Clinical trial results:
Phased Avelumab combined with chemotherapy as first-line treatment for patients with advanced small-cell lung cancer (SCLC).

Summary

EudraCT number	2017-004784-12
Trial protocol	GR
Global end of trial date	12 December 2024

Results information

Result version number	v1 (current)
This version publication date	15 June 2025
First version publication date	15 June 2025

Trial information

Trial identification

Sponsor protocol code	HE1/17 - PAVE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03568097
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	Messoghion Ave. 41, Athens, Greece, 115 26
Public contact	Clinical Trials, Hellenic Cooperative Oncology Group (HeCOG), 0030 2106912520, hecogoff@otenet.gr
Scientific contact	Clinical Trials, Hellenic Cooperative Oncology Group (HeCOG), 0030 2106912520, hecogoff@otenet.gr

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	23 December 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of phased avelumab administration along with first-line chemotherapy for patients with advanced small-cell lung cancer, primarily by determining whether phased avelumab administration and maintenance treatment could prolong Progression-Free Survival (PFS) and 1-year PFS.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2018
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	Greece: 55
Worldwide total number of subjects	55
EEA total number of subjects	55

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)	24
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled participants between 16 September 2018 and 16 September 2020 in seven sites.

Pre-assignment

Screening details:

Patients were screened for eligibility prior to entering the study and written informed consent was obtained before any study-related procedures were performed.

Period 1

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

Arms

Arm title	Avelumab + Standard 1st line Chemotherapy

Arm description:

Eligible patients received Cisplatin 80 mg/m² or Carboplatin AUC 5 on Day 1 every three weeks for 4–6 cycles, in combination with Etoposide 100 mg/m² on Days 1–3 every three weeks for 4–6 cycles. Switching between Cisplatin and Carboplatin was permitted for medical reasons.

Avelumab 10 mg/kg was administered as a 1-hour intravenous infusion diluted in 0.9% saline every two weeks, starting from the third chemotherapy cycle. It continued until the end of chemotherapy and was then given as maintenance treatment every two weeks until disease progression. A ±3-day window for Avelumab administration was allowed without being considered a treatment delay or protocol deviation.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	Bavencio
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg were administered as a 1-hour intravenous infusion every two weeks, starting from the third chemotherapy cycle until the completion of chemotherapy, and subsequently as maintenance treatment every two weeks until disease progression, the occurrence of excessive adverse events, the investigator’s decision, the patient’s refusal to continue treatment, or death, whichever occurred first.

Number of subjects in period 1	Avelumab + Standard 1st line Chemotherapy
Started	55
Completed	38
Not completed	17
Physician decision	2
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Death	4
Progression Disease	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (Overall period)

Reporting group description:

The study included an initial safety run-in, open-label, single-arm part (Part 1), and the actual phase II study (Part 2). During Part 1, at least 6 eligible patients received standard first-line chemotherapy for ES-SCLC and avelumab. Three patients received cisplatin 80mg/m2 and three carboplatin AUC 5 D1 every three weeks for 4-6 cycles. The dose and schedule were confirmed for use in the phase II study if no dose-limiting toxicities (DLTs) were observed after 3 patients completed at least 4 cycles (2 initial chemotherapy-alone cycles plus 2 more with avelumab).

Reporting group values	Overall trial (Overall period)	Total	
Number of subjects	55	55	
Age categorical			
Patients aged 18 years and above.			
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)	24	24	
From 65-84 years	31	31	
85 years and over	0	0	
Age continuous			
Patients aged 18 years and above.			
Units: years			
median	66		
full range (min-max)	44 to 83	-	
Gender categorical			
Male or female patients			
Units: Subjects			
Female	18	18	
Male	37	37	

End points

End points reporting groups

Reporting group title	Avelumab + Standard 1st line Chemotherapy

Reporting group description:

Eligible patients received Cisplatin 80 mg/m² or Carboplatin AUC 5 on Day 1 every three weeks for 4–6 cycles, in combination with Etoposide 100 mg/m² on Days 1–3 every three weeks for 4–6 cycles. Switching between Cisplatin and Carboplatin was permitted for medical reasons.

Avelumab 10 mg/kg was administered as a 1-hour intravenous infusion diluted in 0.9% saline every two weeks, starting from the third chemotherapy cycle. It continued until the end of chemotherapy and was then given as maintenance treatment every two weeks until disease progression. A ±3-day window for Avelumab administration was allowed without being considered a treatment delay or protocol deviation.

Primary: Progression Free Survival (1 - YEAR PFS)

End point title	Progression Free Survival (1 - YEAR PFS)[1]

End point description:

End point type	Primary

End point timeframe:

Progression-Free Survival (PFS) is defined as the time from the date of study entry to the date of disease progression, death from any cause, or last follow-up.

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 comparison was performed as no control arm was included. The 1-year PFS rate is reported descriptively with 95% CI in the accompanying KM Plot.

End point values	Avelumab + Standard 1st line Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: months				
median (confidence interval 95%)	6.0 (5.0 to 7.0)			

Attachments (see zip file)	Kaplan - Meier for PFS/Kaplan - Meier for PFS.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

End point type	Secondary

End point timeframe:

The OS is defined as the time from date of study entry to the date of death, regardless of the actual cause of the patients' death or date of last contact.

End point values	Avelumab + Standard 1st line Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: months				
median (confidence interval 95%)	10.3 (7.53 to 12.0)			

Attachments (see zip file)	Kaplan - Meier for OS/Kaplan - Meier for OS.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the proportion of patients with confirmed Complete Response (CR) or confirmed Partial Response (PR) as best overall response to treatment, based on Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 guidelines.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 6 weeks (±14 days) up to Week 48, then every 12 weeks until radiologic progression. Patients with brain metastases had surveillance MRI ~every 12 weeks or earlier if clinically indicated.

End point values	Avelumab + Standard 1st line Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Percentage				
number (not applicable)	69.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

CR: Disappearance of all evidence of target and non-target lesions.
PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions.
SD: Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR.
PD was defined as at least a 20 percent increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions.

End point type	Secondary

End point timeframe:

DOR was defined per RECIST 1.1 as the time from first documented CR or PR to the first occurrence of PD or death from any cause within 12 weeks after the last tumor assessment, whichever came first, in patients with confirmed response.

End point values	Avelumab + Standard 1st line Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: months				
median (confidence interval 95%)	5.6 (4.0 to 6.6)			

Attachments (see zip file)	Kaplan - Meier for DoR/Kaplan - Meier for DoR.png

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Emergent Adverse Events (TEAEs)

End point title	Treatment Emergent Adverse Events (TEAEs)

End point description:

According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03.

End point type	Secondary

End point timeframe:

TEAEs were defined as adverse events (AEs) that occurred between the first dose of study drug administration and up to 90 days after the last dose, which were either absent prior to treatment or had worsened relative to the pretreatment state.

End point values	Avelumab + Standard 1st line Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Subjects (Cases)				
Grade 1 & 2	265			
Grade 3 & 4	57			
Grade 5	4			

Attachments (see zip file)	TEAEs_Table/TEAEs_Table.xlsx

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (QoL) questionnaires

End point title	Quality of Life (QoL) questionnaires

End point description:

EQ-5D-5L: A generic health status questionnaire assessing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses generate a health profile converted into a single index score ranging from 0.59 (worst health) to 1.00 (best health). Change from baseline was measured.

EORTC QLQ-C30: A cancer-specific tool with 30 questions covering 15 domains, including global health status (GHS), functional domains (physical, role, cognitive, emotional, social), and symptoms. Scores range from 0 (very poor QoL) to 100 (excellent QoL). Change from baseline in GHS was evaluated.

EORTC QLQ-LC13: A lung cancer–specific module assessing symptoms and treatment-related side effects via 13 items. Scores range from 0 (no symptom burden) to 100 (severe symptom burden). Change from baseline was assessed for symptom impact.

End point type	Secondary

End point timeframe:

All QoL tools were completed on Day 1 of each cycle. During the Maintenance phase, they were completed every 2 cycles (approximately once a month). QoL assessments were performed prior to any study procedures and treatment.

End point values	Avelumab + Standard 1st line Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	55[2]			
Units: Index				
arithmetic mean (confidence interval 95%)	66.67 (65.41 to 67.93)			

Notes:

[2] - The data refer exclusively to the EQ-5D-5L questionnaire.

Attachments (see zip file)	Quality of Life (QoL) questionnaires/Quality of Life (QoL) Marginal Mean Response Model /Marginal Mean Response

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period for the trial began upon signature of the informed consent form by the study subject and ended 90 days after the last dose of study treatment.

Adverse event reporting additional description:

According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Avelumab + Standard 1st line Chemotherapy

Reporting group description:

All adverse events (AEs) that occurred during the defined period were documented in the source records and in the CRF and/or eCRF, regardless of their relationship to the study treatment.

Serious adverse events	Avelumab + Standard 1st line Chemotherapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 55 (43.64%)		
number of deaths (all causes)	51		
number of deaths resulting from adverse events	7		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death not otherwise specified (NOS)	Additional description: Death not otherwise specified (NOS)		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fever			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatic Hyperplasia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary hemorrhage	Additional description: Haemoptysis		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hip fracture	Additional description: fractured ischium		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Myocardial infarction			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Epileptic Seizure			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stroke			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences causally related to treatment / all	9 / 9		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	2 / 2		
Gastrointestinal disorders			
Infectious enterocolitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Syndrome of inappropriate antidiuretic hormone (SIADH)	Additional description: Syndrome of inappropriate antidiuretic hormone		

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Herpes Zoster			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcus aureus bacteremia (SAB)			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Infection			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Candida Infection			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Avelumab + Standard 1st line Chemotherapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 55 (96.36%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	6		
Hypotension			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Superior vena cava syndrome			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Edema limbs			

subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	22 / 55 (40.00%)		
occurrences (all)	36		
Fever			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hypothermia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary hemorrhage			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Dyspnea			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Hiccups			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Laryngeal hemorrhage			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Pharyngolaryngeal pain			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Pneumothorax			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	6		
Alkaline phosphatase increased			
subjects affected / exposed	10 / 55 (18.18%)		
occurrences (all)	14		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	3		
Blood bilirubin increased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	14		
Creatinine increased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
GGT increased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Lipase increased			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Lymphocyte count increased			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	17 / 55 (30.91%)		
occurrences (all)	32		
Platelet count decreased			
subjects affected / exposed	18 / 55 (32.73%)		
occurrences (all)	41		
Serum amylase increased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Weight gain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Weight loss			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
White blood cell decreased			
subjects affected / exposed	16 / 55 (29.09%)		
occurrences (all)	29		
Increased amylase			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Supraventricular tachycardia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hypersomnia			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 55 (49.09%)		
occurrences (all)	38		
Leukocytosis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Thrombocytosis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Diarrhea			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Esophagitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Ileus			

subjects affected / exposed occurrences (all) Mucositis oral subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1 2 / 55 (3.64%) 2 4 / 55 (7.27%) 7 2 / 55 (3.64%) 2		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	 4 / 55 (7.27%) 4 4 / 55 (7.27%) 4 4 / 55 (7.27%) 4		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	 1 / 55 (1.82%) 1		
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) Hyperthyroidism subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all)	 1 / 55 (1.82%) 1 6 / 55 (10.91%) 8 4 / 55 (7.27%) 4		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Bone Pain			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Infections and infestations			
Rash pustular			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Respiratory disorders			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Lower respiratory infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	3		
Hypercalcemia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	4		
Hyperglycemia			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	11		
Hyperkalemia			

subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	11		
Hypernatremia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	3		
Hyperuricemia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	7		
Hypocalcemia			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	10		
Hypoglycemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	3		
Hypokalemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Hypomagnesemia			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Hypophosphatemia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Hyperphosphatemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Uric Acid decreased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hyponatremia			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2018	1. Amendment of the Informed Consent Form (ICF) 2. Addition of five new investigational sites 3. Principal Investigator (PI) change at an already approved site
25 June 2020	1. Protocol amendment 2. Amendment of the Informed Consent Form (ICF) 3. Investigator's Brochure (IB) update 4. Addition of three new investigational sites
29 June 2021	1. Extension of the clinical trial duration (by one year) 2. Addition of one new investigational site
30 May 2022	1. Extension of the clinical trial duration (by one year)
09 June 2023	1. Extension of the clinical trial duration (by one year)
04 June 2024	1. Extension of the clinical trial duration (by one year)
11 December 2024	1. Protocol amendment 2. Amendment of the Informed Consent Form (ICF) 3. Update of the Investigator's Brochure (IB) Justification: Amendment was submitted by the sponsor on 11-Dec-2024, thus prior to global end of the trial. However the sponsor received the approval of the Regulatory Authority on 07-Jan-2025.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported