Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Sarilumab in Patients with Polymyalgia Rheumatica

Summary

EudraCT number	2017-002989-42
Trial protocol	DK DE BE FR HU GB EE NL ES IT
Global end of trial date	19 May 2021

Results information

Result version number	v1 (current)
This version publication date	02 June 2022
First version publication date	02 June 2022

Trial information

Trial identification

Sponsor protocol code	EFC15160

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03600818
WHO universal trial number (UTN)	U1111-1201-0777

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	07 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of KEVZARA® (sarilumab) in subjects with polymyalgia rheumatica (PMR) as assessed by the proportion of subjects with sustained remission at Week 52 for sarilumab with a 14 weeks corticosteroid (CS) tapering regimen as compared to placebo with a 52 weeks CS tapering regimen.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

All subjects were required to be on greater than or equal to (>=) 7.5 milligrams (mg) of oral CS daily.

Evidence for comparator: -

Actual start date of recruitment	09 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Switzerland: 4

Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Russian Federation: 4
Worldwide total number of subjects	118
EEA total number of subjects	58

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	85
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 78 active centres (randomised at least 1 subject) in 17 countries. A total of 196 subjects were screened between 09 October 2018 and 19 March 2020, of whom 78 were screen failures. Screen failures were mainly due to not meeting inclusion criteria.

Pre-assignment

Screening details:

Subjects were randomised to two treatment groups in a 1:1 ratio by interactive response technology. A total of 118 subjects were enrolled and randomised in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo+52 Week taper

Arm description:

Subjects received sarilumab-matching placebo as subcutaneous (SC) injection every 2 weeks (q2w) up to 52 weeks along with the combination of prednisone and/or prednisone-matching placebo according to the protocol-defined schedule. Subjects received prednisone/prednisone-matching placebo tapering oral daily doses for 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone or Prednisone matched to placebo tapering oral doses daily for 52 weeks according to the protocol-defined schedule.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to sarilumab, single SC injection q2w for 52 weeks.

Arm title	Sarilumab 200mg q2w+14 Week Taper

Arm description:

Subjects received sarilumab 200 mg as SC injection q2w up to 52 weeks along with the combination of prednisone and/or prednisone-matching placebo according to the protocol-defined schedule. Subjects received prednisone tapering oral daily doses during the first 14 weeks and prednisone-matching placebo from Week 14 up to Week 52.

Arm type	Experimental

Investigational medicinal product name	Sarilumab 200 mg
Investigational medicinal product code	SAR153191, REGN88
Other name	Kevzara®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Sarilumab 200 mg, single SC injection q2w for 52 weeks.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone or Prednisone matched to placebo tapering oral doses daily for 52 weeks according to the protocol-defined schedule.

Number of subjects in period 1	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper
Started	58	60
Safety analysis set	58	59
Completed	36	42
Not completed	22	18
Randomised and not treated	-	1
Other-unspecified	5	3
Adverse event	4	7
Lack of efficacy	9	4
Withdrawal by subject	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo+52 Week taper
Reporting group description:	
Subjects received sarilumab-matching placebo as subcutaneous (SC) injection every 2 weeks (q2w) up to 52 weeks along with the combination of prednisone and/or prednisone-matching placebo according to the protocol-defined schedule. Subjects received prednisone/prednisone-matching placebo tapering oral daily doses for 52 weeks.	
Reporting group title	Sarilumab 200mg q2w+14 Week Taper
Reporting group description:	
Subjects received sarilumab 200 mg as SC injection q2w up to 52 weeks along with the combination of prednisone and/or prednisone-matching placebo according to the protocol-defined schedule. Subjects received prednisone tapering oral daily doses during the first 14 weeks and prednisone-matching placebo from Week 14 up to Week 52.	

Reporting group values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper	Total
Number of subjects	58	60	118
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	69.1	68.8	
standard deviation	± 8.5	± 7.8	-
Gender categorical Units: Subjects			
Male	21	15	36
Female	37	45	82
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	48	50	98
More than one race	0	0	0
Unknown or Not Reported	8	9	17

End points

End points reporting groups

Reporting group title	Placebo+52 Week taper

Reporting group description:

Subjects received sarilumab-matching placebo as subcutaneous (SC) injection every 2 weeks (q2w) up to 52 weeks along with the combination of prednisone and/or prednisone-matching placebo according to the protocol-defined schedule. Subjects received prednisone/prednisone-matching placebo tapering oral daily doses for 52 weeks.

Reporting group title	Sarilumab 200mg q2w+14 Week Taper

Reporting group description:

Subjects received sarilumab 200 mg as SC injection q2w up to 52 weeks along with the combination of prednisone and/or prednisone-matching placebo according to the protocol-defined schedule. Subjects received prednisone tapering oral daily doses during the first 14 weeks and prednisone-matching placebo from Week 14 up to Week 52.

Primary: Percentage of Subjects Achieving Sustained Remission at Week 52

End point title	Percentage of Subjects Achieving Sustained Remission at Week 52

End point description:

Sustained remission was defined as meeting all of the following parameters: achievement of disease remission (defined as resolution of signs and symptoms of PMR, and normalisation of C-reactive protein [CRP] [less than {<}10 milligrams per litre {mg/L}]) not later than Week 12, absence of disease flare (defined as recurrence of signs and symptoms attributable to active PMR plus an increase in CS dose due to PMR or elevation of erythrocyte sedimentation rate [ESR] attributable to active PMR plus an increase in CS dose due to PMR) from Week 12 through Week 52, sustained reduction of CRP (to <10 mg/L, with absence of successive elevations to >=10 mg/L) from Week 12 through Week 52, and successful adherence to prednisone taper from Week 12 through Week 52. Intent-to-treat (ITT) population that included all subjects who were allocated to a randomised treatment group and were analysed according to treatment group allocated.

End point type	Primary

End point timeframe:

At Week 52

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: percentage of subjects				
number (not applicable)	10.3	28.3		

Statistical analyses

Statistical analysis title	Sarilumab versus Placebo
Comparison groups	Placebo+52 Week taper v Sarilumab 200mg q2w+14 Week Taper

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0193 [1]
Method	Fisher exact
Parameter estimate	Difference in percentage
Point estimate	18
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.15
upper limit	31.82

Notes:

[1] - Threshold for significance at 0.05 level.

Secondary: Total Cumulative Corticosteroid Dose

End point title	Total Cumulative Corticosteroid Dose

End point description:

Cumulative dose of CS used for PMR disease was defined as the dose taken up to the end of treatment, including expected prednisone in tapering regimen per protocol, add-on prednisone, CS used in rescue therapy and the use of commercial prednisone (an excess of less than or equal to [<=]100 mg of prednisone during the study treatment period). The total cumulative CS dose was based on the total number of days with complete or partial intake, no imputation was done on missed tablets. Analysis was performed on ITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: milligrams				
arithmetic mean (standard deviation)	2235.8 (± 839.4)	1039.5 (± 612.2)		

Statistical analyses

Statistical analysis title	Sarilumab versus Placebo

Statistical analysis description:

A hierarchical testing procedure was used to control the overall type I error. If the primary endpoint reaches statistical significance then the secondary endpoint for total cumulative CS dose was tested next.

Comparison groups	Placebo+52 Week taper v Sarilumab 200mg q2w+14 Week Taper

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Wilcoxon rank-sum test

Notes:

[2] - Threshold for significance at 0.05 level.

Secondary: Number of Subjects Who Achieved Disease Remission up to Week 12

End point title	Number of Subjects Who Achieved Disease Remission up to Week 12

End point description:

Disease remission was defined as resolution of signs and symptoms of PMR, and normalisation of CRP (< 10 mg/L). The status of normalisation of CRP (<10 mg/L) was determined based on the last two non-missing post-baseline CRP values measured up to Week 12. If at least one of the value was <10 mg/L, then it was considered as normalisation of CRP. Subjects who took rescue CS due to active PMR prior to Week 12 or who permanently withdrew from the study treatment prior to Week 12 were considered as not achieved disease remission by Week 12. During the initial 12 weeks of prednisone taper, treatment for one flare before Week 12 was permitted if it was successfully treated with a low dose (<=5 mg/day) prednisone add-on taper regimen (completed prior to Week 12) and provided that all other sustained remission parameters were met. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: subjects	22	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Absence of Disease Flare From Week 12 Through Week 52

End point title	Number of Subjects With Absence of Disease Flare From Week 12 Through Week 52

End point description:

Disease flare was defined as either recurrence of signs and symptoms attributable to active PMR plus an increase in CS dose due to PMR, or elevation of ESR attributable to active PMR plus an increase in CS dose due to PMR. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Week 12 Through Week 52

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: subjects	19	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Sustained Reduction of CRP From Week 12 Through Week 52

End point title	Number of Subjects With Sustained Reduction of CRP From Week 12 Through Week 52

End point description:

Normalisation (sustained reduction) of CRP was defined as CRP levels <10 mg/L. If there were two or more consecutive visits with CRP >=10 mg/L, then it was categorised as no normalisation of CRP. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Week 12 through Week 52

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: subjects	26	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Successful Adherence to the Prednisone Taper From Week 12 Through Week 52

End point title	Number of Subjects With Successful Adherence to the Prednisone Taper From Week 12 Through Week 52

End point description:

Successful adherence to the prednisone taper from Week 12 through Week 52 was defined as subjects who did not take rescue therapy from Week 12 through Week 52 and any excess prednisone (beyond the per protocol CS tapering regimen) with a cumulative dose of <=100 mg (or equivalent), such as

those employed to manage adverse event (AE) not related to PMR. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From Week 12 through Week 52

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: subjects	14	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Polymyalgia Rheumatica Flare After Clinical Remission up to Week 52

End point title	Time to First Polymyalgia Rheumatica Flare After Clinical Remission up to Week 52

End point description:

Time to first PMR flare was defined as the duration (in days) from randomisation to first PMR flare after clinical remission (defined as resolution of signs and symptoms and normalisation of CRP [<10 mg/L]) and up to 52 weeks. Disease flare was defined as either the recurrence of signs or symptoms attributable to active plus an increase in CS dose due to PMR or elevation of ESR attributable to active PMR plus an increase in CS dose due to PMR. Kaplan-Meier method was used for the analysis. Subjects who never achieved remission were censored at randomisation day; and those who achieved clinical remission and never flared were censored at the end of treatment assessment date up to Week 52. Analysis was performed on ITT population. Here, '99999' is used as a space filler which denotes that at Week 52 the cumulative incidence was less than 50% in the Kaplan-Meier plot. Hence, the upper limit of confidence interval and median value was not reached.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	60		
Units: days				
median (confidence interval 95%)	99.00 (1.000 to 154.000)	99999 (93.000 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Glucocorticoid Toxicity Index (C-GTI): Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS) at Week 52

End point title	Composite Glucocorticoid Toxicity Index (C-GTI): Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS) at Week 52

End point description:

GTI assessed glucocorticoid (GC) related morbidity and GC-sparing ability of other therapies; composed of 2 components: C-GTI and Specific List. C-GTI contained 9 domains and Specific List contained 23 items (11 domains), used as complementary tool. C-GTI score; sum of 9 domain-specific scores at each visit and Cumulative GTI score; sum of C-GTI scores across each visit. 2 cumulative GTI scores: CWS and AIS at Week 52 are reported in this endpoint. CWS assessed cumulative GC toxicity regardless of whether toxicity had lasting effects or was transient. AIS assessed new therapy effectiveness in decreasing any Baseline GC toxicity over time. Negative scores reflect improvement in CS toxicities from Baseline. CWS, composite score ranged; 0 to 439 and for AIS, composite score ranged; -346 to 439. Both CWS and AIS, minimum score implies least toxicity and maximum score implies most toxicity. ITT. 'Number of subjects analysed'=subjects evaluable for endpoint.

End point type	Secondary

End point timeframe:

At Week 52

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	60		
Units: units on a scale				
least squares mean (standard error)				
CWS	57.22 (± 6.678)	52.32 (± 6.507)		
AIS	2.57 (± 6.275)	-4.02 (± 6.115)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events

	(TESAEs)

End point description:

An AE was defined as any untoward medical occurrence in a subject who received study drug and did not necessarily had to have a causal relationship with the treatment. Serious AEs (SAEs) were any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. TEAEs were the AEs that developed or worsened or became serious during the TEAE period (defined as the time from the first dose of the investigational medicinal product (IMP) to the last dose of the IMP +60 days). Analysis was performed on safety population that included all subjects who had received at least one dose or part of a dose of IMP and were analysed according to the treatment actually received.

End point type	Secondary

End point timeframe:

From first dose (i.e. Day 1) up to 60 days after last dose date of study drug (i.e. up to Week 60)

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: subjects				
Any TEAE	49	56		
TESAE	12	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Potentially Clinically Significant Vital Signs Abnormalities During TEAE Period

End point title	Number of Subjects with Potentially Clinically Significant Vital Signs Abnormalities During TEAE Period

End point description:

Criteria for potentially clinically significant vital sign abnormalities:

Systolic Blood Pressure (SBP): <= 95 millimeters of mercury (mmHg) and decrease from baseline (DFB) >= 20 mmHg; >= 160 mmHg and increase from baseline (IFB) >= 20 mmHg.

Diastolic blood pressure (DBP): <=45 mmHg and DFB >=10 mmHg; >=110 mmHg and IFB >=10 mmHg.

Heart Rate (HR): <= 50 beats per min (bpm) and DFB >=20 bpm; >=120 bpm and IFB >= 20 bpm.

Weight: >=5% DFB; >=5% IFB.

TEAE period was defined as the time from the first dose of the IMP to the last dose of the IMP +60 days. Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint and ‘n’= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

From first dose (i.e., Day 1) up to 60 days after last dose date of study drug (i.e., up to Week 60)

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	58		
Units: subjects				
SBP <=95 mmHg and DFB >=20 mmHg (n=58,58)	0	2		
SBP >=160 mmHg and IFB >=20 mmHg (n=58,58)	4	5		
DBP <=45 mmHg and DFB >=10 mmHg (n=58,58)	1	0		
DBP >=110 mmHg and IFB >=10 mmHg (n=58,58)	1	1		
HR <=50 bpm and DFB >= 20 bpm (n=58,58)	1	0		
HR >=120 bpm and IFB >=20 bpm (n=58,58)	1	0		
Weight >=5% DFB (n=56,58)	2	5		
Weight >=5% IFB (n=56,58)	9	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Abnormalities - Hematological Parameter

End point title	Number of Subjects With Potentially Clinically Significant Abnormalities - Hematological Parameter

End point description:

Criteria for potentially clinically significant laboratory abnormalities included:

Hemoglobin (Hb): <= 115 grams per liter (g/L) (Male [M]), <= 95 g/L (Female [F]); >= 185 g/L (M), >= 165 g/L (F); DFB >= 20 g/L .

Hematocrit: <= 0.37 volume/volume (v/v) (M); <= 0.32 v/v (F); >= 0.55 v/v (M); >= 0.5 v/v (F).

Erythrocytes: >=6 Tera/ liter (L).

Platelets: < 100 Giga/L, >= 700 Giga/L.

Leukocytes: < 3.0 Giga/L (Non-Black [NB]); < 2.0 Giga/L (Black [B]), >= 16.0 Giga/L.

Neutrophils: < 1.5 Giga/L (NB); < 1.0 Giga/L (B).

Lymphocytes: > 4.0 Giga/L.

Monocytes: > 0.7 Giga/L.

Basophils: > 0.1 Giga/L.

Eosinophils: > 0.5 Giga/L or > upper limit of normal (ULN) (if ULN >= 0.5 Giga/L).

Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable

for this endpoint.

End point type	Secondary

End point timeframe:

From first dose (i.e., Day 1) up to 60 days after last dose date of study drug (i.e., up to Week 60)

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	58		
Units: subjects				
Hb: <= 115 g/L (M), <= 95 g/L (F)	1	1		
Hb: >=185 g/L(M), >=165 g/L(F)	0	1		
Hb: DFB >=20 g/L	3	2		
Hematocrit: <= 0.37 v/v(M); <=0.32 v/v(F)	1	1		
Hematocrit: >=0.55 v/v(M); >=0.5 v/v(F)	0	0		
Erythrocytes: >=6 Tera/L	0	0		
Platelets: < 100 Giga/L	0	2		
Platelets: >= 700 Giga/L	0	0		
Leukocytes:<3.0Giga/L(NB); <2.0Giga/L(B)	0	11		
Leukocytes: >= 16.0 Giga/L	1	1		
Neutrophils:<1.5Giga/L(NB);<1.0Giga/L (B)	0	18		
Lymphocytes: > 4.0 Giga/L	4	2		
Monocytes: > 0.7 Giga/L	12	8		
Basophils: > 0.1 Giga/L	16	13		
Eosinophils:>0.5 Giga/L; >ULN (if ULN>=0.5Giga/L)	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Abnormalities - Metabolic Parameters

End point title	Number of Subjects With Potentially Clinically Significant Abnormalities - Metabolic Parameters

End point description:

Criteria for potentially clinically significant abnormalities:

Glucose: <=3.9 millimoles per liter (mmol/L) and < lower limit of normal (LLN); >=11.1 mmol/L (unfasted [ufas]); >=7 mmol/L (fasted [fas]).

HbA1c: >8%.

Cholesterol: >=7.74 mmol/L.

Triglycerides: >=4.6 mmol/L.

C Reactive Protein (CRP): >2 ULN or >10 mg/L (if ULN not provided). Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint and 'n'= subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

From first dose (i.e., Day 1) up to 60 days after last dose date of study drug (i.e., up to Week 60)

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	58		
Units: subjects				
Glucose: <=3.9 mmol/L and <LLN (n=56,57)	1	2		
Glucose:>=11.1mmol/L(ufas)/>=7mmol/L(fas)(n=56,57)	14	5		
HbA1c: >8% (n=58,58)	4	2		
Cholesterol: >=7.74 mmol/L (n=58,58)	4	8		
Triglycerides: >=4.6 mmol/L (n=58,58)	1	3		
CRP: >2 ULN or >10 mg/L (n=58,58)	37	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Abnormalities - Renal Function

End point title	Number of Subjects With Potentially Clinically Significant Abnormalities - Renal Function

End point description:

Criteria for potentially clinically significant abnormalities:

Creatinine: >=150 micromol/L (adults); >=30% change from Baseline, >=100% change from Baseline.

Creatinine clearance: >=60 to <90 milliliters per minute (mL/min); >=30 to <60 mL/min; >=15 to <30 mL/min; <15 mL/min.

Blood urea nitrogen: >=17 mmol/L.

Urate: <120 micromol/L; >408 micromol/L.

Analysis was performed on safety population. Here, 'number of subjects analysed'= subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose (i.e., Day 1) up to 60 days after last dose date of study drug (i.e., up to Week 60)

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	58		
Units: subjects				
Creatinine: >=150 micromol/L (adults)	2	2		
Creatinine: >=30% change from Baseline	3	14		
Creatinine: >=100% change from Baseline	0	1		
Creatinine clearance: >=60 to <90 mL/min	30	29		
Creatinine clearance: >=30 to <60 mL/min	13	17		
Creatinine clearance: >=15 to <30 mL/min	0	1		
Creatinine clearance: <15 mL/min	0	0		
Blood urea nitrogen: >=17 mmol/L	0	0		
Urate: <120 micromol/L	0	0		
Urate: >408 micromol/L	16	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Abnormalities - Liver Function

End point title	Number of Subjects With Potentially Clinically Significant Abnormalities - Liver Function

End point description:

Criteria for potentially clinically significant abnormalities:

Albumin: <= 25 g/L.

Alanine Aminotransferase (ALT): >3 ULN; >5 ULN; >10 ULN.

Aspartate Aminotransferase (AST): >3 ULN; >5 ULN; >10 ULN; >20 ULN.

Alkaline Phosphatase: >1.5 ULN.

Bilirubin: >1.5 ULN; >2 ULN.

ALT and Total Bilirubin: ALT > 3 ULN and Bilirubin > 2 ULN

Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose (i.e., Day 1) up to 60 days after last dose date of study drug (i.e., up to Week 60)

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	58		
Units: subjects				
Albumin: <= 25 g/L	0	0		
ALT: >3 ULN	2	0		
ALT: >5 ULN	1	0		
ALT: >10 ULN	0	0		
AST: >3 ULN	1	0		
AST: >5 ULN	1	0		
AST: >10 ULN	1	0		
AST: >20 ULN	0	0		
Alkaline Phosphatase: >1.5 ULN	1	0		
Bilirubin: >1.5 ULN	1	1		
Bilirubin: >2 ULN	0	0		
ALT > 3 ULN and Bilirubin > 2 ULN	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Antidrug Antibodies (ADA) Response

End point title	Number of Subjects With Treatment-emergent Antidrug Antibodies (ADA) Response

End point description:

ADA response categories: 1) Treatment-boosted ADA positive subject: Subject with a positive ADA assay response at Baseline and with at least a 4-fold increase in titer compared to Baseline during TEAE period. 2) Treatment-emergent ADA positive subject: Subject with non-positive assay (meaning negative or missing) response at Baseline but with a positive assay response during the TEAE period (defined as the time from the first dose of the IMP to the last dose of the IMP +60 days). Analysis was performed on ADA population which included subjects who had received at least one dose or part of a dose of IMP and were analysed according to the treatment actually received with at least one post dose evaluable ADA sample.

End point type	Secondary

End point timeframe:

From first dose (i.e., Day 1) up to 60 days after last dose date of study drug (i.e., up to Week 60)

End point values	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	56		
Units: subjects				
Treatment-boosted ADA	0	0		
Treatment-emergent ADA	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Serum Trough Concentration (Ctrough) of Sarilumab

End point title	Pharmacokinetics (PK): Serum Trough Concentration (Ctrough) of Sarilumab[3]

End point description:

Ctrough was pre dose concentration of drug. Analysis was performed on PK analysis population: all subjects who had received at least one dose or part of a dose of IMP, were analysed according to the treatment actually received and had at least 1 post-dose non-missing serum sarilumab concentration value. Here, 'n' = subjects with available data for each specified category. Data for this endpoint was not planned to be collected and analysed for placebo arm (Placebo+52 Week Taper) as pre-specified in the protocol.

End point type	Secondary

End point timeframe:

Pre-dose on Week 0 (Baseline), Week 2, 4, 12, 16, 24, and 52

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: Endpoint is reporting data for applicable arm in the study.

End point values	Sarilumab 200mg q2w+14 Week Taper			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=58)	0.00 (± 0.00)			
Week 2 (n=56)	5209.02 (± 4357.37)			
Week 4 (n=50)	9259.25 (± 7668.95)			
Week 12 (n=46)	17494.20 (± 11146.33)			
Week 16 (n=42)	23082.86 (± 15878.92)			
Week 24 (n=40)	27289.75 (± 17927.73)			
Week 52 (n=33)	27604.95 (± 24880.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Serum Drug Concentration of Sarilumab Post-dose at Week 24

End point title	Pharmacokinetics: Serum Drug Concentration of Sarilumab Post-dose at Week 24[4]

End point description:

Serum concentrations of functional sarilumab were analysed using validated enzyme linked immunosorbent assay. Analysis was performed on PK population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint. Data for this endpoint was not planned to be collected and analysed for placebo arm (Placebo+52 Week Taper) as pre-specified in the protocol.

End point type	Secondary

End point timeframe:

Post-dose at Week 24

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: Endpoint is reporting data for applicable arm in the study.

End point values	Sarilumab 200mg q2w+14 Week Taper			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ng/mL				
arithmetic mean (standard deviation)	35757.69 (± 15353.96)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose (i.e., Day 1) of IMP to last dose date of IMP + 60 days (i.e., up to Week 60).

Adverse event reporting additional description:

Reported AEs were TEAEs that developed/worsened in grade or became serious during TEAE period (defined as the time from the first dose of the IMP to the last dose of the SC IMP + 60 days). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Placebo+52 Week taper

Reporting group description:

Subjects received sarilumab-matching placebo as subcutaneous (SC) injection every 2 weeks (q2w) up to 52 weeks along with the combination of prednisone and/or prednisone-matching placebo according to the protocol-defined schedule. Subjects received prednisone/prednisone-matching placebo tapering oral daily doses for 52 weeks.

Reporting group title	Sarilumab 200mg q2w+14 Week Taper

Reporting group description:

Subjects received sarilumab 200 mg as SC injection q2w up to 52 weeks along with the combination of prednisone and/or prednisone-matching placebo according to the protocol-defined schedule. Subjects received prednisone tapering oral daily doses during the first 14 weeks and prednisone-matching placebo from Week 14 up to Week 52.

Serious adverse events	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 58 (20.69%)	8 / 59 (13.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Alanine Aminotransferase Increased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erdheim-Chester Disease			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur Fracture			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Intramural Haematoma			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giant Cell Arteritis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Emergency			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic Hypotension			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Pollakiuria			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Spinal Stenosis			

alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia Rheumatica			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Covid-19			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Discitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection Bacterial			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo+52 Week taper	Sarilumab 200mg q2w+14 Week Taper	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 58 (72.41%)	42 / 59 (71.19%)	
Injury, poisoning and procedural complications			
Accidental Overdose			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	4	
Fall			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	6 / 58 (10.34%)	3 / 59 (5.08%)	
occurrences (all)	6	3	
Limb Injury			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Skin Laceration			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 58 (5.17%)	1 / 59 (1.69%)	
occurrences (all)	5	1	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 58 (3.45%)	6 / 59 (10.17%)	
occurrences (all)	2	6	
Nervous system disorders			
Cognitive Disorder			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)	
occurrences (all)	4	4	
Headache			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	5 / 58 (8.62%)	1 / 59 (1.69%)	
occurrences (all)	5	1	
Sciatica			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			
Increased Tendency To Bruise			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	4 / 58 (6.90%)	4 / 59 (6.78%)	
occurrences (all)	4	4	
Leukopenia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	4 / 59 (6.78%)	
occurrences (all)	0	4	
Neutropenia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	7 / 59 (11.86%)	
occurrences (all)	0	9	
General disorders and administration site conditions			
Fatigue			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	3	
Injection Site Pruritus			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	7	
Oedema Peripheral			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	5 / 58 (8.62%)	3 / 59 (5.08%)	
occurrences (all)	5	3	
Eye disorders			
Dry Eye			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	4 / 58 (6.90%)	0 / 59 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Constipation			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	4 / 59 (6.78%)	
occurrences (all)	0	4	
Diarrhoea			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	7 / 59 (11.86%)	
occurrences (all)	1	7	
Gastrooesophageal Reflux Disease			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	4 / 59 (6.78%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Pruritus			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 58 (1.72%)	3 / 59 (5.08%)	
occurrences (all)	1	3	
Rash Pruritic			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	3 / 59 (5.08%)	
occurrences (all)	0	4	
Skin Striae			

alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	4 / 58 (6.90%)	0 / 59 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Depression			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	6 / 58 (10.34%)	5 / 59 (8.47%)	
occurrences (all)	7	5	
Insomnia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	9 / 58 (15.52%)	6 / 59 (10.17%)	
occurrences (all)	9	6	
Mania			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 58 (5.17%)	9 / 59 (15.25%)	
occurrences (all)	3	11	
Back Pain			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	3	4	
Bursitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	5 / 58 (8.62%)	2 / 59 (3.39%)	
occurrences (all)	5	2	
Myalgia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 58 (0.00%)	4 / 59 (6.78%)	
occurrences (all)	0	4	
Osteoarthritis			
alternative dictionary used:			

MedDRA 24.0			
subjects affected / exposed	5 / 58 (8.62%)	6 / 59 (10.17%)	
occurrences (all)	6	6	
Pain In Extremity			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 58 (5.17%)	0 / 59 (0.00%)	
occurrences (all)	3	0	
Rotator Cuff Syndrome			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)	
occurrences (all)	3	2	
Tendonitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 58 (3.45%)	3 / 59 (5.08%)	
occurrences (all)	2	5	
Infections and infestations			
Cystitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)	
occurrences (all)	4	2	
Gastroenteritis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 58 (5.17%)	2 / 59 (3.39%)	
occurrences (all)	4	2	
Influenza			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	4 / 58 (6.90%)	0 / 59 (0.00%)	
occurrences (all)	4	0	
Nasopharyngitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	6 / 58 (10.34%)	2 / 59 (3.39%)	
occurrences (all)	6	2	
Upper Respiratory Tract Infection			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 5	2 / 59 (3.39%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2018	The following changes were done: i) Exclusion criteria: initial wording was modified with the elimination of, "Based on investigators' judgment," and addition of, "Subject who meets any of the following". ii) Additional wording was added in sections pertaining to ALT discontinuation criteria. iii) Language pertaining to the use of legal representative was modified.
19 April 2021	The following changes were done: i) Added clinical trial.gov registration number 'NTC03600818'. ii) Changed total expected number of subjects. iii) Changed statistical significance level from 0.01 to 0.05 and updated power. iv) Changed significant level for analysis of primary efficacy endpoint from 0.01 to 0.05. v)Changed total expected number of subjects, Changed significant level for analysis of secondary efficacy endpoints from 0.01 to 0.05 vi) Updated sample size and power calculations. vii) Revised 99% confidence interval (CI) to 95% CI.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Protracted recruitment timeline exacerbated by COVID-19 pandemic led to pre-mature termination of study, resulting in a change in the total expected number of subjects and change in the statistical significance level.

Notes: