Clinical trial results:
Phase 3, double-blind, placebo-controlled, randomized withdrawal study with open-label extension, to assess the efficacy and safety of Rilonacept treatment in subjects with recurrent pericarditis

Summary

EudraCT number	2018-002719-87
Trial protocol	IT
Global end of trial date	30 June 2022

Results information

Result version number	v1 (current)
This version publication date	24 January 2025
First version publication date	24 January 2025

Trial information

Trial identification

Sponsor protocol code	KPL-914-C002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03737110
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kiniksa Pharmaceuticals (UK), Ltd.
Sponsor organisation address	Third Floor, 23 Old Bond Street, London, United Kingdom, W1S 4PZ
Public contact	Kiniksa Pharmaceuticals (UK), Ltd. c/o Kiniksa Pharmaceuticals Corp., Kiniksa Medical Information Group, +1 7814319100, studyinfo@kiniksa.com
Scientific contact	Kiniksa Pharmaceuticals (UK), Ltd. c/o Kiniksa Pharmaceuticals Corp., Kiniksa Medical Information Group, +1 7814319100, studyinfo@kiniksa.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	12 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2020
Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the efficacy of rilonacept treatment in subjects with recurrent pericarditis.

Protection of trial subjects:

The protocol, informed consent form (ICF), advertisements to be used for the recruitment of study subjects, and any other written information regarding this study was approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before any study procedures were performed. Any subsequent protocol amendments or informed consent revisions were approved by the IRB before any changes were initiated. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with International Council for Harmonisation (ICH) harmonized tripartite guideline E6(R2): Good Clinical Practice (GCP) were maintained by the site.
This study was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of GCP as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.
Written informed consent to participate in the study was obtained from each subject or subject’s parent or legal guardian before any study-specific procedures were performed. Each subject was provided with an ICF describing the study and was given time to read this document and ask questions. Pediatric subjects (ages 12 to 17) signed a written assent form, which explained the study.

Background therapy:

During the single-blind Run-In period, in parallel with treatment with blinded rilonacept, the subjects were tapered off background standard-of-care (SOC) therapy for pericarditis: corticosteroids, NSAIDs, and colchicine. Some subjects used analgesics/opioid analgesics if needed under the Investigator's discretion.

Evidence for comparator:

There was not a comparator medicinal product because patients presented in active flare having failed standard of care therapies.

Actual start date of recruitment	09 January 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	United States: 52

Worldwide total number of subjects	86
EEA total number of subjects	21

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)	7
Adults (18-64 years)	71
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

46 study centers were activated in Australia, Israel, Italy and USA. 31 centers screened subjects, 21 enrolled at least 1 subject. 86 subjects were enrolled, treated, and included in safety analysis set; 61 had been randomized at the time the event-driven trial closure was attained, comprising the ITT analysis set for the primary efficacy endpoint.

Pre-assignment

Screening details:

Patients (12+ year old) with diagnosis recurrent pericarditis, who received a standard-of-care background therapy at stable dose level and were willing and able to taper and discontinue those medications. Screening procedures were repeated at the discretion of the investigator; subjects who initially failed screening were eligible to be rescreened.

Period 1

Period 1 title	Run-in Period (RI)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

All subjects received blinded rilonacept and were blinded to the duration of the RI period and the timing of randomization. Subjects who did not achieve clinical response on rilonacept monotherapy at RI Week 12 were discontinued from study drug, transitioned to SOC pericarditis therapy at the investigator’s discretion, and were followed through the end of the Randomized Withdrawal (RW) period.

Arms

Arm title	Rilonacept (RI)

Arm description:

Single-blinded participants received initial dose of 320 mg (or 4.4 mg/kg in pediatric participants) rilonacept subcutaneous (SC), following by 160 mg (or 2.2 mg/kg in pediatric participants) injections once weekly. In the first week rilonacept was administered in addition to background SOC therapy. During following 9 weeks the background standard-of-care therapy was tapered off, and it was required that rilonacept be administered as monotherapy after Week 10.
Subjects who stopped background SOC therapy, achieved clinical response, and were on rilonacept monotherapy at RI period Week 12 were transitioned to the RW period. Fifteen subjects were still in the RI period at the time when the event-driven RW period ended and randomization closed; these 15 patients continued directly to the Long Term Extension (LTE) period, as they had completed the RI period and had met the definition of clinical response.

Arm type	Experimental
Investigational medicinal product name	Rilonacept
Investigational medicinal product code	KPL-914
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each rilonacept vial contained 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 mL sterile water for injection, the rilonacept vial contained 80 mg/mL rilonacept, 46 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives were present.
First administration of 320 mg (or 4.4 mg/kg in pediatric participants) SC injection, followed by 160 mg (or 2.2 mg/kg in pediatric participants) injections once weekly.

Number of subjects in period 1	Rilonacept (RI)
Started	86
Completed	61
Not completed	25
Physician decision	2
Completed, Continuing directly into LTE	15
Adverse event, non-fatal	4
Not specified	1
Lack of efficacy	3

Period 2

Period 2 title	Randomized Withdrawal Period (RW)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Neither the subject nor any of the site staff, clinical research organization (CRO) staff, or sponsor staff who were involved in the treatment or clinical evaluation of the subjects were aware of the treatment received.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rilonacept (RW)

Arm description:

Participants assigned to Rilonacept 160 mg (or 2.2 mg/kg in pediatric subjects ≥12 and <18 years old) administered by SC injections once weekly.

Arm type	Experimental
Investigational medicinal product name	Rilonacept
Investigational medicinal product code	KPL-914
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each rilonacept vial contained 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 mL sterile water for injection, the rilonacept vial contained 80 mg/mL rilonacept, 46 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives were present. Product was administered as a SC injection of 160 mg (or 2.2 mg/kg in pediatric participants) once weekly.

Arm title	Placebo

Arm description:

Subjects received matching placebo SC injections once weekly.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo is a vial with lyophilized powder. After reconstitution with 2.3 mL sterile water for injection, the placebo vial contained 46 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives were present.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The trial design assessed the efficacy of the IMP vs Placebo in the RW period. The purpose of the Run-in period was to prepare subjects for randomization to rilonacept or placebo at Week 12. The Run-in period was carried out in order for patients to switch from background standard-of care therapy to the monotherapy with the IMP. Pivotal efficacy data were collected in the second period, the Randomized Withdrawal period.

Number of subjects in period 2[2]	Rilonacept (RW)	Placebo
Started	30	31
Completed	29	30
Not completed	1	1
Consent withdrawn by subject	-	1
Completed, Not Continuing into LTE	1	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 86 subjects entered the Run-In period (Period 1), and 61 subjects entered Period 2. Fifteen subjects who were still in the Run-in (RI) period at the time when randomization into the event-driven Randomized Withdrawal (RW) period had ended and the Long-term Extension (LTE) had opened were given the option to enter the LTE directly (after they had completed the RI period and had met the definition of clinical response).

Period 3

Period 3 title	Long-term extension period (LTE)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Rilonacept (LTE)

Arm description:

All participants who had completed the RW period and participants still in the RI period (at the time when the RW period had ended) who met clinical response criteria at Week 12 were eligible for inclusion in the LTE period (up to 24 months of additional open-label rilonacept).

Arm type	Experimental
Investigational medicinal product name	Rilonacept
Investigational medicinal product code	KPL-914
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each rilonacept vial contained 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 mL

sterile water for injection, the rilonacept vial contained 80 mg/mL rilonacept, 46 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives were present. Product was administered as a SC injection of 160 mg (or 2.2 mg/kg in pediatric participants) once weekly.

Number of subjects in period 3[3]	Rilonacept (LTE)
Started	29
Completed	69
Not completed	5
Consent withdrawn by subject	3
Adverse event, non-fatal	1
Lost to follow-up	1
Joined	45
Transffered from Placebo (RW)	30
Transfered from RI directly into LTE	15

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 15 patients completed the RI period continued in LTE period. Patients randomized in Placebo arm of RW joined Rilonacept (RW) arm.

Baseline characteristics

Reporting groups	
Reporting group title	Rilonacept (RW)
Reporting group description:	
Participants assigned to Rilonacept 160 mg (or 2.2 mg/kg in pediatric subjects ≥12 and <18 years old) administered by SC injections once weekly.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo SC injections once weekly.	

Reporting group values	Rilonacept (RW)	Placebo	Total
Number of subjects	30	31	61
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	1	2	3
Adults (18-64 years)	24	27	51
From 65-84 years	5	2	7
Age continuous			
Units: years			
arithmetic mean	48.0	44.8	
full range (min-max)	17 to 71	16 to 67	-
Gender categorical			
Units: Subjects			
Female	16	16	32
Male	14	15	29

Subject analysis sets	
Subject analysis set title	Intent-to-treat analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Intent-to-treat (ITT) analysis set included all subjects who were randomized in the RW period. ITT analysis set was the same as the safety analysis set in the RW period.	

Reporting group values	Intent-to-treat analysis set		
Number of subjects	61		
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	3		
Adults (18-64 years)	51		
From 65-84 years	7		
Age continuous			
Units: years			
arithmetic mean	46.4		
full range (min-max)	16 to 71		
Gender categorical			
Units: Subjects			
Female	32		

Male	29		

End points

End points reporting groups

Reporting group title	Rilonacept (RI)

Reporting group description:

Single-blinded participants received initial dose of 320 mg (or 4.4 mg/kg in pediatric participants) rilonacept subcutaneous (SC), following by 160 mg (or 2.2 mg/kg in pediatric participants) injections once weekly. In the first week rilonacept was administered in addition to background SOC therapy. During following 9 weeks the background standard-of-care therapy was tapered off, and it was required that rilonacept be administered as monotherapy after Week 10.
Subjects who stopped background SOC therapy, achieved clinical response, and were on rilonacept monotherapy at RI period Week 12 were transitioned to the RW period. Fifteen subjects were still in the RI period at the time when the event-driven RW period ended and randomization closed; these 15 patients continued directly to the Long Term Extension (LTE) period, as they had completed the RI period and had met the definition of clinical response.

Reporting group title	Rilonacept (RW)

Reporting group description:

Participants assigned to Rilonacept 160 mg (or 2.2 mg/kg in pediatric subjects ≥12 and <18 years old) administered by SC injections once weekly.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo SC injections once weekly.

Reporting group title	Rilonacept (LTE)

Reporting group description:

All participants who had completed the RW period and participants still in the RI period (at the time when the RW period had ended) who met clinical response criteria at Week 12 were eligible for inclusion in the LTE period (up to 24 months of additional open-label rilonacept).

Subject analysis set title	Intent-to-treat analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Intent-to-treat (ITT) analysis set included all subjects who were randomized in the RW period. ITT analysis set was the same as the safety analysis set in the RW period.

Primary: The primary efficacy endpoint was time to pericarditis recurrence in the Randomized Withdrawal period

End point title	The primary efficacy endpoint was time to pericarditis recurrence in the Randomized Withdrawal period

End point description:

Investigator-assessed pericarditis recurrence was defined as the recurrence of typical pericarditis pain associated with or without supportive objective evidence of pericarditis; these investigator-assessed events were adjudicated according to the Clinical Endpoint Committee (CEC) charter to confirm whether they met objective criteria for inclusion in the primary efficacy endpoint analysis.

Please see ClinicalTrials.gov for full analysis of secondary endpoints.
(https://clinicaltrials.gov/study/NCT03737110?cond=recurrent%20pericarditis&rank=8&tab=results)

End point type	Primary

End point timeframe:

Time from randomization till the end of the RW period (event-driven). The closure of the RW period was triggered when the prespecified number of primary efficacy endpoint (CEC-confirmed pericarditis recurrence) events (N=22) had accrued.

End point values	Rilonacept (RW)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	31		
Units: number				
number (not applicable)				
Time to recurrence (weeks)	0	8.6		

Statistical analyses

Statistical analysis title	Kaplan-Meier method
Comparison groups	Rilonacept (RW) v Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Log Rank
Parameter estimate	Cox proportional hazard
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.18

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs registered from patient enrollment during any period of the study: Run-In Period, Randomized Withdrawal Period (without or with bailout rilonacept) and Long-term Extension Period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	RI Period

Reporting group description:

All patients enrolled in the study and received at least 1 dose of rilonacept.

Reporting group title	RW Period: Rilonacept Only, Before Bailout Rilonacept

Reporting group description: -

Reporting group title	RW Period: Rilonacept, Including Bailout Rilonacept

Reporting group description: -

Reporting group title	RW Period: Placebo Only, Before Bailout Rilonacept

Reporting group description: -

Reporting group title	RW Period: Placebo, Including Bailout Rilonacept

Reporting group description: -

Reporting group title	LTE Period: Overall

Reporting group description: -

Serious adverse events	RI Period	RW Period: Rilonacept Only, Before Bailout Rilonacept	RW Period: Rilonacept, Including Bailout Rilonacept
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 86 (1.16%)	1 / 30 (3.33%)	1 / 30 (3.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 86 (0.00%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			

subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac flutter			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 86 (1.16%)	0 / 30 (0.00%)	0 / 30 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute endocarditis			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus infection			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	RW Period: Placebo Only, Before Bailout Rilonacept	RW Period: Placebo, Including Bailout Rilonacept	LTE Period: Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 31 (3.23%)	3 / 31 (9.68%)	6 / 74 (8.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease			

subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac flutter			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 74 (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

Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 74 (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			
Bile duct stone			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute endocarditis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			

subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 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	RI Period	RW Period: Rilonacept Only, Before Bailout Rilonacept	RW Period: Rilonacept, Including Bailout Rilonacept
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 86 (63.95%)	18 / 30 (60.00%)	18 / 30 (60.00%)
Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 86 (1.16%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	1	2	2
C-reactive protein increased			
subjects affected / exposed	1 / 86 (1.16%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	1	2	2
High density lipoprotein increased			
subjects affected / exposed	0 / 86 (0.00%)	3 / 30 (10.00%)	3 / 30 (10.00%)
occurrences (all)	0	3	3
Lipids increased			
subjects affected / exposed	0 / 86 (0.00%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	0	2	2
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 86 (2.33%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 86 (8.14%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	7	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 86 (2.33%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	2	2	2
Injection site erythema			

subjects affected / exposed	18 / 86 (20.93%)	6 / 30 (20.00%)	7 / 30 (23.33%)
occurrences (all)	18	6	7
Injection site pruritus			
subjects affected / exposed	5 / 86 (5.81%)	4 / 30 (13.33%)	5 / 30 (16.67%)
occurrences (all)	5	4	5
Injection site swelling			
subjects affected / exposed	5 / 86 (5.81%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	5	1	1
Non-cardiac chest pain			
subjects affected / exposed	1 / 86 (1.16%)	3 / 30 (10.00%)	3 / 30 (10.00%)
occurrences (all)	1	3	3
Pyrexia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 86 (5.81%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	5	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 86 (5.81%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	5	1	1
Oropharyngeal pain			
subjects affected / exposed	1 / 86 (1.16%)	3 / 30 (10.00%)	3 / 30 (10.00%)
occurrences (all)	1	3	3
Sinus congestion			
subjects affected / exposed	2 / 86 (2.33%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	2	2	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 86 (9.30%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	8	1	1
Back pain			
subjects affected / exposed	3 / 86 (3.49%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Musculoskeletal chest pain			

subjects affected / exposed	3 / 86 (3.49%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Myalgia			
subjects affected / exposed	9 / 86 (10.47%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	9	1	1
Osteoarthritis			
subjects affected / exposed	1 / 86 (1.16%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	1	2	2
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	0 / 86 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 86 (1.16%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	6 / 86 (6.98%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	6	2	2
Sinusitis			
subjects affected / exposed	1 / 86 (1.16%)	3 / 30 (10.00%)	3 / 30 (10.00%)
occurrences (all)	1	3	3
Urinary tract infection			
subjects affected / exposed	1 / 86 (1.16%)	3 / 30 (10.00%)	3 / 30 (10.00%)
occurrences (all)	1	3	3

Non-serious adverse events	RW Period: Placebo Only, Before Bailout Rilonacept	RW Period: Placebo, Including Bailout Rilonacept	LTE Period: Overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 31 (22.58%)	13 / 31 (41.94%)	43 / 74 (58.11%)
Investigations			
Blood cholesterol increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 74 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	3 / 74 (4.05%)
occurrences (all)	0	0	3
High density lipoprotein increased			

subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Lipids increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	1 / 74 (1.35%)
occurrences (all)	0	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	7 / 74 (9.46%)
occurrences (all)	1	1	7
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	3 / 74 (4.05%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	3 / 74 (4.05%)
occurrences (all)	0	1	3
Injection site erythema			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	3 / 74 (4.05%)
occurrences (all)	0	1	3
Injection site pruritus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 74 (0.00%)
occurrences (all)	0	1	0
Injection site swelling			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 74 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	4 / 74 (5.41%)
occurrences (all)	1	1	4
Pyrexia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	4 / 74 (5.41%)
occurrences (all)	0	0	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	4 / 74 (5.41%)
occurrences (all)	0	0	4

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	1 / 74 (1.35%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	2 / 74 (2.70%)
occurrences (all)	0	0	2
Sinus congestion			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	4 / 74 (5.41%)
occurrences (all)	0	2	4
Back pain			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	4 / 74 (5.41%)
occurrences (all)	1	2	4
Musculoskeletal chest pain			
subjects affected / exposed	4 / 31 (12.90%)	4 / 31 (12.90%)	11 / 74 (14.86%)
occurrences (all)	4	4	11
Myalgia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 74 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 74 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	10 / 74 (13.51%)
occurrences (all)	0	0	10
Influenza			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	0 / 74 (0.00%)
occurrences (all)	1	2	0
Nasopharyngitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	5 / 74 (6.76%)
occurrences (all)	0	0	5

Sinusitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	2 / 74 (2.70%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	5 / 74 (6.76%)
occurrences (all)	0	1	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2019	Amendment 1, 12 April 2019 • Revised one of the criteria for permanent discontinuation of study drug • Added a baseline PK drug level measurement • Removed the 10-subject cap for the cardiac MRI Substudy • Revised the text regarding full physical examinations
10 March 2020	Amendment 2, 10 March 2020 The following changes were made based on discussion with the FDA from the Type B meeting (04 March 2020): • The primary efficacy endpoint analysis to be triggered at 22 CEC-confirmed (adjudicated) pericarditis events. The requirement for 24 weeks of follow-up in the RW period for all subjects was eliminated. • Increased enrolled population to up to 100 subjects and clarified exclusion language regarding antibiotic use • Allowed subjects in the RI when randomization is closed and who met the definition of a clinical responder to directly enter the LTE period • The LTE period was extended to 24 months, and the off-treatment observation follow-up was eliminated and replaced with a 6-week safety follow up. • Added an assessment in the LTE at 18 months from most recent recurrence and allowed subjects at the 18-month decision milestone to either continue rilonacept, suspend treatment and remain in the study for off-treatment observation (and resume open-label rilonacept in event of a subsequent recurrence), or discontinue treatment and exit the study. • Added additional secondary endpoints; made 16 weeks the primary time point in the RW for secondary endpoint and designated analyses at Weeks 8 and 24 as sensitivity analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported