Clinical trial results:
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) (AMA-VACC)

Summary

EudraCT number	2020-005752-38
Trial protocol	DE
Global end of trial date	15 August 2022

Results information

Result version number	v1 (current)
This version publication date	17 August 2023
First version publication date	17 August 2023

Trial information

Trial identification

Sponsor protocol code	CBAF312ADE03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04792567
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate the proportion of participants (concomitantly treated with siponimod and siponimod treatment break) achieving seroconversion (i.e. having SARS-CoV-2 serum functional antibodies) after receiving a modRNA vaccine.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	39
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All participants screened were enrolled, there were no screen failures.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Siponimod - continuous

Arm description:

Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination

Arm type	Experimental
Investigational medicinal product name	Siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg)

Investigational medicinal product name	mRNA-1273 vaccine
Investigational medicinal product code	mRNA-1273
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered 1 month apart

Investigational medicinal product name	BNT162 vaccine
Investigational medicinal product code	BNT162
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered 3 weeks apart

Arm title	Siponimod- interrupted

Arm description:

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

Arm type	Experimental

Investigational medicinal product name	Siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Interrupted treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg)

Investigational medicinal product name	mRNA-1273 vaccine
Investigational medicinal product code	mRNA-1273
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered 1 month apart

Investigational medicinal product name	BNT162 vaccine
Investigational medicinal product code	BNT162
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered 3 weeks apart

Arm title	DMT or no MS treatment

Arm description:

Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination

Arm type	Active comparator
Investigational medicinal product name	Dimethylfumarate, glatirameracetate, interferon, teriflunomide according to respective SmPC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Injection
Routes of administration	Other use

Dosage and administration details:

per clinical routine

Investigational medicinal product name	mRNA-1273 vaccine
Investigational medicinal product code	mRNA-1273
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered 1 month apart

Investigational medicinal product name	BNT162 vaccine
Investigational medicinal product code	BNT162
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered 3 weeks apart

Number of subjects in period 1	Siponimod - continuous	Siponimod-interrupted	DMT or no MS treatment
Started	17	4	20
Completed	17	4	20

Baseline characteristics

Reporting groups	
Reporting group title	Siponimod - continuous
Reporting group description:	
Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	
Reporting group title	Siponimod- interrupted
Reporting group description:	
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	
Reporting group title	DMT or no MS treatment
Reporting group description:	
Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination	

Reporting group values	Siponimod - continuous	Siponimod- interrupted	DMT or no MS treatment
Number of subjects	17	4	20
Age categorical Units: Subjects			
Adults (18-64 years)	16	4	19
From 65-84 years	1	0	1
Age Continuous Units: years			
arithmetic mean	54.6	55.8	48.6
standard deviation	± 5.8	± 2.2	± 12.9
Sex: Female, Male Units: participants			
Female	13	3	16
Male	4	1	4
Race/Ethnicity, Customized Units: Subjects			
Caucasian	14	3	17
African	0	0	0
Other	1	1	2
Missing	2	0	1
Multiple sclerosis diagnosis			
The diagnosis of type of multiple sclerosis (MS) at baseline.			
Units: Subjects			
SPMS Secondary progressive multiple sclerosis	14	1	2
RRMS Relapsing remitting multiple sclerosis	0	0	11
Active SPMS-acute exacerbation or progression	3	3	0
MS Multiple sclerosis, not specified	0	0	6
Active RRMS-acute exacerbation or progression	0	0	1

Reporting group values	Total		
Number of subjects	41		

Age categorical Units: Subjects			
Adults (18-64 years)	39		
From 65-84 years	2		
Age Continuous Units: years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: participants			
Female	32		
Male	9		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	34		
African	0		
Other	4		
Missing	3		
Multiple sclerosis diagnosis			
The diagnosis of type of multiple sclerosis (MS) at baseline.			
Units: Subjects			
SPMS Secondary progressive multiple sclerosis	17		
RRMS Relapsing remitting multiple sclerosis	11		
Active SPMS-acute exacerbation or progression	6		
MS Multiple sclerosis, not specified	6		
Active RRMS-acute exacerbation or progression	1		

End points

End points reporting groups

Reporting group title	Siponimod - continuous
Reporting group description:	
Continuous treatment with siponimod (oral, daily, dose depending on CYP2C9 genotype: 2mg or 1 mg) during SARS-CoV-2 mRNA vaccination	
Reporting group title	Siponimod- interrupted
Reporting group description:	
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	
Reporting group title	DMT or no MS treatment
Reporting group description:	
Baseline disease modifying treatments (DMTs) or no multiple sclerosis treatment during SARS-CoV-2 mRNA vaccination	

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

End point title	Percentage of participants achieving seroconversion one week after receiving second vaccine (EAS)[1]
End point description:	
Participants achieving seroconversion as defined by detection of SARS-CoV-2 serum functional antibodies one week after second dose of vaccine.	
End point type	Primary
End point timeframe:	
At 1 week after vaccination period (defined as 1 week after second dose of vaccine)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was done

End point values	Siponimod - continuous	Siponimod- interrupted	DMT or no MS treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	4	20	
Units: percentage of participants				
number (confidence interval 95%)				
Visit 1/Week 1 after second dose of vaccine	52.9 (27.8 to 77.0)	75.0 (19.4 to 99.4)	90.0 (68.3 to 98.8)	

Statistical analyses

No statistical analyses for this end point

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

End point title	SARS-CoV-2 functional antibodies (% inhibition) by visits (SAF/EAS)
End point 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.

End point type	Secondary

End point timeframe:

Baseline; Week 1, Month 1 and Month 6, after second dose vaccine; 1 month after booster

End point values	Siponimod - continuous	Siponimod-interrupted	DMT or no MS treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	4	20	
Units: antibody titer levels (% inhibition)				
arithmetic 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)	

Statistical analyses

No statistical analyses for this end point

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

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

End point 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.

End point type	Secondary

End point timeframe:

Baseline, Week 1, Month 1 and Month 6 after second dose of vaccine; 1 month after booster

End point values	Siponimod - continuous	Siponimod-interrupted	DMT or no MS treatment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	4	20	
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 Mon after booster missing value n=16,4,18	2	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from screening visit for a maximum of 69 weeks.

Adverse event reporting 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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Siponimod continuous

Reporting group description:

Siponimod continuous

Reporting group title	DMT or No MS Treatment

Reporting group description:

DMT or No MS Treatment

Reporting group title	Siponimod Interrupted

Reporting group description:

Siponimod Interrupted

Serious adverse events	Siponimod continuous	DMT or No MS Treatment	Siponimod Interrupted
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	1 / 4 (25.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			

subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Siponimod continuous	DMT or No MS Treatment	Siponimod Interrupted
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 17 (58.82%)	14 / 20 (70.00%)	3 / 4 (75.00%)
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Blood glucose decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Liver function test increased			
subjects affected / exposed	2 / 17 (11.76%)	0 / 20 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	1
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Flushing			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 17 (5.88%)	2 / 20 (10.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Multiple sclerosis relapse			
subjects affected / exposed	2 / 17 (11.76%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
VIth nerve paralysis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	3 / 17 (17.65%)	2 / 20 (10.00%)	0 / 4 (0.00%)
occurrences (all)	3	2	0
Influenza like illness			
subjects affected / exposed	0 / 17 (0.00%)	2 / 20 (10.00%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Peripheral swelling			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)	2 / 20 (10.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Chills			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	3 / 17 (17.65%)	0 / 20 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	1
Eye disorders			

Visual impairment			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	2 / 17 (11.76%)	2 / 20 (10.00%)	1 / 4 (25.00%)
occurrences (all)	2	3	1
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 17 (23.53%)	5 / 20 (25.00%)	0 / 4 (0.00%)
occurrences (all)	4	5	0
Injection site pustule			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 20 (0.00%) 0	1 / 4 (25.00%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2021	a) prolongation of the visit window for investigational visit 1, b) classification of adverse events according to the Common Toxicity Criteria (CTC) AE grade (version 5 or higher) c) start and optional prolongation of screening period d) optional booster/refresher SARS-CoV-2 vaccinations if suggested by local regulations e) more detailed description of IMP documentation
25 September 2021	a) termination of recruitment, b) optional treatment interruption according to SmPC also in cohort 1 in case of a booster vaccination c) an additional study visit in case of a SARS-CoV-2 booster vaccination

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported