Clinical trial results:
An Open-label, Active-Controlled, Safety and Efficacy Study of Oral Baricitinib in Patients from 2 Years to Less Than 18 Years Old with Active Juvenile Idiopathic Arthritis-Associated Uveitis or Chronic Anterior Antinuclear Antibody Positive Uveitis

Summary

EudraCT number	2019-000119-10
Trial protocol	GB FR DE IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	02 August 2024
First version publication date	02 August 2024

Trial information

Trial identification

Sponsor protocol code	I4V-MC-JAHW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04088409
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16277

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001220-PIP01-11
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	Interim
Date of interim/final analysis	17 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2023
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The reason for this study is to see if the study drug baricitinib given orally is safe and effective in participants with active juvenile idiopathic
arthritis (JIA)-associated uveitis or chronic anterior antinuclear
antibody-positive uveitis from 2 years to less than 18 years old.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 October 2019
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	France: 4
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 15
Worldwide total number of subjects	29
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)	16
Adolescents (12-17 years)	13
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 30 participants were enrolled in the study. One participant (in baricitinib arm) withdrew from the study before administration of the study drug. This study is conducted in 2 parts. Part A (24 weeks) and Part B (260 weeks). Participants assigned to baricitinib and completed the Part A as a responder continued receiving (contd..)

Pre-assignment

Screening details:

(contd..) baricitinib until the end of study or discontinuation from the study.

Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Baricitinib

Arm description:

Participants ≥9 to <18 years of age were administered 4 milligrams (mg) baricitinib once daily (QD). Participants <9 years of age were administered 2 mg baricitinib QD.
Participants <6 years of age received an oral suspension. Participants ≥6 to <12 years of age had the option of receiving an oral suspension. Participants >12 years of age were supplied tablets.

Arm type	Experimental
Investigational medicinal product name	Baricitinib
Investigational medicinal product code	
Other name	LY3009104
Pharmaceutical forms	Tablet, Oral drops, suspension
Routes of administration	Oral use

Dosage and administration details:

Administered orally

Arm title	Adalimumab

Arm description:

Participants received adalimumab administered subcutaneously (SC) once every 2 weeks. The dose was based on body weight: 20 mg every 2 weeks for participants weighing <30 kilograms (kg), or 40 mg
every 2 weeks for participants weighing ≥30 kg.

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered SC

Number of subjects in period 1	Baricitinib	Adalimumab
Started	24	5
Received At Least 1 Dose of Study Drug	24	5
Completed	10	0
Not completed	14	5
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	-
Did Not Meet Randomization Criteria	2	-
Lost to follow-up	1	-
Per Protocol, Participants Discontinued Study	-	4
Lack of efficacy	9	-

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Baricitinib

Arm description:

Participants ≥9 to <18 years of age were administered 4 milligrams (mg) baricitinib once daily (QD). Participants <9 years of age were administered 2 mg baricitinib QD.
Participants <6 years of age received an oral suspension. Participants ≥6 to <12 years of age had the option of receiving an oral suspension. Participants >12 years of age were supplied tablets.

Arm type	Experimental
Investigational medicinal product name	Baricitinib
Investigational medicinal product code	
Other name	LY3009104
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally

Number of subjects in period 2	Baricitinib
Started	10
Completed	0
Not completed	10
Ongoing Treatment	10

Baseline characteristics

Reporting groups	
Reporting group title	Baricitinib
Reporting group description:	
Participants ≥9 to <18 years of age were administered 4 milligrams (mg) baricitinib once daily (QD). Participants <9 years of age were administered 2 mg baricitinib QD. Participants <6 years of age received an oral suspension. Participants ≥6 to <12 years of age had the option of receiving an oral suspension. Participants >12 years of age were supplied tablets.	
Reporting group title	Adalimumab
Reporting group description:	
Participants received adalimumab administered subcutaneously (SC) once every 2 weeks. The dose was based on body weight: 20 mg every 2 weeks for participants weighing <30 kilograms (kg), or 40 mg every 2 weeks for participants weighing ≥30 kg.	

Reporting group values	Baricitinib	Adalimumab	Total
Number of subjects	24	5	29
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	11.60	6.60	
standard deviation	± 3.53	± 2.51	-
Gender categorical Units: Subjects			
Female	14	5	19
Male	10	0	10
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	0	2
Not Hispanic or Latino	12	4	16
Unknown or Not Reported	10	1	11
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	20	4	24
More than one race	0	0	0
Unknown or Not Reported	4	0	4
Region of Enrollment Units: Subjects			
France	4	0	4
Germany	1	1	2
Italy	3	2	5
Spain	3	0	3
United Kingdom	13	2	15

Subject analysis sets

Subject analysis set title	Baricitinib
Subject analysis set type	Per protocol

Subject analysis set description:

Participants ≥9 to <18 years of age were administered 4 mg baricitinib QD. Participants <9 years of age were administered 2 mg baricitinib QD.
Participants <6 years of age received an oral suspension. Participants ≥6 to <12 years of age had the option of receiving an oral suspension. Participants >12 years of age were supplied tablets.

Reporting group values	Baricitinib		
Number of subjects	24		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	11.60		
standard deviation	± 3.53		
Gender categorical Units: Subjects			
Female	14		
Male	10		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	12		
Unknown or Not Reported	10		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	20		
More than one race	0		
Unknown or Not Reported	4		
Region of Enrollment Units: Subjects			
France	4		
Germany	1		
Italy	3		
Spain	3		
United Kingdom	13		

End points

End points reporting groups

Reporting group title	Baricitinib

Reporting group description:

Participants ≥9 to <18 years of age were administered 4 milligrams (mg) baricitinib once daily (QD). Participants <9 years of age were administered 2 mg baricitinib QD.
Participants <6 years of age received an oral suspension. Participants ≥6 to <12 years of age had the option of receiving an oral suspension. Participants >12 years of age were supplied tablets.

Reporting group title	Adalimumab

Reporting group description:

Participants received adalimumab administered subcutaneously (SC) once every 2 weeks. The dose was based on body weight: 20 mg every 2 weeks for participants weighing <30 kilograms (kg), or 40 mg
every 2 weeks for participants weighing ≥30 kg.

Reporting group title	Baricitinib

Reporting group description:

Participants ≥9 to <18 years of age were administered 4 milligrams (mg) baricitinib once daily (QD). Participants <9 years of age were administered 2 mg baricitinib QD.
Participants <6 years of age received an oral suspension. Participants ≥6 to <12 years of age had the option of receiving an oral suspension. Participants >12 years of age were supplied tablets.

Subject analysis set title	Baricitinib
Subject analysis set type	Per protocol

Subject analysis set description:

Participants ≥9 to <18 years of age were administered 4 mg baricitinib QD. Participants <9 years of age were administered 2 mg baricitinib QD.
Participants <6 years of age received an oral suspension. Participants ≥6 to <12 years of age had the option of receiving an oral suspension. Participants >12 years of age were supplied tablets.

Primary: Part A: Percentage of Responders for Baricitinib at Week 24

End point title	Part A: Percentage of Responders for Baricitinib at Week 24[1][2]

End point description:

Response was defined according to the Standardization of Uveitis Nomenclature (SUN) criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero through week 24, in the eye most severely affected at baseline.
Analysis population description: All participants who received at least one dose of baricitinib in Part A.

End point type	Primary

End point timeframe:

Week 24

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 inferential statistics was planned for this 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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Percentage of participants				
number (not applicable)	33.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SUN Grade of Cells in the Anterior Chamber in the Most Severely Affected Eye

End point title	Change from Baseline in SUN Grade of Cells in the Anterior Chamber in the Most Severely Affected Eye[3]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: Score on a Scale				
number (not applicable)				

Notes:

[4] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SUN Grade of Cells in the Anterior Chamber in the Less Severely Affected Eye (If Applicable)

End point title	Change from Baseline in SUN Grade of Cells in the Anterior Chamber in the Less Severely Affected Eye (If Applicable)[5]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: score on a Scale				
number (not applicable)				

Notes:

[6] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders in Participants with Bilateral Uveitis Disease at Baseline

End point title	Percentage of Responders in Participants with Bilateral Uveitis Disease at Baseline[7]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Week 24

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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: Percentage of Participants				
number (not applicable)				

Notes:

[8] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Visual Acuity Measured by Age-AppropriateLogarithm of the Minimum Angle of Resolution (LogMAR) Test

End point title	Change from Baseline in Visual Acuity Measured by Age-AppropriateLogarithm of the Minimum Angle of Resolution (LogMAR) Test[9]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: Score on a Scale				
number (not applicable)				

Notes:

[10] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Vitreous Haze

End point title	Change from Baseline in Vitreous Haze[11]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[11] - 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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[12]			
Units: Score on a Scale				
number (not applicable)				

Notes:

[12] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Grade of Flare in the Anterior Chamber

End point title	Change from Baseline in Grade of Flare in the Anterior Chamber[13]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[13] - 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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: Score on a Scale				
number (not applicable)				

Notes:

[14] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Inactive Anterior Uveitis (usingSUN Definition)

End point title	Percentage of Participants with Inactive Anterior Uveitis (usingSUN Definition)[15]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[15] - 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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: Percentage of Participants				
number (not applicable)				

Notes:

[16] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Inactive Anterior Uveitis Disease (Using SUNDefinition)

End point title	Time to Inactive Anterior Uveitis Disease (Using

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[17] - 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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[18]			
Units: Weeks				
number (not applicable)				

Notes:

[18] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who are Able to Taper ConcomitantTopical Corticosteroids to <2 Drops Per Day

End point title	Percentage of Participants who are Able to Taper ConcomitantTopical Corticosteroids to <2 Drops Per Day[19]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[19] - 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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[20]			
Units: Percentage of Participants				
number (not applicable)				

Notes:

[20] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric American College of Rheumatology (PediACR30) Response Rate (For Participants with JIA-U)

End point title	Pediatric American College of Rheumatology (PediACR30) Response Rate (For Participants with JIA-U)[21]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[21] - 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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[22]			
Units: Percentage of Participants				
number (not applicable)				

Notes:

[22] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Overall Uveitis-Related Disability

End point title	Change from Baseline in Overall Uveitis-Related Disability[23]

End point description:

Outcome data will be provided after the study is completed.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[23] - 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: Descriptive statistics was added in baseline period reporting arms. The complete results will be disclosed after the study is completed.

End point values	Baricitinib			
Subject group type	Reporting group			
Number of subjects analysed	0[24]			
Units: Score on a Scale				
number (not applicable)				

Notes:

[24] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline To Up To 55 Weeks

Adverse event reporting additional description:

I4V-MC-JAHW

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Adalimumab

Reporting group description: -

Reporting group title	Baricitinib

Reporting group description: -

Serious adverse events	Adalimumab	Baricitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	2 / 24 (8.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
intentional overdose			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 5 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
uveitis			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 5 (0.00%)	1 / 24 (4.17%)	
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			
juvenile idiopathic arthritis			
alternative dictionary used: MedDRA 26.1			

subjects affected / exposed	1 / 5 (20.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Adalimumab	Baricitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	16 / 24 (66.67%)	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
blood triglycerides increased			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
blood bilirubin increased			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
bilirubin conjugated increased			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
mean platelet volume decreased			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

neutrophil count decreased alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0	
Injury, poisoning and procedural complications injection related reaction alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0	
Nervous system disorders headache alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 24 (12.50%) 3	
General disorders and administration site conditions adverse drug reaction alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0	
illness alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0	
pyrexia alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	3 / 24 (12.50%) 3	
Blood and lymphatic system disorders iron deficiency anaemia alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0	
Eye disorders macular oedema alternative dictionary used: MedDRA 26.1			

subjects affected / exposed	1 / 5 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
abdominal pain upper			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
nausea			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 5 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	4	
vomiting			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 5 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 5 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
oropharyngeal pain			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 5 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
acne			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 5 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
bone development abnormal			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

covid-19			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
nasopharyngitis			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
otitis media			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
urinary tract infection			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 5 (20.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2019	- Clarified statements in Schedule of Activities section, Inclusion and Exclusion Criteria; - Updated information related to Study Assessments and Procedures.
31 May 2019	-Specified number of participants enrolled; -Updated sample size determination secondary analyses table to make the information more specific.
14 August 2020	-Updated study figure for the overall design; - Updated terms in the Schedule of Activities section.
07 November 2020	-Updated study figure for the overall design; - Updated terms in the Schedule of Activities section.
14 June 2023	-Updated cohorts and study figure for more clarity; - Editorial changes made throughout the protocol to improve the clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported