNA vaccination	Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination	
Number of Participants [units: participants]	17	4	20	41
Baseline Analysis Population Description				
Age Continuous (units: years)				

Analysis Population Type:
Mean ± Standard Deviation

	54.6±5.8	55.8±2.2	48.6±12.9	51.8±10.2
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	13	3	16	32
Male	4	1	4	9
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants				
Caucasian	14	3	17	34
African	0	0	0	0
Other	1	1	2	4
Missing	2	0	1	3
Study Specific Characteristic **Multiple sclerosis diagnosis** (units: participants) Description: The diagnosis of type of multiple sclerosis at baseline. Analysis Population Type: Participants Count of Participants (Not Applicable)				
SPMS Secondary progressive multiple sclerosis (SPMS)	14	1	2	17
Relapsing remitting multiple sclerosis (RRMS)	0	0	11	11
active SPMS (with acute exacerbation or progression)	3	3	0	6
Multiple sclerosis (MS), not specified	0	0	6	6
active RRMS (with acute exacerbation or progression)	0	0	1	1

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Primary Outcome Result(s)

Percentage of participants achieving seroconversion one week after receiving second vaccine (EAS)

Description	Participants who had detectable SARS-CoV-2 serum functional antibodies one week after second dose of vaccine.
Time Frame	At 1 week after vaccination period (defined as 1 week after second dose of vaccine)
Analysis Population Description	Efficacy analysis set (EAS) - all participants who had a valid primary endpoint (i. e. determination of functional antibodies to SARS-CoV-2 at Week 1 after second dose of vaccine)

	Siponimod - continuous	Siponimod- interrupted	DMT or no MS treatment
Arm/Group Description	Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	Siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) with treatment interruption (for approx. 2-3 months) for the purpose of a SARS-CoV-2 mRNA vaccination	Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination
Number of Participants Analyzed [units: participants]	17	4	20
Percentage of participants achieving seroconversion one week after receiving second vaccine (EAS) (units: percentage of participants)			
Visit 1/Week 1 after second dose of vaccine Yes n=17,4,20	52.9	75.0	90.0

Secondary Outcome Result(s)

SARS-CoV-2 functional antibodies (% inhibition) by visits (SAF/EAS)

Description	Measurement of antibody-mediated blockage (i.e. presence of functional SARS-CoV-2 antibodies) was performed to quantify functional SARS-CoV-2 neutralizing antibodies and was calculated as % inhibition to the in-assay control.

Time Frame	Baseline; Week 1, Month 1 and Month 6 after second dose of vaccine; 1 month after booster
Analysis Population Description	Safety analysis set (received any study drug) and efficacy analysis set (participants with a valid primary endpoint)

	Siponimod - continuous	Siponimod- interrupted	DMT or no MS treatment
Arm/Group Description	Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	Siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) with treatment interruption (for approx. 2-3 months) for the purpose of a SARS-CoV-2 mRNA vaccination	Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination
Number of Participants Analyzed [units: participants]	17	4	20
SARS-CoV-2 functional antibodies (% inhibition) by visits (SAF/EAS) (units: antibody titer levels (% inhibition))	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Screening n=17,4,20	-3.8 ± 5.0	-0.3 ± 11.1	-2.6 ± 8.2
Visit 1/Week 1 n=17,4,20	38.1 ± 34.8	64.0 ± 41.8	82.6 ± 26.7
Visit 2/Month 1 n=16,4,20	40.1 ± 27.2	87.5 ± 16.4	86.8 ± 21.5
Visit 3/Month 6 n=16,4,20	43.2 ± 32.8	68.3 ± 34.5	77.3 ± 27.1
1 Month after booster n=16,4,18	62.3 ± 30.3	96.5 ± 2.4	96.8 ± 2.8

Number of patients reactive to INFg or IL-2 SARS-CoV-2 by visit SAF/EAS

Description	The release of IFNg or IL-2 after stimulation with a SARS-CoV-2/PAN corona peptide-mix measured by enzyme-linked immunosorbent spot (ELIspot) assay from peripheral blood mononuclear cells indicates the presence of SARS-CoV-2 reactive T-cells, i.e. a T-cell response.
Time Frame	Baseline; Week 1, Month 1 and Month 6 after second dose of vaccine; 1 month after booster

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Analysis Population Description: Safety analysis set (received any study drug) and efficacy analysis set (participants with a valid primary endpoint)

	Siponimod - continuous	Siponimod- interrupted	DMT or no MS treatment
Arm/Group Description	Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	Siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) with treatment interruption (for approx. 2-3 months) for the purpose of a SARS-CoV-2 mRNA vaccination	Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination
Number of Participants Analyzed [units: participants]	17	4	20
Number of patients reactive to INFg or IL-2 SARS-CoV-2 by visit SAF/EAS (units: participants)			
Screening reactive n=17,4,20	0	0	1
Screening not reactive n=17,4,20	10	3	19
Screening missing value n=17,4,20	7	1	0
Visit 1/Week 1 reactive n=17,4,20	7	3	12
Visit 1/Week 1 not reactive n=17,4,20	8	1	8
Visit 1/Week 1 missing value n=17,4,20	2	0	0
Visit 2/Month 1 reactive n=16,4,20	0	1	14
Visit 2/Month 1 not reactive n=16,4,20	16	3	6
Visit 2/Month 1 missing value n=16,4,20	0	0	0
Visit 3/Month 6 reactive n=17,4,20	4	1	14
Visit 3/Month 6 not reactive n=17,4,20	11	3	5
Visit 3/Month 6 missing value n=17,4,20	2	0	1
Visit 1 Month after booster reactive n=16,4,18	4	2	15

Visit 1 Month after booster not reactive n=16,4,18	10	2	3
Visit 1 Month after booster missing value n=16,4,18	2	0	0

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	Adverse events were reported from screening visit for a maximum of 69 weeks.
Additional Description	The signing of the Informed Consent was considered the start of treatment for this trial because participants entered the trial on treatment as part of their clinical routine.
Source Vocabulary for Table Default	MedDRA (23.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Siponimod continuous N = 17	**Siponimod Interrupted N = 4**	**DMT or No MS Treatment N = 20**

Arm/Group Description	Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	Siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) with treatment interruption (for approx. 2-3 months) for the purpose of a SARS-CoV-2 mRNA vaccination	Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination
Total Number Affected	0	0	0
Total Number At Risk	17	4	20

Serious Adverse Events

Time Frame	Adverse events were reported from screening visit for a maximum of 69 weeks.
Additional Description	The signing of the Informed Consent was considered the start of treatment for this trial because participants entered the trial on treatment as part of their clinical routine.
Source Vocabulary for Table Default	MedDRA (23.1)
Collection Approach for Table Default	Systematic Assessment

	Siponimod continuous N = 17	**Siponimod Interrupted N = 4**	**DMT or No MS Treatment N = 20**
Arm/Group Description	Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	Siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) with treatment interruption (for approx. 2-3 months) for the	Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination

		purpose of a SARS-CoV-2 mRNA vaccination	
Total # Affected by any Serious Adverse Event	1	1	1
Total # at Risk by any Serious Adverse Event	17	4	20
Infections and infestations			
Acute sinusitis	0 (0.00%)	0 (0.00%)	1 (5.00%)
Escherichia urinary tract infection	1 (5.88%)	0 (0.00%)	0 (0.00%)
Gastroenteritis rotavirus	0 (0.00%)	0 (0.00%)	1 (5.00%)
Nervous system disorders			
Epilepsy	0 (0.00%)	1 (25.00%)	0 (0.00%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events were reported from screening visit for a maximum of 69 weeks.
Additional Description	The signing of the Informed Consent was considered the start of treatment for this trial because participants entered the trial on treatment as part of their clinical routine.
Source Vocabulary for Table Default	MedDRA (23.1)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 2%

	Siponimod continuous N = 17	Siponimod Interrupted N = 4	DMT or No MS Treatment N = 20
Arm/Group Description	Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	Siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) with treatment interruption (for approx. 2-3 months) for the purpose of a SARS-CoV-2 mRNA vaccination	Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination
Total # Affected by any Other Adverse Event	10	3	16
Total # at Risk by any Other Adverse Event	17	4	20
Blood and lymphatic system disorders			
Lymphopenia	3 (17.65%)	1 (25.00%)	0 (0.00%)
Ear and labyrinth disorders			
Vertigo	0 (0.00%)	0 (0.00%)	1 (5.00%)
Eye disorders			
Visual impairment	1 (5.88%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders			
Nausea	0 (0.00%)	0 (0.00%)	1 (5.00%)
General disorders and administration site conditions			
Chills	0 (0.00%)	1 (25.00%)	1 (5.00%)
Fatigue	1 (5.88%)	0 (0.00%)	2 (10.00%)
Influenza like illness	0 (0.00%)	1 (25.00%)	2 (10.00%)

Injection site erythema	0 (0.00%)	0 (0.00%)	1 (5.00%)
Injection site pain	3 (17.65%)	0 (0.00%)	2 (10.00%)
Peripheral swelling	0 (0.00%)	1 (25.00%)	0 (0.00%)
Pyrexia	1 (5.88%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders			
Primary biliary cholangitis	0 (0.00%)	0 (0.00%)	1 (5.00%)
Immune system disorders			
Immunisation reaction	0 (0.00%)	0 (0.00%)	1 (5.00%)
Infections and infestations			
Bronchitis	0 (0.00%)	0 (0.00%)	1 (5.00%)
COVID-19	4 (23.53%)	0 (0.00%)	5 (25.00%)
Herpes zoster reactivation	0 (0.00%)	0 (0.00%)	1 (5.00%)
Injection site pustule	1 (5.88%)	0 (0.00%)	0 (0.00%)
Rhinitis	1 (5.88%)	0 (0.00%)	1 (5.00%)
Urinary tract infection	1 (5.88%)	1 (25.00%)	0 (0.00%)
Injury, poisoning and procedural complications			
Upper limb fracture	1 (5.88%)	0 (0.00%)	0 (0.00%)
Investigations			
Blood glucose decreased	0 (0.00%)	1 (25.00%)	0 (0.00%)
Blood pressure increased	0 (0.00%)	1 (25.00%)	1 (5.00%)
Body temperature increased	0 (0.00%)	0 (0.00%)	1 (5.00%)
Liver function test increased	2 (11.76%)	1 (25.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			

Back pain	1 (5.88%)	0 (0.00%)	0 (0.00%)
Bursitis	0 (0.00%)	0 (0.00%)	1 (5.00%)
Muscle tightness	0 (0.00%)	0 (0.00%)	1 (5.00%)
Myalgia	1 (5.88%)	0 (0.00%)	0 (0.00%)
Pain in extremity	2 (11.76%)	1 (25.00%)	2 (10.00%)
Nervous system disorders			
Band sensation	0 (0.00%)	0 (0.00%)	1 (5.00%)
Dizziness	1 (5.88%)	0 (0.00%)	2 (10.00%)
Headache	1 (5.88%)	1 (25.00%)	1 (5.00%)
Multiple sclerosis relapse	2 (11.76%)	0 (0.00%)	1 (5.00%)
VIth nerve paralysis	1 (5.88%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders			
Depression	0 (0.00%)	1 (25.00%)	0 (0.00%)
Reproductive system and breast disorders			
Menstrual disorder	1 (5.88%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (5.88%)	0 (0.00%)	0 (0.00%)
Vascular disorders			
Flushing	1 (5.88%)	0 (0.00%)	0 (0.00%)
Hypertension	0 (0.00%)	1 (25.00%)	0 (0.00%)

Other Relevant Findings

Conclusion:

The results of the study showed that the majority of siponimod-treated participants mounts humoral and cellular immune responses under continuous siponimod therapy. Booster vaccination increased immune response in both participants with interrupted and continuous siponimod treatment. The data did not sufficiently support interruption of siponimod treatment for the purpose of vaccination.

Date of Clinical Trial Report

May 8, 2023