Clinical trial results:
An open-label, Phase I/II multicenter clinical trial of VXM01 in combination with avelumab in patients with progressive glioblastoma following standard treatment with or without second surgery.

Summary

EudraCT number	2017-003076-31
Trial protocol	DE NL
Global end of trial date	15 August 2022

Results information

Result version number	v1
This version publication date	22 July 2023
First version publication date	22 July 2023

Trial information

Trial identification

Sponsor protocol code	VXM01-AVE-04-INT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02718430
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	VAXIMM GmbH
Sponsor organisation address	Landteilstrasse 24, Mannheim, Germany, 68163
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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	22 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2022
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:

To examine the safety and tolerability of VXM01 in combination with avelumab

Protection of trial subjects:

-A Data Safety Monitoring Board (DSMB) was convened to periodically assess the trial conduct and data in terms of risk-benefit balance and provide recommendations to Vaximm regarding the trial's continuation or modification. Furthermore, the DSMB was consulted in case a treatment-limiting toxicity (TLT) was classified as possibly related to either of the IMPs.
-The first 3 non-resectable patients treated with the VXM01 106 CFU/mL dose in combination with avelumab were included in a staggered fashion (1+2). For safety reasons, there was a time interval of at least 5 weeks between dosing of the first patient and the following 2 patients (TLT observation period). If no TLTs were observed, the VXM01 vaccine dose was to be increased to 107 CFU/mL, after review of the safety data by the DSMB.
-Similarly, also the first 3 patients treated with the VXM01 107 CFU/mL dose in combination with avelumab were included in a staggered fashion (1+2). If the safety and tolerability were considered acceptable for the VXM01 107 CFU/mL dose in combination with avelumab, all patients treated with VXM01 106 CFU/mL dose in combination with avelumab could be treated with the higher dose (intra-dose escalation allowed) after general approval by the DSMB, at the investigator's discretion.
-Subjects were given pre-treatment with an anti-histamine and paracetamol prior to receiving the first 4 doses of Avelumab to prevent infusion-related reactions. Premedication was administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reaction.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 27
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	21
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 2 centers in Germany and 1 center in France. There was one site activated in The Netherlands but no patients were enrolled. The trial was terminated earlier in NL and FR at the same time. The recruitment phase was approximately 23 months (Nov18 - Nov19 and Aug20 - Jul22). First patient was included in 20Nov2018.

Pre-assignment

Screening details:

For each patient, the trial consisted of a screening period of approximately 3 weeks.
Only patients meeting all inclusion and none of the exclusion criteria were included into the treatment phase. The criteria were assessed at screening and a re-check was performed at the inclusion visit (Day 0).

Pre-assignment period milestones

Number of subjects started	32[1]
Intermediate milestone: Number of subjects	INFORMED CONSENT OBTAINED: 32
Intermediate milestone: Number of subjects	ELIGIBILITY CRITERIA MET: 28
Number of subjects completed	28

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion Criteria 5 Was Not Met: 1
Reason: Number of subjects	Exclusion Criteria 13 Was Met: 1
Reason: Number of subjects	Inclusion Criteria 7 and 13 Were Not Met: 1
Reason: Number of subjects	Inclusion Criteria 15 Was Not Met: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 32 patients entered the pre-assignment period, however, 4 of those patients did not meet the eligibility criteria and thus were not enrolled in the trial.

Period 1

Period 1 title	TREATMENT
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study, blinding not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	VXM01 10^6 CFU/mL Non-resectable

Arm description:

Low-dose VXM01 treatment, non-resectable patients

Arm type	Experimental
Investigational medicinal product name	VXM01
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

VXM01 vaccine was administered as 4 single oral prime administrations on Day 1, 3, 5 and 7, followed by single oral boosting administrations every 4 weeks (from Week 4 to 48 in non-resectable patients). In case of patient-specific prolongation, additional 12 doses
of VXM01 vaccine were given.

Arm title	VXM01 10^7 CFU/mL Non-resectable

Arm description:

High dose VXM01 treatment, non-resectable patients

Arm type	Experimental
Investigational medicinal product name	VXM01
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

VXM01 vaccine was administered as 4 single oral prime administrations on Day 1, 3, 5 and 7, followed by single oral boosting administrations every 4 weeks (from Week 4 to 48 in non-resectable patients). In case of patient-specific prolongation, additional 12 doses of VXM01 vaccine were given.

Arm title	VXM01 10^7 CFU/mL Resectable

Arm description:

High dose VXM01 treatment, resectable patients

Arm type	Experimental
Investigational medicinal product name	VXM01
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

VXM01 vaccine was administered as 4 single oral prime administrations on Day 1, 3, 5 and 7, followed by single oral boosting administrations every 4 weeks (from Week 8 to 48 in resectable patients).
In case of patient-specific prolongation, additional 12 doses of VXM01 vaccine were given.

Number of subjects in period 1	VXM01 10^6 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Resectable
Started	3	22	3
Tumor Resection	0 [2]	0 [3]	2 [4]
Completed	3	22	3

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The milestone "Tumor resection" is only applicable to the Resectable arm, however, it is not possible to remove this milestone from the other arms in the EudraCT system.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The milestone "Tumor resection" is only applicable to the Resectable arm, however, it is not possible to remove this milestone from the other arms in the EudraCT system.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One patient in the Resectable arm did not under go tumor resection due to a clinical decision.

Period 2

Period 2 title	FOLLOW UP
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study, blinding not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	VXM01 10^6 CFU/mL Non-resectable

Arm description:

Low-dose VXM01 treatment, non-resectable patients

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	VXM01 10^7 CFU/mL Non-resectable

Arm description:

High dose VXM01 treatment, non-resectable patients

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	VXM01 10^7 CFU/mL Resectable

Arm description:

High dose VXM01 treatment, resectable patients

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	VXM01 10^6 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Resectable
Started	3	22	3
Completed	1	0	0
Not completed	2	22	3
Death Due To Progressive Disease	2	20	2
In follow-up	-	2	1

Baseline characteristics

Reporting groups

Reporting group title	TREATMENT

Reporting group description: -

Reporting group values	TREATMENT	Total	
Number of subjects	28	28	
Age categorical			
Adult			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	21	21	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous			
Units: years			
median	60		
standard deviation	± 9.5	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	22	22	

Subject analysis sets

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

included all patients who received any trial drug after trial entry.

Subject analysis set title	Per-protocol analysis set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

included all patients who received trial drug in compliance with the scheduled treatment regimen, underwent re-operation if in the resectable subgroup and without any major protocol deviations.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

all patients who received at least one dose of the trial drug and for which at least one post-dose safety assessment is available.

Reporting group values	Full analysis set (FAS)	Per-protocol analysis set (PPS)	Safety analysis set (SAF)
Number of subjects	28	23	28
Age categorical			
Adult			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	21	17	21
From 65-84 years	7	6	7
85 years and over			
Age continuous			
Units: years			
median	58		58
standard deviation	± 9.5	±	± 9.5
Gender categorical			
Units: Subjects			
Female	6	6	6
Male	22	17	22

End points

End points reporting groups

Reporting group title	VXM01 10^6 CFU/mL Non-resectable
Reporting group description:	
Low-dose VXM01 treatment, non-resectable patients	
Reporting group title	VXM01 10^7 CFU/mL Non-resectable
Reporting group description:	
High dose VXM01 treatment, non-resectable patients	
Reporting group title	VXM01 10^7 CFU/mL Resectable
Reporting group description:	
High dose VXM01 treatment, resectable patients	
Reporting group title	VXM01 10^6 CFU/mL Non-resectable
Reporting group description:	
Low-dose VXM01 treatment, non-resectable patients	
Reporting group title	VXM01 10^7 CFU/mL Non-resectable
Reporting group description:	
High dose VXM01 treatment, non-resectable patients	
Reporting group title	VXM01 10^7 CFU/mL Resectable
Reporting group description:	
High dose VXM01 treatment, resectable patients	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
included all patients who received any trial drug after trial entry.	
Subject analysis set title	Per-protocol analysis set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
included all patients who received trial drug in compliance with the scheduled treatment regimen, underwent re-operation if in the resectable subgroup and without any major protocol deviations.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
all patients who received at least one dose of the trial drug and for which at least one post-dose safety assessment is available.	

Primary: Safety and Tolerability

End point title	Safety and Tolerability[1]
End point description:	
Safety and tolerability up to 60 weeks after first IMP administration (including end of study [EoS] visit, Week 60), incidence of AEs (number of patients with event[s])	
End point type	Primary
End point timeframe:	
up to 60 weeks after first IMP administration (including end of study [EoS] visit, Week 60)	

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: Due to the early phase open-label design of this study, no statistical analysis has been performed on the primary endpoint of safety and tolerability. Results were presented in tabular summaries of incidence.

End point values	VXM01 10^6 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Resectable	Safety analysis set (SAF)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	22	3	28
Units: Number of Events				
AE	30	218	29	277
TEAE	30	198	28	256
SAE	0	11	0	11

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response

End point title	Best Overall Response

End point description:

Best overall response (BOR) on MRI according to iRANO in patients with or without surgery prior to trial entry (up to re-operation), derived using iRANO 2015 guidelines.

End point type	Secondary

End point timeframe:

Until progressive disease occurs, for resectable patients up to (re-)operation.

End point values	VXM01 10^6 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Resectable	Full analysis set (FAS)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	22	3	28
Units: Best Overall Response				
Partial Response	1	2	0	3
Stable Disease	0	1	2	3
Progressive Disease	2	19	1	22

End point values	Per-protocol analysis set (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Best Overall Response				
Partial Response	1			
Stable Disease	3			
Progressive Disease	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response[2]

End point description:

Duration of Response (DoR) on MRI according to iRANO in patients with or without surgery prior to trial entry (up to re-operation)

End point type	Secondary

End point timeframe:

Up to end of trial

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The Duration of Response can only be determined in patients with a partial or complete response. In the arm "10^7 CFU/mL Resectable" (Arm 3) no patients had a partial or complete response, thus duration of response could not be determined for this arm.

End point values	VXM01 10^6 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Non-resectable	Full analysis set (FAS)	Per-protocol analysis set (PPS)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	1	2	3	1
Units: Months				
median (full range (min-max))	5.6 (5.6 to 5.6)	6.9 (2.7 to 11.1)	5.6 (2.7 to 11.1)	2.7 (2.7 to 2.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Response

End point title	Clinical Response

End point description:

Clinical response as assessed by time-to-progression (TTP), PFS, recurrence-free survival after re-operation (RFS) and overall survival (OS) up to end of trial.

End point type	Secondary

End point timeframe:

Up to end of trial

End point values	VXM01 10^6 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Resectable	Full analysis set (FAS)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	22	3	28
Units: Months				
median (full range (min-max))				
Time-to-progression	2.5 (1.2 to 13.8)	2.7 (1.4 to 13.8)	0.6 (0.3 to 22.1)	2.7 (0.3 to 22.1)

Progression-free survival	2.5 (1.2 to 13.8)	2.7 (1.4 to 13.8)	0.6 (0.3 to 22.1)	2.7 (0.3 to 22.1)
Overall survival	14.5 (5.6 to 38.2)	10.8 (3.8 to 19.6)	16.9 (2.2 to 23.1)	11.2 (2.2 to 38.2)

End point values	Per-protocol analysis set (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Months				
median (full range (min-max))				
Time-to-progression	2.7 (0.3 to 22.1)			
Progression-free survival	2.7 (0.3 to 22.1)			
Overall survival	11.2 (2.2 to 23.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected as soon as the patient consented to the ICF, during each visit until 30 days after last administration of the trial medication and at day 90 after last treatment administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	VXM01 10^6 CFU/mL Non-resectable

Reporting group description:

Low-dose VXM01 treatment, non-resectable patients

Reporting group title	VXM01 10^7 CFU/mL Non-resectable

Reporting group description:

High dose VXM01 treatment, non-resectable patients

Reporting group title	VXM01 10^7 CFU/mL Resectable

Reporting group description:

High dose VXM01 treatment, resectable patients

Serious adverse events	VXM01 10^6 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Resectable
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	7 / 22 (31.82%)	0 / 3 (0.00%)
number of deaths (all causes)	2	20	2
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (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
Epilepsy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (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
Status epilepticus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (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

Cerebrovascular accident			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (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
Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (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
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (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
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	VXM01 10^6 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Non-resectable	VXM01 10^7 CFU/mL Resectable
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	22 / 22 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	11 / 22 (50.00%)	2 / 3 (66.67%)
occurrences (all)	1	16	2
Influenza like illness			
subjects affected / exposed	2 / 3 (66.67%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	7	4	0
Gait disturbance			
subjects affected / exposed	1 / 3 (33.33%)	0 / 22 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 3 (33.33%)	0 / 22 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Depression			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Anxiety			

subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Persistent depressive disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Personality change			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Psychomotor retardation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 22 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	13 / 22 (59.09%)	3 / 3 (100.00%)
occurrences (all)	0	40	6
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	6 / 22 (27.27%)	2 / 3 (66.67%)
occurrences (all)	0	13	7
Lipase increased			
subjects affected / exposed	0 / 3 (0.00%)	4 / 22 (18.18%)	1 / 3 (33.33%)
occurrences (all)	0	5	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 22 (13.64%)	1 / 3 (33.33%)
occurrences (all)	0	5	1
Blood potassium decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	2 / 3 (66.67%)
occurrences (all)	0	2	4
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 3 (0.00%)	3 / 22 (13.64%)	0 / 3 (0.00%)
occurrences (all)	0	6	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Blood potassium increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Lymphocyte count increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Amylase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Gamma-glutamyltransferase decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Alanine aminotransferase decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			

subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	2 / 3 (66.67%)	3 / 22 (13.64%)	1 / 3 (33.33%)
occurrences (all)	2	3	1
Aphasia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 22 (13.64%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Brain oedema			
subjects affected / exposed	2 / 3 (66.67%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Fine motor skill dysfunction			
subjects affected / exposed	1 / 3 (33.33%)	1 / 22 (4.55%)	1 / 3 (33.33%)
occurrences (all)	1	1	1
Headache			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Cognitive disorder			
subjects affected / exposed	1 / 3 (33.33%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Ataxia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dizziness			

subjects affected / exposed	1 / 3 (33.33%)	0 / 22 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dysarthria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dysdiadochokinesis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Facial paralysis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Paresis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	1 / 3 (33.33%)	4 / 22 (18.18%)	0 / 3 (0.00%)
occurrences (all)	1	5	0
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	3 / 22 (13.64%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Oral dysaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Adrenal insufficiency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Autoimmune thyroiditis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 22 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Trigger finger			
subjects affected / exposed	1 / 3 (33.33%)	0 / 22 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 22 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 22 (9.09%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 22 (4.55%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 22 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 22 (4.55%) 1	0 / 3 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2018	Protocol V2.0_05Sep2018 -Update and revision based on comments from Ethics Committes and Competent Authorities in France, Germany and the Netherlands Protocol V3.0_21Sep2018 -Update and revision based on comments from the ANSM in France Protocol V4.0_31Oct2018 -Update based on CCMO comments (vital sign measurements defined and added reference for immune-related cardiac events treatment guidelines) AND Record archiving period changed from 15 to 25 years. Germany -Protocol V2.0 submitted during question and answer rounds of the initial submission -Protocol V3.0 and V4.0 submitted with Substantial Amendment 01 on 12Nov2018 Netherlands -Protocol V2.0, V3.0 and V4.0 submitted in Substantial Amendment 01 on 27Feb2019 France -Protocol V2.0 and V3.0 submitted during question and answer rounds of the initial submission (Protocol V4.0 submitted with Global Substantial Amendment of protocol V5.0_11Jun2019)
01 July 2019	Global Substantial Amendments performed in Jul2019 to align protocol and introduce gut microbiome analysis Substantial Amendment (SA) in Germany: Protocol V5.0_11Jun2019 submitted on 01Jul2019 to CA and EC. SA in Netherlands: Protocol V5.0_11Jun2019 submitted on 04Jul2019 to CA and EC. SA in France: Protocol V4.0_31Oct2018 and V5.0_11Jun2019 submitted on 05Jul2019 to CA and EC.
20 November 2019	Global Substantial Amendment (SA) to: -Update of the avelumab safety information regarding pancreatitis in accordance with the current version of the Investigator's Brochure. -Update of the approval status of avelumab -Upates of the administrative section regarding members of the study team Germany: Protocol V6.0_05Nov2019 submitted on 20Nov2019 and 21Nov2019 to CA and EC Netherlands: Protocol V6.0_05Nov2019 submitted on 21Nov2019 and 20Nov2019 to CA and EC France: Protocol V6.0_05Nov2019 submitted on 18Nov2019 to CA and EC

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 November 2019	Patient enrolment was placed on temporary hold on 01Nov2019 due to funding issues at the sponsor. There was no effect on patients who were already enrolled in the trial; their treatment continued as per protocol. Patient enrolment was restarted on 01Aug2020 in Germany only and only at 2 German sites.	01 August 2020

Notes:

Limitations and caveats

None reported