Clinical trial results:
A Phase 1/2 Pharmacokinetic Multi-tumor Study of Subcutaneous Formulation of Ipilimumab Monotherapy and in Combination with Subcutaneous Nivolumab

Summary

EudraCT number	2019-004380-40
Trial protocol	GB IT
Global end of trial date	18 January 2023

Results information

Result version number	v1 (current)
This version publication date	06 January 2024
First version publication date	06 January 2024

Trial information

Trial identification

Sponsor protocol code	CA209-76U

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04311710
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	06 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to evaluate the PK, safety, and tolerability of high concentrations of ipilimumab administered subcutaneously with and without rHuPH20 as monotherapy and in combination with SC nivolumab with rHuPH20 in participants with one of the following advanced or metastatic tumor types: melanoma, HCC, mUC, NSCLC, and RCC.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2020
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	Italy: 14
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	21
EEA total number of subjects	14

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)	13

From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

21 participants were treated.

Period 1

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

Arms

Arm title	Part 1 Arm A

Arm description:

4 mg/kg ipilimumab (BMS-734016) + rHuPH20 administered subcutaneously every 3 weeks X 1 cycle (one cycle is 21 days) followed by 3 mg/kg ipilimumab + 1 mg/kg nivolumab (BMS-936558) administered intravenously every 3 weeks X 3 cycles followed by 480 mg nivolumab administered intravenously every 4 weeks for up to 104 weeks.

Arm type	Experimental
Investigational medicinal product name	BMS-734016 + BMS-936558
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg (BMS-734016) + 1 mg/kg (BMS-936558) Q3W x 3 cycles

Investigational medicinal product name	BMS-936558
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

480 mg monotherapy Q4W until completion for 104 weeks

Investigational medicinal product name	BMS-734016+ rHuPH20
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

4 mg/kg Q3W x 1 cycle

Number of subjects in period 1	Part 1 Arm A
Started	21
Completed	3
Not completed	18
Adverse event, non-fatal	1
Death	1
Other Reason	2
Study Drug Toxicity	10
Disease Progression	4

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 Arm A
Reporting group description:	
4 mg/kg ipilimumab (BMS-734016) + rHuPH20 administered subcutaneously every 3 weeks X 1 cycle (one cycle is 21 days) followed by 3 mg/kg ipilimumab + 1 mg/kg nivolumab (BMS-936558) administered intravenously every 3 weeks X 3 cycles followed by 480 mg nivolumab administered intravenously every 4 weeks for up to 104 weeks.	

Reporting group values	Part 1 Arm A	Total	
Number of subjects	21	21	
Age Categorical 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)	13	13	
From 65-84 years	8	8	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	60.1		
standard deviation	± 13.04	-	
Gender Categorical Units: Subjects			
Female	7	7	
Male	14	14	
Ethnicity Units: Subjects			
Not Hispanic or Latino	18	18	
Not reported	3	3	
Race (NIH/OMB) Units: Subjects			
White	21	21	

End points

End points reporting groups

Reporting group title	Part 1 Arm A

Reporting group description:

4 mg/kg ipilimumab (BMS-734016) + rHuPH20 administered subcutaneously every 3 weeks X 1 cycle (one cycle is 21 days) followed by 3 mg/kg ipilimumab + 1 mg/kg nivolumab (BMS-936558) administered intravenously every 3 weeks X 3 cycles followed by 480 mg nivolumab administered intravenously every 4 weeks for up to 104 weeks.

Primary: AUC (0-21d) of ipilimumab

End point title	AUC (0-21d) of ipilimumab[1]

End point description:

Area under the concentration-time curve from time 0 to 21 days postdose

End point type	Primary

End point timeframe:

Day 1 Cycle 1 pre-dose, 24, 48, 72, 168, 336 hours post-dose. End-of-infusion on Cycle 2 Day 1 (Cycle 1 = 3 weeks)

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: Only summary statistics planned for this endpoint.

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)	9931.24 (± 25)			

Statistical analyses

No statistical analyses for this end point

Primary: Time of Maximum Observed Concentration (Tmax) of Ipilimumab

End point title	Time of Maximum Observed Concentration (Tmax) of Ipilimumab[2]

End point description:

End point type	Primary

End point timeframe:

Day 1 Cycle 1 pre-dose, 24, 48, 72, 168, 336 hours post-dose. End-of-infusion on Cycle 2 Day 1 (Cycle 1 = 3 weeks)

Notes:

[2] - 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: Only summary statistics planned for this endpoint.

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: hours				
median (full range (min-max))	72.08 (48.00 to 168.13)			

Statistical analyses

No statistical analyses for this end point

Primary: Cmax

End point title	Cmax[3]

End point description:

Maximum observed serum concentration of ipilimumab

End point type	Primary

End point timeframe:

Day 1 Cycle 1 pre-dose, 24, 48, 72, 168, 336 hours post-dose. End-of-infusion on Cycle 2 Day 1 (Cycle 1 = 3 weeks)

Notes:

[3] - 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: Only summary statistics planned for this endpoint.

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ug/mL				
geometric mean (geometric coefficient of variation)	28.91 (± 27)			

Statistical analyses

No statistical analyses for this end point

Primary: Cavg21d

End point title	Cavg21d[4]

End point description:

Average concentration of ipilimumab during 21 days post-first dose

End point type	Primary

End point timeframe:

Day 1 Cycle 1 pre-dose, 24, 48, 72, 168, 336 hours post-dose. End-of-infusion on Cycle 2 Day 1 (Cycle 1 = 3 weeks)

Notes:

[4] - 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: Only summary statistics planned for this endpoint.

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ug/mL				
geometric mean (geometric coefficient of variation)	19.47 (± 24)			

Statistical analyses

No statistical analyses for this end point

Primary: C21d

End point title	C21d[5]

End point description:

Observed concentration of ipilimumab at 21 days postdose

End point type	Primary

End point timeframe:

Day 1 Cycle 1 pre-dose, 24, 48, 72, 168, 336 hours post-dose. End-of-infusion on Cycle 2 Day 1 (Cycle 1 = 3 weeks)

Notes:

[5] - 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: Only summary statistics planned for this endpoint.

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ug/mL				
geometric mean (geometric coefficient of variation)	12.03 (± 29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

From first dose up to 30 days post last dose (up to approximately 25 months)

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants				
Total	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Serious AEs (SAEs)

End point title	Number of Participants with Serious AEs (SAEs)

End point description:

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
-Results in death
-Is life-threatening
-Requires inpatient hospitalization or causes prolongation of existing hospitalization
-Results in persistent or significant disability/incapacity
-Is a congenital anomaly/birth defect
-Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention to prevent one of the other serious outcomes listed in the definition above.)

End point type	Secondary

End point timeframe:

From first dose up to 100 days post last dose (up to approximately 27 months)

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants				
Total	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Laboratory Abnormalities

End point title	Number of Participants with Laboratory Abnormalities

End point description:

The number of participants experiencing laboratory test abnormalities. Laboratory analysis was performed on the following: hematology, liver and kidney function, and other chemistry testing.

End point type	Secondary

End point timeframe:

From first dose up to 30 days post last dose (up to approximately 25 months)

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants				
Hemoglobin (g/L) Grades 1-3	15			
Platelet Count (10^9/L) Grades 1-4	9			
Leukocytes (10^9/L) Grades 1-4	5			
Lymphocytes (Absolute) (10^9/L) Grades 1-4	8			
Neutrophil (Absolute) (10^9/L) Grades 1-4	4			
Alkaline Phosphatase (g/L) Grades 1-4	6			
Aspartate Aminotransferase (U/L) Grades 1-4	10			
Alanine Aminotransferase (U/L) Grades 1-4	9			
Bilirubin (Total) (umol/L) Grades 1-4	6			
Creatinine (umol/L) Grades 1-4	8			
Hypernatremia (mmol/L) Grades 1-4	1			
Hyponatremia (mmol/L) Grades 1-4	11			
Hyperkalemia (mmol/L) Grades 1-4	0			
Hypokalemia (mmol/L) Grades 1-4	7			
Hypercalcemia (mmol/L) Grades 1-4	2			
Hypocalcemia (mmol/L) Grades 1-4	11			
Hypermagnesemia (mmol/L) Grades 1-4	0			
Hypomagnesemia (mmol/L) Grades 1-4	6			
Hypoglycemia (mmol/L) Grades 1-4	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Died During the Study

End point title	Number of Participants who Died During the Study
End point description:	
Number of participants who died	
End point type	Secondary
End point timeframe:	
From first dose up to 100 days post last dose (up to approximately 27 months)	

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) Leading to Discontinuation

End point title	Number of Participants with Adverse Events (AEs) Leading to Discontinuation

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

From first dose up to 30 days post last dose (up to approximately 25 months)

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants				
Total	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anaphylactic, Hypersensitivity, Injection, and Infusion Reactions

End point title	Number of Participants with Anaphylactic, Hypersensitivity, Injection, and Infusion Reactions

End point description:

The number of participants with AEs in the broad standardized MedDRA query (SMQ) of Anaphylactic Reaction and the select AE hypersensitivity/ injection/infusion reaction category.
MedDRA = Medical Dictionary for Regulatory Activities
SMQ = standardized MedDRA queries

End point type	Secondary

End point timeframe:

From first dose up to 2 days after study drug administration (up to approximately 24 months)

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants				
Anaphylactic reaction	0			
Hypersensitivity reaction	0			
Injection reaction	2			
Infusion-related reaction	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Develop Anti-ipilimumab Antibodies

End point title	Number of Participants who Develop Anti-ipilimumab Antibodies

End point description:

-ADA (anti-drug antibody)-positive: A subject with at least one ADA-positive sample relative to baseline (ADA-negative at baseline or ADA titer to be at least 4-fold or greater (≥) than baseline positive titer at any time after initiation of treatment)
-Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline
-ADA-negative: A participant with no ADA-positive sample after initiation of treatment

End point type	Secondary

End point timeframe:

Day 1 Cycle 1 pre-dose, 24 hours post-dose, and Day 1 pre-dose of Cycles 2-6 (Cycle 1-4 = 3 weeks each and cycle 5-26 = 4 weeks each)

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants				
ADA Negative	21			
ADA Positive	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-nivolumab Antibodies

End point title	Number of Participants with Anti-nivolumab Antibodies

End point description:

-ADA (anti-drug antibody)-positive: A subject with at least one ADA-positive sample relative to baseline (ADA-negative at baseline or ADA titer to be at least 4-fold or greater (≥) than baseline positive titer at any time after initiation of treatment)
-Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline
-ADA-negative: A participant with no ADA-positive sample after initiation of treatment

End point type	Secondary

End point timeframe:

Day 1 pre-dose of Cycles 2-6, 10, 14, 18, 22, and 26 (Cycle 1-4 = 3 weeks each and cycle 5-26 = 4 weeks each)

End point values	Part 1 Arm A			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: participants				
ADA Positive	6			
Neutralizing Positive	2			
ADA Negative	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from first dose to study completion (up to approximately 30 months) SAEs and NSAEs were assessed from first dose to 100 days following last dose (up to approximately 27 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	PART 1 ARM A

Reporting group description:

4 mg/kg ipilimumab (BMS-734016) + rHuPH20 administered subcutaneously every 3 weeks X 1 cycle (one cycle is 21 days) followed by 3 mg/kg ipilimumab + 1 mg/kg nivolumab (BMS-936558) administered intravenously every 3 weeks X 3 cycles followed by 480 mg nivolumab administered intravenously every 4 weeks for up to 104 weeks.

Serious adverse events	PART 1 ARM A		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 21 (76.19%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Haemophagocytic lymphohistiocytosis				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Respiratory failure				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Immune-mediated lung disease				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Amylase increased				
subjects affected / exposed	2 / 21 (9.52%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	2 / 21 (9.52%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femur fracture				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Accidental overdose				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Seizure				

subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis ulcerative				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Autoimmune colitis				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Immune-mediated hepatitis				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				

Adrenal insufficiency			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthyroidism			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Immune-mediated myositis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PART 1 ARM A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 21 (28.57%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	5		
Oedema peripheral			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	4		
Feeling cold			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Blood albumin decreased			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 21 (33.33%)		
occurrences (all)	11		
Amylase increased			
subjects affected / exposed	6 / 21 (28.57%)		
occurrences (all)	22		
Alanine aminotransferase increased			
subjects affected / exposed	7 / 21 (33.33%)		
occurrences (all)	11		
Blood bilirubin increased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	5		
Blood phosphorus decreased			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	6		
Blood magnesium decreased			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	7		
Blood lactate dehydrogenase increased			

subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	4		
Blood creatinine increased			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	7		
Blood chloride decreased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Blood calcium decreased			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	6		
Blood sodium decreased			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	6		
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	7		
Lipase increased			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	10		
Protein total decreased			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Blood urea increased			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 21 (47.62%)		
occurrences (all)	13		
Thrombocytopenia			

subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	4		
Neutropenia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Lymphopenia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	7		
Leukopenia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	9 / 21 (42.86%)		
occurrences (all)	18		
Dyspepsia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	5		
Colitis			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		

Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	 2 / 21 (9.52%) 3		
Skin and subcutaneous tissue disorders Vitiligo subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Papule subjects affected / exposed occurrences (all)	 3 / 21 (14.29%) 3 4 / 21 (19.05%) 4 3 / 21 (14.29%) 3 3 / 21 (14.29%) 3		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) Hyperthyroidism subjects affected / exposed occurrences (all)	 4 / 21 (19.05%) 4 4 / 21 (19.05%) 4		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	 3 / 21 (14.29%) 3 2 / 21 (9.52%) 2		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	 4 / 21 (19.05%) 4		
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 4		
Hyperglycaemia subjects affected / exposed occurrences (all)	6 / 21 (28.57%) 8		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Vitamin D deficiency subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported