



Clinical trial results:

Tracking the immune response to SARS-CoV-2 modRNA vaccines in an open-label multicenter study in participants with relapsing multiple sclerosis treated with ofatumumab s.c. (KYRIOS)

Summary

EudraCT number	2021-000307-20
Trial protocol	DE
Global end of trial date	13 June 2023

Results information

Result version number	v1 (current)
This version publication date	21 June 2024
First version publication date	21 June 2024

Trial information

Trial identification

Sponsor protocol code	COMB157GDE01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04869358
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	13 June 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the proportion of RMS patients having established SARSCoV-2-specific T-cells after receiving a modRNA vaccine (initial vaccination or booster) either before or after starting ofatumumab treatment.²

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	27 May 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: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	33
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Thirty-seven participants were screened and 34 participants met the criteria for entry into the trial.

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	Cohort 1a

Arm description:

Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment.

Arm type	Experimental
Investigational medicinal product name	SARS-CoV-2 modRNA vaccine (initial vaccination or booster)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
standard clinical routine

Investigational medicinal product name	ofatumumab
Investigational medicinal product code	OMB157
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

dose was 20 mg subcutaneous (s.c.) monthly

Arm title	Cohort 1b
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Arm description:

Patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment.

Arm type	Experimental
Investigational medicinal product name	SARS-CoV-2 modRNA vaccine (initial vaccination or booster)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

standard clinical routine

Investigational medicinal product name	ofatumumab
Investigational medicinal product code	OMB157
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
dose was 20 mg subcutaneous (s.c.) monthly

Arm title	Cohort 2a
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Arm description:

Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose).

Arm type	Experimental
Investigational medicinal product name	ofatumumab
Investigational medicinal product code	OMB157
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
dose was 20 mg subcutaneous (s.c.) monthly

Investigational medicinal product name	SARS-CoV-2 modRNA vaccine (initial vaccination or booster)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
standard clinical routine

Arm title	Cohort 2b
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Arm description:

Patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose).

Arm type	Experimental
Investigational medicinal product name	SARS-CoV-2 modRNA vaccine (initial vaccination or booster)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
standard clinical routine

Investigational medicinal product name	ofatumumab
Investigational medicinal product code	OMB157
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
dose was 20 mg subcutaneous (s.c.) monthly

Number of subjects in period 1	Cohort 1a	Cohort 1b	Cohort 2a
Started	6	8	5
Completed	5	8	5
Not completed	1	0	0
Wish to have children.	1	-	-

Number of subjects in period 1	Cohort 2b
Started	15
Completed	15
Not completed	0
Wish to have children.	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1a
Reporting group description: Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment.	
Reporting group title	Cohort 1b
Reporting group description: Patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment.	
Reporting group title	Cohort 2a
Reporting group description: Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose).	
Reporting group title	Cohort 2b
Reporting group description: Patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose).	

Reporting group values	Cohort 1a	Cohort 1b	Cohort 2a
Number of subjects	6	8	5
Age categorical Units: Subjects			
Adults (18-64 years)	6	7	5
From 65-84 years	0	1	0
Age Continuous Units: years			
arithmetic mean	32.5	47.1	32.4
standard deviation	± 8.1	± 14.1	± 7.7
Sex: Female, Male Units:			
Female	5	5	4
Male	1	3	1
Race/Ethnicity, Customized Units: Subjects			
Caucasian	6	8	5
Missing	0	0	0

Reporting group values	Cohort 2b	Total	
Number of subjects	15	34	
Age categorical Units: Subjects			
Adults (18-64 years)	15	33	
From 65-84 years	0	1	
Age Continuous Units: years			
arithmetic mean	45.5	-	
standard deviation	± 12.4	-	

Sex: Female, Male			
Units:			
Female	9	23	
Male	6	11	
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	13	32	
Missing	2	2	

Subject analysis sets

Subject analysis set title	Total
Subject analysis set type	Full analysis
Subject analysis set description: All cohorts	
Subject analysis set title	Total
Subject analysis set type	Full analysis
Subject analysis set description: All cohorts	
Subject analysis set title	Total
Subject analysis set type	Full analysis
Subject analysis set description: All cohorts	
Subject analysis set title	Cohort 1
Subject analysis set type	Full analysis
Subject analysis set description: Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment or patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment.	
Subject analysis set title	Cohort 2
Subject analysis set type	Full analysis
Subject analysis set description: Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose) or patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose).	

Reporting group values	Total	Total	Total
Number of subjects	32	34	28
Age categorical			
Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age Continuous			
Units: years			
arithmetic mean	68.8		5.3
standard deviation	±	±	± 13.2
Sex: Female, Male			
Units:			
Female			
Male			

Race/Ethnicity, Customized Units: Subjects			
Caucasian			
Missing			

Reporting group values	Cohort 1	Cohort 2	
Number of subjects	14	20	
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age Continuous Units: years			
arithmetic mean			
standard deviation	±	±	
Sex: Female, Male Units:			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
Caucasian			
Missing			

End points

End points reporting groups

Reporting group title	Cohort 1a
Reporting group description: Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment.	
Reporting group title	Cohort 1b
Reporting group description: Patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment.	
Reporting group title	Cohort 2a
Reporting group description: Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose).	
Reporting group title	Cohort 2b
Reporting group description: Patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose).	
Subject analysis set title	Total
Subject analysis set type	Full analysis
Subject analysis set description: All cohorts	
Subject analysis set title	Total
Subject analysis set type	Full analysis
Subject analysis set description: All cohorts	
Subject analysis set title	Total
Subject analysis set type	Full analysis
Subject analysis set description: All cohorts	
Subject analysis set title	Cohort 1
Subject analysis set type	Full analysis
Subject analysis set description: Patients received first SARS-CoV-2 vaccination within the study prior to starting ofatumumab treatment or patients had already completed initial vaccination cycle and received a booster vaccine within the study prior to starting ofatumumab treatment.	
Subject analysis set title	Cohort 2
Subject analysis set type	Full analysis
Subject analysis set description: Patients who received their first SARS-CoV-2 vaccination within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose) or patients who had already completed their initial vaccination cycle and received a booster vaccine within the study while already stable on ofatumumab treatment for at least 4 weeks (since the first dose).	

Primary: Percentage of participants having established SARS-CoV-2-specific T cells after receiving a modRNA vaccine

End point title	Percentage of participants having established SARS-CoV-2-specific T cells after receiving a modRNA vaccine ^[1]
End point description: Participants who established SARS-CoV-2-specific T cells as defined by detection of SARS-CoV-2 reactive T-cells, measured by e.g. ELISpot assay from T-cells that were stimulated with SARS-CoV-2 peptide mix, either 1 month after second dose of vaccine or 1 month after booster vaccine in participants who received the respective vaccine before or after starting ofatumumab treatment.	
End point type	Primary

End point timeframe:

1 month after second dose of vaccine or booster 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 were planned for this endpoint.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Cohort 2b
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	4	15
Units: percentage of participants				
number (confidence interval 95%)	80.0 (28.4 to 99.5)	87.5 (47.3 to 99.7)	100.0 (39.8 to 100.0)	46.7 (21.3 to 73.4)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: percentage of participants				
number (confidence interval 95%)	68.8 (50 to 83.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who maintained T-cell response after receiving a modRNA vaccine

End point title	Percentage of participants who maintained T-cell response after receiving a modRNA vaccine
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End point description:

Participants who maintained detectable SARS-CoV-2 reactive T-cells (measured by e.g. ELISpot assay from T-cells that were stimulated with SARS-CoV-2 peptide mix) after second dose of vaccine or 6 and 12 months after booster vaccine in participants who received the vaccine before or after starting ofatumumab treatment. First booster vaccination was optional for cohorts 1a and 2a. In cohorts 1b and 2b the time points "Month 1 after Vacc" and "1 Month after booster" are identical.

End point type	Secondary
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End point timeframe:

At Week 1, Months 6, 12 and 18 after second dose of vaccine or 1 Month after 1st booster, 1 Month after 2nd booster

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Cohort 2b
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	5	15
Units: percentage of participants				
number (confidence interval 95%)				
Week 1 after vacc n=4,0,5,0,9	100.0 (39.8 to 100.0)	999.9 (999.9 to 999.9)	100.0 (47.8 to 100.0)	999.9 (999.9 to 999.9)
Month 6 after vacc n=4,8,5,14,31	100 (39.8 to 100.0)	62.5 (24.5 to 91.5)	60.0 (14.7 to 94.7)	57.1 (28.9 to 82.3)
Month 12 after vacc n=5,5,5,15,30	100.0 (47.8 to 100.0)	100.0 (47.8 to 100.0)	80.0 (28.4 to 99.5)	93.3 (68.1 to 99.8)
Month 18 after vacc n=4,0,4,0,8	50.0 (6.76 to 93.2)	999.9 (999.9 to 999.9)	100.0 (39.8 to 100.0)	999.9 (999.9 to 999.9)
Month 1 after 1st booster n=4,8,3,15,30	75.0 (19.4 to 99.4)	87.5 (47.3 to 99.7)	66.7 (9.43 to 99.2)	46.7 (21.3 to 73.4)
Month 1 after 2nd booster n=2,4,0,10,16	100.0 (15.8 to 100.0)	75.0 (19.4 to 99.4)	999.9 (999.9 to 999.9)	80.0 (44.4 to 97.5)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 95%)				
Week 1 after vacc n=4,0,5,0,9	100.0 (66.4 to 100.0)			
Month 6 after vacc n=4,8,5,14,31	64.5 (45.4 to 80.8)			
Month 12 after vacc n=5,5,5,15,30	93.3 (77.9 to 99.2)			
Month 18 after vacc n=4,0,4,0,8	93.3 (77.9 to 99.2)			
Month 1 after 1st booster n=4,8,3,15,30	63.3 (43.9 to 80.1)			
Month 1 after 2nd booster n=2,4,0,10,16	81.3 (54.4 to 96.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Increase in specific T-cells after receiving an modRNA booster vaccine

End point title	Increase in specific T-cells after receiving an modRNA booster vaccine
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End point description:

Patients having established SARS-CoV-2-specific T cells as defined by detection of SARS-CoV-2 reactive T-cells, measured by e.g. ELISpot assay from T-cells that were stimulated with SARS-CoV-2 peptide mix 1 month after booster vaccine in participants who received the respective vaccine before or after starting ofatumumab treatment. The fold change of SI from last value before booster to Month 1 is the ratio of SI at Month 1 divided by SI at last value before booster.

End point type	Secondary
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End point timeframe:

Last value before 2nd booster vaccination to month 1 after 2nd booster vaccination

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Cohort 2b
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	7	3	14
Units: stimulation index				
arithmetic mean (standard deviation)	0.8 (± 0.9)	12.6 (± 25.5)	2.0 (± 2.1)	3.6 (± 4.4)

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: stimulation index				
arithmetic mean (standard deviation)	5.3 (± 13.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of RMS participants with quantifiable levels of SARS-CoV-2 serum functional antibodies by visits and subcohorts (EAS)

End point title	Percentage of RMS participants with quantifiable levels of SARS-CoV-2 serum functional antibodies by visits and subcohorts (EAS)
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End point description:

Level of SARS-CoV-2 serum functional antibodies were measured by a central laboratory using a neutralizing antibody detection kit.

End point type	Secondary
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End point timeframe:

Baseline, Week 1 after Vacc, Month 1, 6, 12 after Vacc, 1 month after 1st booster, 1 month after 2nd booster

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Cohort 2b
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	5	15
Units: percentage of participants				
number (confidence interval 95%)				
Baseline0 positive n=6,8, 5,14	0 (0 to 45.9)	100.0 (63.1 to 100.0)	0 (0 to 52.2)	71.4 (41.9 to 91.6)
Week 1 after Vacc positive n=5,0,5,0	100.0 (47.8 to 100.0)	999.9 (999.9 to 999.9)	40.0 (5.27 to 85.3)	999.9 (999.9 to 999.9)

Month 1 after Vacc positive n=5,8,4,15	100.0 (47.8 to 100.0)	100.0 (63.1 to 100.0)	25.0 (0.63 to 80.6)	93.3 (68.1 to 99.8)
Month 6 after Vacc positive n=5,8,5,15	100.0 (47.8 to 100.0)	100.0 (63.1 to 100.0)	40.0 (5.3 to 85.3)	73.3 (44.9 to 92.2)
Month 12 after Vacc positive n=5,7,5,14	100.0 (47.8 to 100.0)	100.0 (59.0 to 100.0)	40.0 (5.3 to 85.3)	92.9 (66.1 to 99.8)
Month 1 after 1st booster positive n=5,8,5,15	100.0 (47.8 to 100.0)	100.0 (63.1 to 100.0)	66.7 (9.4 to 99.2)	93.3 (68.1 to 99.8)
Month 1 after 2nd booster positive n=2,4,0,10	100.0 (15.8 to 100.0)	100.0 (39.8 to 100.0)	0 (0 to 0)	90.0 (55.5 to 99.7)

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 specific CD4+ effector memory T-cells

End point title	SARS-CoV-2 specific CD4+ effector memory T-cells
End point description:	Phenotypic description of the cellular immune response was performed at the central laboratory. T-cells were stimulated with SARS-CoV-2 peptide mix and analyzed for IFNg- and IL4 secretion using FACS analysis. Results are inconclusive due to low participant numbers.
End point type	Secondary
End point timeframe:	Baseline, Months 1 ,6, 12 and 18 after vaccination of vaccine or 1,6 and 12 months after booster vaccine

End point values	Cohort 1	Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	20		
Units: % of CD4+/CD8+ cells				
arithmetic mean (standard deviation)				
BL before initial Vacc IL4 basal n=4,5	2.458 (± 4.915)	0.262 (± 05.86)		
BL before initial Vacc IL4 stim.n=4,5	2.583 (± 5.165)	0.264 (± 0.59)		
BL before initial Vacc INFg basal n=4,5	0.555 (± 0.549)	0.03 (± 0.067)		
BL before initial Vacc INGg stim n=4,5	0.235 (± 0.191)	0.146 (± 0.326)		
Month 1 after Vacc IL4 basal n=12,19	0.396 (± 2.318)	1.209 (± 6.919)		
Month 1 after Vacc IL4 stim. n=12,19	0.719 (± 0.62)	2.449 (± 0.283)		
Month 1 after Vacc INFg basal n=12,19	0.258 (± 2.165)	0.171 (± 0.917)		
Month 1 after Vacc INFg stim. n=12,19	0.947 (± 2.165)	0.381 (± 0.917)		
Month 6 after Vacc IL4 basal n=12,20	0.662 (± 1.44)	0.061 (± 0.273)		
Month 6 after Vacc IL4 stim.n=12,20	0.93 (± 2.043)	0.44 (± 0.197)		
Month 6 after Vacc INFg basal n=12,20	0.236 (± 0.344)	0.123 (± 0.205)		

Month 6 after Vacc INFg stim.n=12,20	0.305 (± 0.352)	0.342 (± 0.644)		
Month 12 after Vacc IL4 basal n=10,17	0.361 (± 1.142)	1.078 (± 2.468)		
Month 12 after Vacc IL4 stim.n=10,17	0.174 (± 0.55)	1.031 (± 2.491)		
Month 12 after Vacc INFg basal n=10,17	0.132 (± 0.192)	0.226 (± 0.478)		
Month12 after Vacc INFg stim. n=10,17	0.122 (± 0.26)	0.757 (± 2.332)		
Month 18 after Vacc IL4 basal n=4,5	2.368 (± 4.735)	0.118 (± 0.264)		
Month 18 after Vacc IL4 stim.l n=4,5	1.833 (± 3.665)	0.176 (± 0.394)		
Month 18 after Vacc INFg basal l n=4,5	0.148 (± 0.295)	0.11 (± 0.246)		
Month 18 after Vacc INFg stim.l n=4,5	0.138 (± 0.159)	0.12 (± 0.268)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until the end of the treatment period plus an additional 30 day safety follow up period for a maximum time of 22 months.

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Cohort 1a
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Reporting group description:

Cohort 1a

Reporting group title	Cohort 2a
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Reporting group description:

Cohort 2a

Reporting group title	Cohort 2b
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Reporting group description:

Cohort 2b

Reporting group title	Cohort 1b
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Reporting group description:

Cohort 1b

Serious adverse events	Cohort 1a	Cohort 2a	Cohort 2b
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	1 / 15 (6.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neurilemmoma benign			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 15 (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

Serious adverse events	Cohort 1b		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neurilemmoma benign			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Cohort 1a	Cohort 2a	Cohort 2b
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	5 / 5 (100.00%)	15 / 15 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
General disorders and administration			

site conditions			
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	1 / 15 (6.67%)
occurrences (all)	0	1	3
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	4
Chills			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Vaccination site reaction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Injection site swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Injection site pain			
subjects affected / exposed	3 / 6 (50.00%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	4	1	0
Peripheral swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Immune-mediated adverse reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			

Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Breast mass subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Erectile dysfunction subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Asthma subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	1 / 15 (6.67%) 1
Dry throat subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Pleurisy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	0 / 15 (0.00%) 0
Throat irritation subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Psychiatric disorders			
Sleep disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	1 / 15 (6.67%) 1
Adjustment disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	0 / 15 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	1 / 15 (6.67%) 1

Epicondylitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Infusion related reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Radius fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	3 / 6 (50.00%)	4 / 5 (80.00%)	3 / 15 (20.00%)
occurrences (all)	4	6	3
Meralgia paraesthetica			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Multiple sclerosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Multiple sclerosis relapse			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Peripheral nerve lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	1 / 15 (6.67%) 1
Sciatica subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	1 / 15 (6.67%) 2
Gastrointestinal disorders Dental caries subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	0 / 15 (0.00%) 0
Dry mouth subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	1 / 15 (6.67%) 1
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Onychoclasia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	1 / 15 (6.67%) 1
Hand dermatitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	1 / 15 (6.67%) 1
Alopecia			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	1 / 15 (6.67%) 1
Acne subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	1 / 15 (6.67%) 1
Skin exfoliation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	1 / 15 (6.67%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	1 / 15 (6.67%) 1
Back pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 5 (20.00%) 2	0 / 15 (0.00%) 0
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	0 / 15 (0.00%) 0
Muscle twitching subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	1 / 15 (6.67%) 1
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	0 / 15 (0.00%) 0
Pain in extremity			

subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Spinal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Musculoskeletal stiffness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	3 / 15 (20.00%)
occurrences (all)	2	1	3
Oral herpes			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	2 / 6 (33.33%)	5 / 5 (100.00%)	9 / 15 (60.00%)
occurrences (all)	2	5	9
Bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Abscess limb			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	0 / 15 (0.00%)
occurrences (all)	3	1	0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort 1b		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pregnancy, puerperium and perinatal conditions			

Pregnancy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
General disorders and administration site conditions			
Influenza like illness subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Fatigue subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Chills subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Asthenia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Gait disturbance subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Vaccination site reaction subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Swelling face subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Injection site swelling subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Injection site pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Peripheral swelling subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Immune system disorders			

Immune-mediated adverse reaction subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all) Breast mass subjects affected / exposed occurrences (all) Erectile dysfunction subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Dry throat subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleurisy subjects affected / exposed occurrences (all) Throat irritation subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all) Adjustment disorder subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Epicondylitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Infusion related reaction			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Radius fracture			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Skin abrasion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Meralgia paraesthetica			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Multiple sclerosis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Multiple sclerosis relapse			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Peripheral nerve lesion			

<p>subjects affected / exposed occurrences (all)</p> <p>Restless legs syndrome subjects affected / exposed occurrences (all)</p> <p>Sciatica subjects affected / exposed occurrences (all)</p>	<p>1 / 8 (12.50%) 1</p> <p>0 / 8 (0.00%) 0</p> <p>1 / 8 (12.50%) 2</p>		
<p>Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)</p>	<p>0 / 8 (0.00%) 0</p>		
<p>Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)</p>	<p>0 / 8 (0.00%) 0</p>		
<p>Gastrointestinal disorders Dental caries subjects affected / exposed occurrences (all)</p> <p>Abdominal pain upper subjects affected / exposed occurrences (all)</p> <p>Dry mouth subjects affected / exposed occurrences (all)</p> <p>Nausea subjects affected / exposed occurrences (all)</p>	<p>1 / 8 (12.50%) 1</p> <p>0 / 8 (0.00%) 0</p> <p>1 / 8 (12.50%) 1</p> <p>0 / 8 (0.00%) 0</p>		
<p>Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)</p> <p>Onychoclasia subjects affected / exposed occurrences (all)</p> <p>Hand dermatitis</p>	<p>1 / 8 (12.50%) 1</p> <p>0 / 8 (0.00%) 0</p>		

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Alopecia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Acne subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Urticaria subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Skin exfoliation subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Back pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2		
Muscle twitching subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Musculoskeletal chest pain			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Pain in extremity subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Spinal pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Infections and infestations			
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Oral herpes subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Fungal skin infection subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Folliculitis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
COVID-19 subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Bacterial infection subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		

Abscess limb			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2021	Main changes included: an additional interim analysis as well as prolongation of the study period in order to investigate sustainability of SARS-CoV-2 vaccination induced immune reaction and reaction towards possible additional booster vaccinations. Furthermore, vadditional exploratory endpoints were added to investigate the immune response towards these additional vaccinations.
20 September 2021	Main changes in the amendment included: splitting of each cohort into two subcohorts (1a, 1b and 2a, 2b), corresponding changes in the treatment schedule, adaption of the primary endpoint and the exclusion criteria, and the addition of an interim analysis.
15 March 2022	Main changes included: termination of recruitment, addition of a study visit and omitting of study exclusion after use of prohibited medication.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Notes: