Clinical trial results:
A randomized, open-label, phase II study of canakinumab or pembrolizumab as monotherapy or in combination as neoadjuvant therapy in subjects with resectable non-small cell lung cancer (CANOPY-N)

Summary

EudraCT number	2018-004813-42
Trial protocol	ES FR HU NL GR DE BE
Global end of trial date	15 August 2022

Results information

Result version number	v1 (current)
This version publication date	28 June 2023
First version publication date	28 June 2023

Trial information

Trial identification

Sponsor protocol code	CACZ885V2201C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03968419
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 August 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective/endpoint was to assess the MPR rate (≤10% of residual viable tumor cells) on the resected specimen per central review at the time of surgery in all subjects randomized to canakinumab alone and in combination with pembrolizumab treatment arms.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2019
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	Belgium: 2
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	88
EEA total number of subjects	40

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)	31
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 29 centers across 12 countries.

Pre-assignment

Screening details:

Screening assessments were done within 28 days prior to randomization. A total of 163 participants were screened. Of them, 88 participants were randomized. After treatment completion or discontinuation, all subjects were followed for safety for up to 130 days following the last dose of study treatment (safety follow-up period).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Canakinumab monotherapy

Arm description:

Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

200 mg of canakinumab administered via subcutaneous injections once every 3 weeks for a maximum duration of 6 weeks

Arm title	Canakinumab + pembrolizumab

Arm description:

Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery

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

Dosage and administration details:

200 mg of pembrolizumab administered via infusion once every 3 weeks for a maximum duration of 6 weeks

Investigational medicinal product name	Canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

200 mg of canakinumab administered via subcutaneous injections once every 3 weeks for a maximum

duration of 6 weeks

Arm title	Pembrolizumab monotherapy

Arm description:

Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery

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

Dosage and administration details:

200 mg of pembrolizumab administered via infusion once every 3 weeks for a maximum duration of 6 weeks

Number of subjects in period 1	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy
Started	35	35	18
Completed	35	35	17
Not completed	0	0	1
Adverse event, non-fatal	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Canakinumab monotherapy
Reporting group description:	
Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	
Reporting group title	Canakinumab + pembrolizumab
Reporting group description:	
Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	
Reporting group title	Pembrolizumab monotherapy
Reporting group description:	
Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery	

Reporting group values	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy
Number of subjects	35	35	18
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	11	5
From 65-84 years	20	24	13
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	65.5	67.1	66.1
standard deviation	± 9.88	± 6.98	± 5.61
Sex: Female, Male Units: Participants			
Female	13	14	9
Male	22	21	9
Race/Ethnicity, Customized Units: Subjects			
White	20	25	12
Asian	7	3	2
Black or African American	1	1	0
American Indian or Alaska Native	0	1	0
Unknown	7	5	4

Reporting group values	Total		
Number of subjects	88		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	31		
From 65-84 years	57		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	36		
Male	52		
Race/Ethnicity, Customized Units: Subjects			
White	57		
Asian	12		
Black or African American	2		
American Indian or Alaska Native	1		
Unknown	16		

End points

End points reporting groups

Reporting group title	Canakinumab monotherapy
Reporting group description:	
Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	
Reporting group title	Canakinumab + pembrolizumab
Reporting group description:	
Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	
Reporting group title	Pembrolizumab monotherapy
Reporting group description:	
Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery	

Primary: Major Pathological Response (MPR) rate at the time of surgery in subjects randomized to canakinumab monotherapy and in combination with pembrolizumab based on central review

End point title	Major Pathological Response (MPR) rate at the time of surgery in subjects randomized to canakinumab monotherapy and in combination with pembrolizumab based on central review[1][2]
End point description:	
MPR was defined as the percentage of participants with major pathological response (defined as ≤10% residual viable tumor cells on surgical samples). Any participant who had >10% residual viable cancer cells, or started new antineoplastic therapy prior to surgery, or did not have the surgery performed, or had the surgery performed but with unevaluable MPR result, was considered as a non-responder. MPR was assessed at the time of surgery in all subjects randomized to canakinumab monotherapy and in combination with pembrolizumab based on central review.	
End point type	Primary
End point timeframe:	
At time of surgery (up to 6 weeks after first dose of study treatment)	

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 analyses were planned for this primary end point

[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: This endpoint specifically pertains to subjects who were randomized to receive canakinumab monotherapy or canakinumab in combination with pembrolizumab.

End point values	Canakinumab monotherapy	Canakinumab + pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Percentage of participants				
number (confidence interval 95%)	2.9 (0.07 to 14.92)	17.1 (6.56 to 33.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Canakinumab antidrug antibodies (ADA) prevalence

End point title	Canakinumab antidrug antibodies (ADA) prevalence[3]

End point description:

Canakinumab ADA prevalence at baseline was calculated as the percentage of participants who had a canakinumab ADA positive result at baseline

End point type	Secondary

End point timeframe:

Predose (0 hour) on Day 1 of Cycle 1 (Cycle=21 days)

Notes:

[3] - 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: This endpoint specifically pertains to subjects who were randomized to receive canakinumab (as monotherapy or in combination with pembrolizumab).

End point values	Canakinumab monotherapy	Canakinumab + pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Canakinumab ADA incidence

End point title	Canakinumab ADA incidence[4]

End point description:

Canakinumab ADA incidence on treatment was calculated as the percentage of participants who were canakinumab treatment-induced ADA positive (post-baseline ADA positive with ADA-negative sample at baseline) and canakinumab treatment-boosted ADA positive (post-baseline ADA positive with titer that is at least the fold titer change greater than the ADA-positive baseline titer)

End point type	Secondary

End point timeframe:

From baseline (Predose on Day 1 of Cycle 1) up to 130 days after last dose of study treatment (assessed up to 24.6 weeks). Cycle = 21 days

Notes:

[4] - 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: This endpoint specifically pertains to subjects who were randomized to receive canakinumab (as monotherapy or in combination with pembrolizumab).

End point values	Canakinumab monotherapy	Canakinumab + pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pembrolizumab ADA prevalence

End point title	Pembrolizumab ADA prevalence[5]

End point description:

Pembrolizumab ADA prevalence at baseline was calculated as the percentage of participants who had a pembrolizumab ADA positive result at baseline

End point type	Secondary

End point timeframe:

Predose (0 hour) on Day 1 of Cycle 1 (Cycle = 21 days)

Notes:

[5] - 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: This endpoint specifically pertains to subjects who were randomized to receive pembrolizumab (as monotherapy or in combination with canakinumab).

End point values	Canakinumab + pembrolizumab	Pembrolizumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: Participants	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Pembrolizumab ADA incidence

End point title	Pembrolizumab ADA incidence[6]

End point description:

Pembrolizumab ADA incidence on treatment was calculated as the percentage of participants who were pembrolizumab treatment-induced ADA positive (post-baseline ADA positive with ADA-negative sample at baseline) and pembrolizumab treatment-boosted ADA positive (post-baseline ADA positive with titer that is at least the fold titer change greater than the ADA-positive baseline titer)

End point type	Secondary

End point timeframe:

From baseline (Predose on Day 1 of Cycle 1) up to 26 days after last dose of study treatment (assessed up to 10.7 weeks). Cycle = 21 days

Notes:

[6] - 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: This endpoint specifically pertains to subjects who were randomized to receive pembrolizumab (as monotherapy or in combination with canakinumab).

End point values	Canakinumab + pembrolizumab	Pembrolizumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: Participants	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) based on local investigator assessment using RECIST v1.1

End point title	Overall response rate (ORR) based on local investigator assessment using RECIST v1.1

End point description:

ORR is defined as the percentage of subjects with confirmed best overall response of complete response (CR) or partial response (PR), as per local investigator's assessment by RECIST 1.1.
CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.
PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters

End point type	Secondary

End point timeframe:

From date of randomization to date of surgery, assessed up to 6 weeks

End point values	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	18	
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.00 to 10.00)	8.6 (1.80 to 23.06)	11.1 (1.38 to 34.71)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum canakinumab concentration

End point title	Serum canakinumab concentration[7]

End point description:

Canakinumab serum concentrations were determined at the specified time points.

End point type	Secondary

End point timeframe:

Predose (0 hour) on Day 1 of Cycles 1 and 2 (Cycle =21 days)

Notes:

[7] - 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: This endpoint specifically pertains to subjects who were randomized to receive canakinumab (as monotherapy or in combination with pembrolizumab).

End point values	Canakinumab monotherapy	Canakinumab + pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: microgram/miliLiter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1	0 (± 0)	0 (± 0)		
Cycle 2	10.9 (± 32.9)	10.3 (± 41.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum pembrolizumab concentration

End point title	Serum pembrolizumab concentration[8]

End point description:

Pembrolizumab serum concentrations were determined at the specified time points.

End point type	Secondary

End point timeframe:

Predose (0 hour) and 0.5 hours post dose on Day 1 of Cycle 1 and predose on Cycle 2 (Cycle =21 days)

Notes:

[8] - 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: This endpoint specifically pertains to subjects who were randomized to receive pembrolizumab (as monotherapy or in combination with canakinumab).

End point values	Canakinumab + pembrolizumab	Pembrolizumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	17		
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 predose	0 (± 0)	0 (± 0)		
Cyle 1 0.5 hours post dose	65.5 (± 23.8)	65.5 (± 19.9)		
Cycle 2 predose	16.0 (± 43.4)	35.5 (± 13.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical feasibility rate

End point title	Surgical feasibility rate

End point description:

Surgical feasibility rate was defined as the percentage of subjects who underwent surgery following study treatment.

End point type	Secondary

End point timeframe:

Up to 6 weeks after first dose

End point values	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	18	
Units: Percentage of participants				
number (confidence interval 95%)	91.4 (76.94 to 98.20)	97.1 (85.08 to 99.93)	100 (81.47 to 100.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Major Pathological Response (MPR) rate at the time of surgery in subjects randomized to pembrolizumab monotherapy based on central review

End point title	Major Pathological Response (MPR) rate at the time of surgery in subjects randomized to pembrolizumab monotherapy based on central review[9]

End point description:

MPR was defined as the percentage of participants with major pathological response (defined as ≤10% residual viable tumor cells on surgical samples). Any participant who had >10% residual viable cancer cells, or started new antineoplastic therapy prior to surgery, or did not have the surgery performed, or had the surgery performed but with unevaluable MPR result, was considered as a non-responder.
MPR was assessed at the time of surgery in all subjects randomized to pembrolizumab monotherapy arm based on central review.

End point type	Secondary

End point timeframe:

At time of surgery (up to 6 weeks after first dose)

Notes:

[9] - 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: This endpoint specifically pertains to subjects who were randomized to receive pembrolizumab monotherapy

End point values	Pembrolizumab monotherapy			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)	16.7 (3.58 to 41.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Difference in Major Pathological Response (MPR) rate between the canakinumab plus pembrolizumab arm and the pembrolizumab arm based on central review

End point title	Difference in Major Pathological Response (MPR) rate between the canakinumab plus pembrolizumab arm and the pembrolizumab arm based on central review[10]

End point description:

MPR was defined as the percentage of participants with ≤10% residual viable tumor cells on surgical samples. MPR was assessed at the time of surgery based on central review. The difference in MPR rate between the canakinumab plus pembrolizumab arm and the pembrolizumab arm based on central review along with the Chang and Zhang confidence interval was assessed.

End point type	Secondary

End point timeframe:

At time of surgery (up to 6 weeks after first dose of study treatment)

Notes:

[10] - 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: This endpoint specifically pertains to subjects who were randomized to receive pembrolizumab monotherapy or canakinumab in combination with pembrolizumab.

End point values	Canakinumab + pembrolizumab	Pembrolizumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: Percentage of participants				
number (confidence interval 95%)	17.1 (6.56 to 33.65)	16.7 (3.58 to 41.42)		

Statistical analyses

Statistical analysis title	Difference in MPR rate
Comparison groups	Pembrolizumab monotherapy v Canakinumab + pembrolizumab
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.56
upper limit	21.23

Secondary: Major Pathological Response (MPR) rate at the time of surgery in all subjects based on local review

End point title	Major Pathological Response (MPR) rate at the time of surgery in all subjects based on local review

End point description:

MPR was defined as the percentage of participants with major pathological response (defined as ≤10% residual viable tumor cells on surgical samples). Any participant who had >10% residual viable cancer cells, or started new antineoplastic therapy prior to surgery, or did not have the surgery performed, or had the surgery performed but with unevaluable MPR result, was considered as a non-responder.
MPR was assessed at the time of surgery in all subjects based on local review.

End point type	Secondary

End point timeframe:

At time of surgery (up to 6 weeks after first dose)

End point values	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	18	
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.00 to 10.00)	20.0 (8.44 to 36.94)	22.2 (6.41 to 47.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Major Pathological Response (MPR) rate based on the levels of biomarkers

End point title	Major Pathological Response (MPR) rate based on the levels of biomarkers

End point description:

MPR was defined as the percentage of participants with major pathological response (defined as ≤10% residual viable tumor cells on surgical samples). Any participant who had >10% residual viable cancer cells, or started new antineoplastic therapy prior to surgery, or did not have the surgery performed, or had the surgery performed but with unevaluable MPR result, was considered as a non-responder.
MPR rate was analyzed by the biomarker subgroups at baseline. Biomarkers included PD-L1, CD8, hs-CRP and hs-IL-6.

End point type	Secondary

End point timeframe:

From date of randomization up to 6 weeks after first dose

End point values	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	18	
Units: Percentage of participants				
number (confidence interval 95%)				
PD-L1: <1%	0 (0.00 to 26.46)	7.1 (0.18 to 33.87)	14.3 (0.36 to 57.87)	
PD-L1: 1-49%	6.7 (0.17 to 31.95)	15.4 (1.92 to 45.45)	16.7 (0.42 to 64.12)	
PD-L1: >=50%	0 (0.00 to 45.93)	42.9 (9.90 to 81.59)	0 (0.00 to 70.76)	
hs-CRP: <2mg/L	12.5 (0.32 to 52.65)	7.7 (0.19 to 36.03)	37.5 (8.52 to 75.51)	
hs-CRP: >=2mg/L	0 (0.0 to 13.23)	22.7 (7.82 to 45.37)	0 (0.00 to 33.63)	
hs-IL-6: <Q1 (2.52 mg/L)	16.7 (0.42 to 64.12)	12.5 (0.32 to 52.65)	14.3 (0.36 to 57.87)	
hs-IL-6: >=Q1 (2.52 pg/mL) to <Q2 (5.36 pg/mL)	0 (0.00 to 36.94)	10 (0.25 to 44.50)	33.3 (0.84 to 90.57)	
hs-IL-6: >=Q2 (5.36 pg/mL) to <Q3 (12.03 pg/mL)	0 (0.00 to 36.94)	28.6 (3.67 to 70.96)	16.7 (0.42 to 64.12)	
hs-IL-6: >=Q3 (12.03 pg/mL)	0 (0.00 to 30.85)	20.0 (2.52 to 55.61)	0 (0.00 to 97.50)	
CD8: <3%	0 (0.00 to 26.46)	13.0 (2.78 to 33.59)	0 (0.00 to 52.18)	
CD8: >=3%	0 (0.00 to 18.53)	22.2 (2.81 to 60.01)	33.3 (4.33 to 77.72)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From day of first dose of study medication to 130 days after last dose of study medication, up to 25.6 weeks	
Adverse event reporting additional description:	
Any sign or symptom that occurs during the study treatment plus the 130 days post treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Canakinumab monotherapy
Reporting group description:	
Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	
Reporting group title	Pembrolizumab monotherapy
Reporting group description:	
Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery	
Reporting group title	Canakinumab + pembrolizumab
Reporting group description:	
Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	

Serious adverse events	Canakinumab monotherapy	Pembrolizumab monotherapy	Canakinumab + pembrolizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 35 (28.57%)	4 / 18 (22.22%)	9 / 35 (25.71%)
number of deaths (all causes)	3	1	2
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative respiratory failure			

subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (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
Hepatobiliary disorders			
Immune-mediated hepatitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (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
Pleural effusion			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			

subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 35 (8.57%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyopneumothorax			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Endocarditis			

subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Canakinumab monotherapy	Pembrolizumab monotherapy	Canakinumab + pembrolizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 35 (80.00%)	14 / 18 (77.78%)	27 / 35 (77.14%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	2 / 35 (5.71%)
occurrences (all)	2	1	2

Chest pain			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	2 / 35 (5.71%)
occurrences (all)	2	1	2
Fatigue			
subjects affected / exposed	9 / 35 (25.71%)	4 / 18 (22.22%)	5 / 35 (14.29%)
occurrences (all)	9	4	5
Influenza like illness			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 35 (2.86%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 35 (11.43%)	1 / 18 (5.56%)	6 / 35 (17.14%)
occurrences (all)	4	1	6
Dysphonia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 18 (5.56%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Cough			
subjects affected / exposed	4 / 35 (11.43%)	2 / 18 (11.11%)	6 / 35 (17.14%)
occurrences (all)	5	2	6
Productive cough			
subjects affected / exposed	2 / 35 (5.71%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences (all)	2	0	1
Haemoptysis			
subjects affected / exposed	0 / 35 (0.00%)	2 / 18 (11.11%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Dyspnoea exertional			

subjects affected / exposed	1 / 35 (2.86%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
Blood bilirubin increased			
subjects affected / exposed	4 / 35 (11.43%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences (all)	5	0	0
Blood creatinine increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences (all)	2	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	2	1	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	2	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	2 / 35 (5.71%)
occurrences (all)	2	1	2
Lipase increased			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	2	1	1
Lymphocyte count decreased			
subjects affected / exposed	4 / 35 (11.43%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	5	1	0
SARS-CoV-2 test negative			
subjects affected / exposed	2 / 35 (5.71%)	3 / 18 (16.67%)	3 / 35 (8.57%)
occurrences (all)	2	3	3
Activated partial thromboplastin time			

prolonged			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 35 (2.86%)	2 / 18 (11.11%)	3 / 35 (8.57%)
occurrences (all)	1	2	3
Amylase increased			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	3	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	3 / 35 (8.57%)
occurrences (all)	1	0	3
Bilirubin conjugated increased			
subjects affected / exposed	4 / 35 (11.43%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	4	1	1
SARS-CoV-2 test positive			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	2	1	1
Weight decreased			
subjects affected / exposed	1 / 35 (2.86%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	1	1	1
White blood cell count decreased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 35 (0.00%)	2 / 18 (11.11%)	6 / 35 (17.14%)
occurrences (all)	0	2	6
Wound complication			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 35 (2.86%)	2 / 18 (11.11%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Dysgeusia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Dizziness			
subjects affected / exposed	1 / 35 (2.86%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 35 (25.71%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	10	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	3 / 35 (8.57%)
occurrences (all)	2	1	3
Diarrhoea			
subjects affected / exposed	1 / 35 (2.86%)	0 / 18 (0.00%)	6 / 35 (17.14%)
occurrences (all)	3	0	7
Dry mouth			
subjects affected / exposed	0 / 35 (0.00%)	2 / 18 (11.11%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
Nausea			
subjects affected / exposed	4 / 35 (11.43%)	3 / 18 (16.67%)	3 / 35 (8.57%)
occurrences (all)	7	3	3
Vomiting			
subjects affected / exposed	2 / 35 (5.71%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	2	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Ecchymosis			

subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 35 (2.86%)	1 / 18 (5.56%)	4 / 35 (11.43%)
occurrences (all)	1	1	4
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	5 / 35 (14.29%)
occurrences (all)	0	1	5
Hypothyroidism			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	3 / 35 (8.57%)
occurrences (all)	0	1	3
Musculoskeletal and connective tissue disorders			
Polyarthritis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 18 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	3
Musculoskeletal chest pain			
subjects affected / exposed	1 / 35 (2.86%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	1	1	1
Arthralgia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	1	1	1
Infections and infestations			
Enterocolitis infectious			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0

Erysipelas			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 18 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
Post procedural infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Wound infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 35 (17.14%)	0 / 18 (0.00%)	1 / 35 (2.86%)
occurrences (all)	6	0	1
Hyperglycaemia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 18 (5.56%)	4 / 35 (11.43%)
occurrences (all)	1	1	4
Hypoalbuminaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 18 (5.56%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Hypophosphataemia			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 18 (5.56%) 1	0 / 35 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2020	The main rationale for this amendment was to implement the request from the Health Authority to modify the target population for Major Pathological Response (MPR) from "evaluable subjects" to "randomized subjects". Changes to inclusion/exclusion criteria were made to allow for more clarity and flexibility for the enrollment/randomization. The EOT visit window was changed to within 21 days after the permanent discontinuation of study treatment but before the surgery to provide more flexibility to the site and patient. The surgery-related safety was added as an exploratory objective.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported