Clinical trial results:
Phase II multicentre, randomized, open-label study to evaluate the safety and efficacy of avelumab with gemcitabine/carboplatin versus gemcitabine/carboplatin alone in patients with unresectable or metastatic urothelial carcinoma (UC) who have not received prior systemic therapy and who are ineligible to receive cisplatin-based therapy

Summary

EudraCT number	2017-004260-36
Trial protocol	ES
Global end of trial date	31 August 2022

Results information

Result version number	v1 (current)
This version publication date	15 February 2024
First version publication date	15 February 2024

Trial information

Trial identification

Sponsor protocol code	MS100070_0160

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03390595
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Associació Per a la Recerca Oncològica (APRO)
Sponsor organisation address	Calle Vilarrúbias número 20, Sabadell, Spain, 08202
Public contact	Juan Berges (Clinical Operations), Pivotal, S.L.U., +34 91708150, juan.berges@pivotalcr.com
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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	28 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2022
Global end of trial reached?	Yes
Global end of trial date	31 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of avelumab given pre-emptively and alternate/sequential way with gemcitabine/carboplatin compared to gemcitabine/carboplatin alone in terms of objective response rate (ORR) of subjects with unresectable or metastatic UC who have not received prior systemic therapy and who are ineligible to receive a cisplatin based chemotherapy regimen.

Protection of trial subjects:

-This study was conducted in accordance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki and also in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), as well as all other applicable country and regional legal and regulatory requirements.
-The DSMB was responsible for safeguarding the interests of trial participants
-Investigators were trained to conduct this study in accordance with the study protocol and ICH GCP guidelines. Written commitments were obtained from investigators to comply with GCP and to conduct the study in accordance with the protocol. The investigators were responsible for ensuring that this protocol, the site's ICF, and other information that will be presented to potential subjects were reviewed and approved by the appropriate IRB/IEC prior to enrolment of any study subject.
-Study-related data will be used by the sponsor in accordance with local data protection law.
-The Informed Consent forms were designed following the Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Background therapy:

6 cycles of Carboplatin/gemcitabine (carboplatin 5AUC day +1, gemcitabine 1000mg/m2 day +1 and +8) every 3 weeks.
More than 50% of patients are ineligible to receive cisplatin due to impaired renal function, poor performance status or other comorbidities (hearing loss, neuropathy, heart failure) (9). For these unfit cases, carboplatin-based combinations such as carboplatin-gemcitabine are considered valid alternative options, although they are associated with inferior OS compared to cisplatin-based chemotherapy.

Evidence for comparator:

2 cycles of induction avelumab 10mg/kg every 2 weeks followed by 6 cycles of carboplatin/gemcitabine plus avelumab (carboplatin 5AUC day +1, gemcitabine 1000mg/m2 day +1 and +8 and avelumab 10mg/kg day +15) every 3 weeks followed by avelumab monotherapy 10mg/kg every 2 weeks until progressive disease or intolerance.

Recently, impressive signs of anti-tumor activity have been reported with several immune check-point inhibitors targeting the programmed cell death-1 (PD-1) receptor and its ligand (PD-L1) in advanced UC patients who have failed first-line platinum-based chemotherapy.
Recently, signs of anti-tumor activity have been reported with several immune check-point inhibitors targeting the programmed cell death-1 (PD-1) receptor and its ligand (PD-L1) in advanced UC patients who have failed first-line platinum-based chemotherapy.
Avelumab has showed positive results in the maintenance setting in a phase 3 trial.

Actual start date of recruitment	01 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

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)	16
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patient must have histologically confirmed unresectable or metastatic urothelial cancer not previously treated and Ineligible ("unfit") for cisplatin-based chemotherapy

Pre-assignment

Screening details:

107 Signed ICF; 22 were screen failure; 85 were treatment assigned

Pre-assignment period milestones

Number of subjects started	107[1]
Number of subjects completed	85

Pre-assignment subject non-completion reasons

Reason: Number of subjects	screen failure: 22

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: 107 Signed ICF; 22 were excluded; 85 were treatment assigned in Arm A or Arm B

Period 1

Period 1 title	Whole approved population (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental Arm A (Avelumab, CBDCA, Gemcitabine))

Arm description:

Avelumab 10mg/kg every 2 weeks for two cycles; followed by Carboplatin-Gemcitabine-Avelumab treatment for six cycles; followed by Avelumab every 2 weeks.

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	CBDCA
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

5xAUC (area under the curve) day +1, every three weeks

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

Gemcitabine 1000mg/m2 day +1 and +8 every three weeks

Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion

Routes of administration	Intravenous use

Dosage and administration details:

10mg/kg over 60 minutes

Arm title	SoC treatment Arm B (CBDCA´Gemcitabine)

Arm description:

6 cycles of carboplatin/gemcitabine (carboplatin 5AUC day +1, gemcitabine 1000mg/m2 day +1 and +8) every 3 weeks.

Arm type	Active comparator
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	CBDCA
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

5xAUC (area under the curve) day +1, every three weeks

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

Gemcitabine 1000mg/m2 day +1 and +8 every three weeks

Number of subjects in period 1	Experimental Arm A (Avelumab, CBDCA, Gemcitabine))	SoC treatment Arm B (CBDCA´Gemcitabine)
Started	42	43
Completed	42	43

Baseline characteristics

Reporting groups	
Reporting group title	Experimental Arm A (Avelumab, CBDCA, Gemcitabine))
Reporting group description:	
Avelumab 10mg/kg every 2 weeks for two cycles; followed by Carboplatin-Gemcitabine-Avelumab treatment for six cycles; followed by Avelumab every 2 weeks.	
Reporting group title	SoC treatment Arm B (CBDCA´Gemcitabine)
Reporting group description:	
6 cycles of carboplatin/gemcitabine (carboplatin 5AUC day +1, gemcitabine 1000mg/m2 day +1 and +8) every 3 weeks.	

Reporting group values	Experimental Arm A (Avelumab, CBDCA, Gemcitabine))	SoC treatment Arm B (CBDCA´Gemcitabine)	Total
Number of subjects	42	43	85
Age categorical Units: Subjects			
Adults (18-64 years)	6	10	16
From 65-84 years	36	33	69
85 years and over	0	0	0
Age continuous Units: years			
median	74	72.0	
inter-quartile range (Q1-Q3)	68.00 to 78.00	66.00 to 77.00	-
Gender categorical Units: Subjects			
Female	8	11	19
Male	34	32	66

End points

End points reporting groups

Reporting group title	Experimental Arm A (Avelumab, CBDCA, Gemcitabine))
Reporting group description:	
Avelumab 10mg/kg every 2 weeks for two cycles; followed by Carboplatin-Gemcitabine-Avelumab treatment for six cycles; followed by Avelumab every 2 weeks.	
Reporting group title	SoC treatment Arm B (CBDCA´Gemcitabine)
Reporting group description:	
6 cycles of carboplatin/gemcitabine (carboplatin 5AUC day +1, gemcitabine 1000mg/m2 day +1 and +8) every 3 weeks.	
Subject analysis set title	Whole approved population
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who fulfil I/E criteria.	

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
End point description:	
ORR (overall Response Rate) defined as the proportion of subjects in the analysis population who have either CR or PR per RECIST 1.1 and iRECIST criteria by study site radiology review at any time during the study.	
End point type	Primary
End point timeframe:	
16-May-2018 to 24-Aug-2022 (last follow-up)	

End point values	Experimental Arm A (Avelumab, CBDCA, Gemcitabine))	SoC treatment Arm B (CBDCA´Gemcitabine)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: percentage	42	43		

Statistical analyses

Statistical analysis title	Chi-square
Statistical analysis description:	
Chi-square comparing ORR among Arm A and Arm B	
Comparison groups	Experimental Arm A (Avelumab, CBDCA, Gemcitabine)) v SoC treatment Arm B (CBDCA´Gemcitabine)

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05 [2]
Method	Chi-squared

Notes:

[1] - it was hypothesized that the ORR with the avelumab-chemotherapy combination will be equal or greater than 45%; the ORR with standard carboplatin-gemcitabine being around 30%. It was calculated that with a sample of approximately 40 patients (35 evaluable) per arm, we have probability 0.9 of selecting the treatment that has a true response rate of 30%+15%=45% (D=0.15), based on a Simon randomised phase II design, including 10% of drop-outs.

[2] - potency of 90%

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 15-jun-2018 to 24-aug-2022	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Experimental Arm A (Avelumab, CBDCA, Gemcitabine)
Reporting group description: -	
Reporting group title	SoC treatment Arm B (CBDCA, Gemcitabine)
Reporting group description: -	

Serious adverse events	Experimental Arm A (Avelumab, CBDCA, Gemcitabine)	SoC treatment Arm B (CBDCA, Gemcitabine)	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 42 (64.29%)	20 / 43 (46.51%)	
number of deaths (all causes)	35	36	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lung			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Ischaemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	2 / 42 (4.76%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 42 (7.14%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Insomnia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 42 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	2 / 42 (4.76%)	5 / 43 (11.63%)	
occurrences causally related to treatment / all	0 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 42 (4.76%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 42 (2.38%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 42 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	2 / 42 (4.76%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Empyema			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid abscess			
subjects affected / exposed	0 / 42 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	3 / 43 (6.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 42 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 42 (7.14%)	5 / 43 (11.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urosepsis			
subjects affected / exposed	0 / 42 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Hypercalcaemia			
subjects affected / exposed	2 / 42 (4.76%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Experimental Arm A (Avelumab, CBDCA, Gemcitabine)	SoC treatment Arm B (CBDCA, Gemcitabine)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 42 (90.48%)	43 / 43 (100.00%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 42 (52.38%)	29 / 43 (67.44%)	
occurrences (all)	61	67	
Fatigue			
subjects affected / exposed	7 / 42 (16.67%)	3 / 43 (6.98%)	
occurrences (all)	8	5	
General physical health deterioration			
subjects affected / exposed	4 / 42 (9.52%)	0 / 43 (0.00%)	
occurrences (all)	4	0	
Infusion related reaction			
subjects affected / exposed	4 / 42 (9.52%)	0 / 43 (0.00%)	
occurrences (all)	4	0	
Mucosal inflammation			
subjects affected / exposed	4 / 42 (9.52%)	3 / 43 (6.98%)	
occurrences (all)	9	3	
Oedema peripheral			
subjects affected / exposed	7 / 42 (16.67%)	5 / 43 (11.63%)	
occurrences (all)	8	5	
Pain			

subjects affected / exposed	1 / 42 (2.38%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Pyrexia			
subjects affected / exposed	8 / 42 (19.05%)	4 / 43 (9.30%)	
occurrences (all)	13	6	
Oedema			
subjects affected / exposed	7 / 42 (16.67%)	7 / 43 (16.28%)	
occurrences (all)	8	7	
Chest pain			
subjects affected / exposed	1 / 42 (2.38%)	3 / 43 (6.98%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 42 (4.76%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Epistaxis			
subjects affected / exposed	3 / 42 (7.14%)	2 / 43 (4.65%)	
occurrences (all)	3	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 42 (2.38%)	2 / 43 (4.65%)	
occurrences (all)	1	3	
Investigations			
Alanine aminotransferase			
subjects affected / exposed	5 / 42 (11.90%)	2 / 43 (4.65%)	
occurrences (all)	9	5	
Aspartate aminotransferase			
subjects affected / exposed	5 / 42 (11.90%)	1 / 43 (2.33%)	
occurrences (all)	8	3	
Blood bilirubin increased			
subjects affected / exposed	0 / 42 (0.00%)	2 / 43 (4.65%)	
occurrences (all)	0	4	
Blood creatinine increased			
subjects affected / exposed	3 / 42 (7.14%)	4 / 43 (9.30%)	
occurrences (all)	9	5	
Liver function test abnormal			

subjects affected / exposed	3 / 42 (7.14%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	8 / 42 (19.05%)	0 / 43 (0.00%)	
occurrences (all)	11	0	
Cardiac disorders			
Hypothyroidism			
subjects affected / exposed	2 / 42 (4.76%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 42 (4.76%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Dysgeusia			
subjects affected / exposed	3 / 42 (7.14%)	2 / 43 (4.65%)	
occurrences (all)	4	2	
Neuropathy peripheral			
subjects affected / exposed	2 / 42 (4.76%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	25 / 42 (59.52%)	27 / 43 (62.79%)	
occurrences (all)	108	76	
Anaemia			
subjects affected / exposed	25 / 42 (59.52%)	33 / 43 (76.74%)	
occurrences (all)	101	112	
Leukopenia			
subjects affected / exposed	6 / 42 (14.29%)	3 / 43 (6.98%)	
occurrences (all)	18	4	
Thrombocytopenia			
subjects affected / exposed	28 / 42 (66.67%)	19 / 43 (44.19%)	
occurrences (all)	104	60	
Lymphopenia			
subjects affected / exposed	1 / 42 (2.38%)	2 / 43 (4.65%)	
occurrences (all)	1	2	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 42 (7.14%)	7 / 43 (16.28%)	
occurrences (all)	3	8	
Constipation			
subjects affected / exposed	8 / 42 (19.05%)	10 / 43 (23.26%)	
occurrences (all)	8	13	
Diarrhoea			
subjects affected / exposed	11 / 42 (26.19%)	11 / 43 (25.58%)	
occurrences (all)	19	15	
Nausea			
subjects affected / exposed	12 / 42 (28.57%)	14 / 43 (32.56%)	
occurrences (all)	15	25	
Stomatitis			
subjects affected / exposed	2 / 42 (4.76%)	1 / 43 (2.33%)	
occurrences (all)	3	2	
Vomiting			
subjects affected / exposed	6 / 42 (14.29%)	5 / 43 (11.63%)	
occurrences (all)	6	6	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	10 / 42 (23.81%)	5 / 43 (11.63%)	
occurrences (all)	11	6	
rash			
subjects affected / exposed	8 / 42 (19.05%)	6 / 43 (13.95%)	
occurrences (all)	11	7	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	7 / 42 (16.67%)	6 / 43 (13.95%)	
occurrences (all)	8	7	
Musculoskeletal and connective tissue disorders			
arthralgia			
subjects affected / exposed	5 / 42 (11.90%)	2 / 43 (4.65%)	
occurrences (all)	5	2	
Back pain			

subjects affected / exposed	6 / 42 (14.29%)	0 / 43 (0.00%)	
occurrences (all)	6	0	
Pain in extremity			
subjects affected / exposed	3 / 42 (7.14%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	3 / 42 (7.14%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Urinary tract infection			
subjects affected / exposed	4 / 42 (9.52%)	7 / 43 (16.28%)	
occurrences (all)	8	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 42 (26.19%)	12 / 43 (27.91%)	
occurrences (all)	12	25	
Hyperglycaemia			
subjects affected / exposed	4 / 42 (9.52%)	0 / 43 (0.00%)	
occurrences (all)	5	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2018	Corrections and clarifications of several aspects detected through the document for a correct understanding of the document in terms of study timelines, evaluations and procedures to be performed in each visit.
06 July 2018	clinical trial protocol modification: study inclusion and exclusion criteria clarification/correction.
25 June 2020	clinical trial protocol modification. The main objective of the protocol is to extend the study for an additional 12 months, up to a maximum of 24 months after the start of treatment of the last patient, trying to achieve a median follow-up of 24-30 months.
21 June 2021	clinical trial protocol modification. The main objective is to extend the study for an additional 12 months, up to a maximum of 36 months after the start of treatment of the last patient, trying to achieve a median follow-up of 36-42 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported