Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2a Study Investigating the Efficacy, Safety, Pharmacokinetic and Biomarker Profiles of CKD-506 Administered to Adult Subjects with Moderate-to-Severe Rheumatoid Arthritis and Inadequate Response to Methotrexate

Summary

EudraCT number	2018-001377-24
Trial protocol	CZ
Global end of trial date	29 October 2019

Results information

Result version number	v1 (current)
This version publication date	15 October 2020
First version publication date	15 October 2020

Trial information

Trial identification

Sponsor protocol code	182RA18009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04204603
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chong Kun Dang Pharmaceutical Corporation (CKD)
Sponsor organisation address	8, Chungjeong-ro, Seodaemun-gu, Seoul, Korea, Republic of, 03742
Public contact	Clinical Trials information, Chong Kun Dang Pharmaceutical Corporation (CKD), hky1@ckdpharm.com
Scientific contact	Clinical Trials information, Chong Kun Dang Pharmaceutical Corporation (CKD), hky1@ckdpharm.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	29 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of CKD-506 on signs and symptoms of RA in subjects with moderate-to-severe RA who are inadequate responders to methotrexate.

Protection of trial subjects:

Any medications, therapies, or procedures (other than those excluded by the clinical study protocol) that are considered necessary to protect subject welfare and will not interfere with the study treatment may be given at the Investigator's discretion.
Subjects must have read and understood the informed consent form (ICF) and sign it.

Background therapy:

methotrexate (MTX)

Evidence for comparator: -

Actual start date of recruitment	30 November 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	Poland: 34
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	Georgia: 17
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	Ukraine: 40
Worldwide total number of subjects	122
EEA total number of subjects	49

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)	102
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening period was 28 days

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo once daily (QD) for 12 weeks

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

Dosage and administration details:

Placebo tablet administrated orally once daily (QD)

Arm title	CKD-506 200 mg QD

Arm description:

CKD-506 200 mg once daily (QD) for 12 weeks

Arm type	Experimental
Investigational medicinal product name	CKD-506
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

CKD-506 tablet administered orally once daily (QD)

Arm title	CKD-506 400 mg QD

Arm description:

CKD-506 400mg once daily (QD) for 12 weeks

Arm type	Experimental
Investigational medicinal product name	CKD-506
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

CKD-506 tablet administered orally once daily (QD)

Arm title	CKD-506 600 mg QD

Arm description:

CKD-506 600 mg once daily (QD) for 12 weeks

Arm type	Experimental
Investigational medicinal product name	CKD-506
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

CKD-506 tablet administered orally once daily (QD)

Number of subjects in period 1	Placebo	CKD-506 200 mg QD	CKD-506 400 mg QD
Started	31	31	30
Completed	30	30	30
Not completed	1	1	0
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	-
Protocol deviation	1	-	-

Number of subjects in period 1	CKD-506 600 mg QD
Started	30
Completed	25
Not completed	5
Consent withdrawn by subject	2
Adverse event, non-fatal	2
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily (QD) for 12 weeks	
Reporting group title	CKD-506 200 mg QD
Reporting group description:	
CKD-506 200 mg once daily (QD) for 12 weeks	
Reporting group title	CKD-506 400 mg QD
Reporting group description:	
CKD-506 400mg once daily (QD) for 12 weeks	
Reporting group title	CKD-506 600 mg QD
Reporting group description:	
CKD-506 600 mg once daily (QD) for 12 weeks	

Reporting group values	Placebo	CKD-506 200 mg QD	CKD-506 400 mg QD
Number of subjects	31	31	30
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	26	24
From 65-84 years	4	5	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.5	52.8	53.3
standard deviation	± 10.57	± 9.76	± 10.80
Gender categorical Units: Subjects			
Female	22	24	26
Male	9	7	4
Methotrexate dose prior to baseline Units: mg/week			
arithmetic mean	16.8	15.9	17.2
standard deviation	± 3.02	± 2.13	± 3.85
Duration of RA disease Units: years			
arithmetic mean	4.7	5.8	6.9
standard deviation	± 4.2	± 6.1	± 4.6

Reporting group values	CKD-506 600 mg QD	Total	

Number of subjects	30	122	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	102	
From 65-84 years	5	20	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.6		
standard deviation	± 13.87	-	
Gender categorical Units: Subjects			
Female	23	95	
Male	7	27	
Methotrexate dose prior to baseline Units: mg/week			
arithmetic mean	16.5		
standard deviation	± 3.75	-	
Duration of RA disease Units: years			
arithmetic mean	5.1		
standard deviation	± 5.0	-	

Subject analysis sets

Subject analysis set title	Safety anaylsis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Safety analysis set defined as ll subjects in the RND set who have taken at least one dose of study treatment.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Full analysis set defined as all Safety analysis set subjects who have a baseline and at least one post-dose 28 joint count Disease Activity Score based on C-Reactive Protein [DAS28(CRP)] value.

Reporting group values	Safety anaylsis set	Full analysis set	
Number of subjects	122	121	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	102	101	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	53.3		
standard deviation	± 11.22	±	
Gender categorical			
Units: Subjects			
Female	95		
Male	27		
Methotrexate dose prior to baseline			
Units: mg/week			
arithmetic mean	16.6		
standard deviation	± 3.25	±	
Duration of RA disease			
Units: years			
arithmetic mean	5.6		
standard deviation	± 5.0	±	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo once daily (QD) for 12 weeks	
Reporting group title	CKD-506 200 mg QD
Reporting group description:	
CKD-506 200 mg once daily (QD) for 12 weeks	
Reporting group title	CKD-506 400 mg QD
Reporting group description:	
CKD-506 400mg once daily (QD) for 12 weeks	
Reporting group title	CKD-506 600 mg QD
Reporting group description:	
CKD-506 600 mg once daily (QD) for 12 weeks	
Subject analysis set title	Safety anaylsis set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Safety analysis set defined as ll subjects in the RND set who have taken at least one dose of study treatment.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set defined as all Safety analysis set subjects who have a baseline and at least one post-dose 28 joint count Disease Activity Score based on C-Reactive Protein [DAS28(CRP)] value.	

Primary: Change from Baseline in the 28 joint count Disease Activity Score based on C-reactive protein (DAS28[CRP]) at Week 12

End point title	Change from Baseline in the 28 joint count Disease Activity Score based on C-reactive protein (DAS28[CRP]) at Week 12
End point description:	
End point type	Primary
End point timeframe:	
Baseline (Week 0) and Week 12	

End point values	Placebo	CKD-506 200 mg QD	CKD-506 400 mg QD	CKD-506 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	30	29
Units: score				
arithmetic mean (standard deviation)	-1.2 (± 1.04)	-1.0 (± 1.11)	-1.3 (± 0.89)	-1.2 (± 1.07)

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	121			

Units: score				
arithmetic mean (standard deviation)	-1.2 (± 1.02)			

Statistical analyses

Statistical analysis title	the dose-response trend
Comparison groups	Placebo v CKD-506 200 mg QD v CKD-506 600 mg QD v CKD-506 400 mg QD
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.5 [1]
Method	Mixed models analysis
Parameter estimate	the dose-trend hypothesis

Notes:

[1] - The estimate for the dose-trend hypothesis at Week 12 was -0.551.

Secondary: Response to treatment based on the American College of Rheumatology 20% response criteria (ACR20) at Week 12

End point title	Response to treatment based on the American College of Rheumatology 20% response criteria (ACR20) at Week 12

End point description:

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	CKD-506 200 mg QD	CKD-506 400 mg QD	CKD-506 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	30	29
Units: subject	15	16	18	16

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	121			
Units: subject	65			

Statistical analyses

No statistical analyses for this end point

Secondary: Response to treatment based on the American College of Rheumatology 50% response criteria (ACR50) at Week 12

End point title	Response to treatment based on the American College of Rheumatology 50% response criteria (ACR50) at Week 12

End point description:

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	CKD-506 200 mg QD	CKD-506 400 mg QD	CKD-506 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	30	29
Units: subject	8	8	9	9

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	121			
Units: subject	34			

Statistical analyses

No statistical analyses for this end point

Secondary: Response to treatment based on the American College of Rheumatology 70% response criteria (ACR70)

End point title	Response to treatment based on the American College of Rheumatology 70% response criteria (ACR70)

End point description:

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	CKD-506 200 mg QD	CKD-506 400 mg QD	CKD-506 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	30	29
Units: subject	2	1	1	3

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	121			
Units: subject	7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: TEAEs are defined as AEs that first occurred, or worsened in severity, after the first administration of study treatment and prior to 28 days (4 weeks) after the last administration of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo once daily (QD) for 12 weeks	
Reporting group title	CKD-506 200 mg QD
Reporting group description: CKD-506 200 mg once daily (QD) for 12 weeks	
Reporting group title	CKD-506 400 mg QD
Reporting group description: CKD-506 400mg once daily (QD) for 12 weeks	
Reporting group title	CKD-506 600 mg QD
Reporting group description: CKD-506 600 mg once daily (QD) for 12 weeks	

Serious adverse events	Placebo	CKD-506 200 mg QD	CKD-506 400 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	CKD-506 600 mg QD		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Placebo	CKD-506 200 mg QD	CKD-506 400 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 31 (25.81%)	5 / 31 (16.13%)	5 / 30 (16.67%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergy to plants			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Gamma-glutamyl transferase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Blood triglycerides increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Blood uric acid increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Liver function test increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Low-density lipoprotein increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Leukocytosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Monocytopenia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Enterocolitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Food poisoning			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Rash			

subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Arthralgia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Onychomycosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Periodontitis			

subjects affected / exposed	0 / 31 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	0 / 30 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	CKD-506 600 mg QD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 30 (46.67%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Immune system disorders			
Allergy to plants			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gamma-glutamyl transferase increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood cholesterol increased			

subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Blood glucose increased				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Blood triglycerides increased				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Blood uric acid increased				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Liver function test increased				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Low-density lipoprotein increased				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Lymphocyte count decreased				
subjects affected / exposed	0 / 30 (0.00%)			
occurrences (all)	0			
Neutrophil count decreased				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Platelet count decreased				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
White blood cell count decreased				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Injury, poisoning and procedural complications				
Arthropod bite				

subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 2		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) Monocytopenia subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 0 / 30 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Enterocolitis subjects affected / exposed occurrences (all) Food poisoning subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 2 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 1 / 30 (3.33%) 1		

Gastrointestinal pain subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Hepatobiliary disorders Liver disorder subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0 1 / 30 (3.33%) 1		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all) Rheumatoid arthritis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Bronchitis	1 / 30 (3.33%) 1		

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Onychomycosis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Periodontitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Hyperlipidaemia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2018	Themain purpose of this amendment was to Remove double barrier contraception in Inclusion Criteria.
26 December 2018	The main purpose of this amendment was to update the secondary/exploratory endpoint and assessment schedule, rescreening informationand clarify study procedure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported