Clinical trial results:
A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Dose Study to Evaluate the Efficacy and Safety of Oral SKI-O-703 in Patients With Active Rheumatoid Arthritis Despite Treatment With Conventional Therapies

Summary

EudraCT number	2018-003330-32
Trial protocol	PL
Global end of trial date	13 October 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	OSCO-P2201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Oscotec Inc.
Sponsor organisation address	Korea Bio-Park, Building A, 9th Floor, 700 Daewangpangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Korea, Republic of, 13488
Public contact	Clinical Trials Information, Oscotec Inc., +82 0316287661, clinical-oct@oscotec.com
Scientific contact	Clinical Trials Information, Oscotec Inc., +82 0316287661, clinical-oct@oscotec.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	23 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2020
Global end of trial reached?	Yes
Global end of trial date	13 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of select (100 mg twice daily [BID], 200 mg BID, and 400 mg BID) doses of SKI-O-703 compared with placebo in subjects with active RA who have had an inadequate response to csDMARDs or previous 1, 2, or more anti-TNFα biologic agents

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.
A written informed consent in compliance with the respective applicable regulatory authority regulations was obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involved risk to the subject.
Before recruitment and enrollment, each prospective subject or his or her legal guardian was given a full explanation of the study and allowed to read the approved ICF. Once the investigator was assured that the subject/legal guardian understood the implications of participating in the study, the subject/legal guardian was asked to give consent to participate in the study by signing the ICF.
The investigator retained the signed original ICF(s) and gave a copy of the signed original form to the subject or legal guardian.

Background therapy:

Subjects were allowed to receive background permitted concomitant medications for RA, including MTX, and other oral DMARDs, in line with current standard of care practices for RA.

Evidence for comparator:

There is no comparator.

Actual start date of recruitment	27 March 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	Ukraine: 46
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	163
EEA total number of subjects	28

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)	128
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential subjects were assessed as per the eligibility criteria. After completing all screening assessments, subjects who met all the inclusion and none of the exclusion criteria were enrolled into the study and were randomly assigned in 1:1:1:1 ratio to receive 1 of the 3 doses of SKI-O-703 (100 mg, 200 mg, or 400 mg) or placebo for 12 weeks.

Pre-assignment

Screening details:

The study included a screening period of up to 28 days.

Period 1

Period 1 title	12-Week Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

This was a double-blind study. Neither the subjects nor the investigator/site personnel were aware of the treatment assignment for the subjects in each cohort. Subject-specific doses were prepared and checked by blinded pharmacy staff and administered by appropriately trained blinded clinic staff as delegated by the Principal Investigator at the study site. Blinding was maintained throughout the study by use of active or placebo dosage forms of similar appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	SKI-O-703 100 mg

Arm description:

Through the the double-blind 12-week treatment period, participants were randomly assigned to SKI-O-703 100 mg.

Arm type	Experimental
Investigational medicinal product name	SKI-O-703 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One SKI-O-703 100 mg capsule and three placebo 100 mg capsules were administered BID, orally, no later than 30 minutes after food.

Arm title	SKI-O-703 200 mg

Arm description:

Through the the double-blind 12-week treatment period, participants were randomly assigned to SKI-O-703 200 mg.

Arm type	Experimental
Investigational medicinal product name	SKI-O-703 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two SKI-O-703 100 mg capsules and two placebo 100g capsules were administered BID, orally, no later

than 30 minutes after food.

Arm title	SKI-O-703 400 mg

Arm description:

Through the the double-blind 12-week treatment period, participants were randomly assigned to SKI-O-703 400 mg.

Arm type	Experimental
Investigational medicinal product name	SKI-O-703 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Four SKI-O-703 100 mg capsules were administered BID, orally, no later than 30 minutes after food.

Arm title	Placebo

Arm description:

Through the the double-blind 12-week treatment period, participants were randomly assigned to Placebo.

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

Dosage and administration details:

Four placebo capsules were administered BID, orally, no later than 30 minutes after food. Placebo capsules were identical in appearance and weight to the SKI-O-703 capsules and contained microcrystalline cellulose and magnesium stearate.

Number of subjects in period 1	SKI-O-703 100 mg	SKI-O-703 200 mg	SKI-O-703 400 mg
Started	41	40	41
Completed	39	37	36
Not completed	2	3	5
Consent withdrawn by subject	2	-	2
Physician decision	-	1	1
Adverse event, non-fatal	-	1	1
Other	-	1	1

Number of subjects in period 1	Placebo
Started	41
Completed	38
Not completed	3

Consent withdrawn by subject	2
Physician decision	-
Adverse event, non-fatal	1
Other	-

Baseline characteristics

Reporting groups	
Reporting group title	SKI-O-703 100 mg
Reporting group description:	
Through the the double-blind 12-week treatment period, participants were randomly assigned to SKI-O-703 100 mg.	

Reporting group title	SKI-O-703 200 mg
Reporting group description:	
Through the the double-blind 12-week treatment period, participants were randomly assigned to SKI-O-703 200 mg.	

Reporting group title	SKI-O-703 400 mg
Reporting group description:	
Through the the double-blind 12-week treatment period, participants were randomly assigned to SKI-O-703 400 mg.	

Reporting group title	Placebo
Reporting group description:	
Through the the double-blind 12-week treatment period, participants were randomly assigned to Placebo.	

Reporting group values	SKI-O-703 100 mg	SKI-O-703 200 mg	SKI-O-703 400 mg
Number of subjects	41	40	41
Age categorical Units: Subjects			
Adults (18-64 years)	31	31	36
From 65-84 years	10	9	5
Age continuous Units: years			
median	57	58	52
full range (min-max)	24 to 77	29 to 72	26 to 82
Gender categorical Units: Subjects			
Female	29	32	33
Male	12	8	8

Reporting group values	Placebo	Total	
Number of subjects	41	163	
Age categorical Units: Subjects			
Adults (18-64 years)	30	128	
From 65-84 years	11	35	
Age continuous Units: years			
median	55		
full range (min-max)	32 to 81	-	
Gender categorical Units: Subjects			
Female	34	128	

Male	7	35	

Subject analysis sets	
Subject analysis set title	Intention-to-treat set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set was defined as all randomized subjects who received at least one dose of study drug (SKI-O-703 or placebo). Subjects were analyzed as randomized. This population was used for all efficacy analyses and summaries of demographics and baseline characteristics data.

Subject analysis set title	Modified ITT set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified ITT (mITT) set was defined as all the subjects who received at least one dose of study drug (SKI-O-703 or placebo) and had at least 1 postbaseline assessment. Subjects were analyzed as randomized.

Subject analysis set title	Per-protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-protocol (PP) set was defined as all the subjects in ITT set who did not have any major protocol deviation(s) which were flagged in the protocol deviation list and were compliant with the treatment. All the efficacy analyses were repeated on PP set. Subjects were analyzed as randomized.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set was defined as all subjects who received at least one dose of study drug (SKI-O-703 or placebo). Subjects were analyzed as treated. This population was used for summaries of safety data.

Reporting group values	Intention-to-treat set	Modified ITT set	Per-protocol set
Number of subjects	163	160	148
Age categorical Units: Subjects			
Adults (18-64 years)	128		
From 65-84 years	35		
Age continuous Units: years			
median	56		
full range (min-max)	24 to 82		
Gender categorical Units: Subjects			
Female	128		
Male	35		

Reporting group values	Safety set		
Number of subjects	163		
Age categorical Units: Subjects			
Adults (18-64 years)	128		
From 65-84 years	35		

Age continuous Units: years			
median	56		
full range (min-max)	24 to 82		
Gender categorical Units: Subjects			
Female	128		
Male	35		

End points

End points reporting groups

Reporting group title	SKI-O-703 100 mg

Reporting group description:

Through the the double-blind 12-week treatment period, participants were randomly assigned to SKI-O-703 100 mg.

Reporting group title	SKI-O-703 200 mg

Reporting group description:

Through the the double-blind 12-week treatment period, participants were randomly assigned to SKI-O-703 200 mg.

Reporting group title	SKI-O-703 400 mg

Reporting group description:

Through the the double-blind 12-week treatment period, participants were randomly assigned to SKI-O-703 400 mg.

Reporting group title	Placebo

Reporting group description:

Through the the double-blind 12-week treatment period, participants were randomly assigned to Placebo.

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

Subject analysis set description:

The ITT set was defined as all randomized subjects who received at least one dose of study drug (SKI-O-703 or placebo). Subjects were analyzed as randomized. This population was used for all efficacy analyses and summaries of demographics and baseline characteristics data.

Subject analysis set title	Modified ITT set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified ITT (mITT) set was defined as all the subjects who received at least one dose of study drug (SKI-O-703 or placebo) and had at least 1 postbaseline assessment. Subjects were analyzed as randomized.

Subject analysis set title	Per-protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-protocol (PP) set was defined as all the subjects in ITT set who did not have any major protocol deviation(s) which were flagged in the protocol deviation list and were compliant with the treatment. All the efficacy analyses were repeated on PP set. Subjects were analyzed as randomized.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set was defined as all subjects who received at least one dose of study drug (SKI-O-703 or placebo). Subjects were analyzed as treated. This population was used for summaries of safety data.

Primary: Analysis of Change from Baseline in DAS28-hsCRP at Week 12

End point title	Analysis of Change from Baseline in DAS28-hsCRP at Week 12

End point description:

The primary efficacy endpoint was the mean change from baseline in DAS28-hsCRP at Week 12 based on 3 individual components including TJC28, SJC28, and hsCRP. DAS28-hsCRP was calculated only when all 3 individual components (TJC28, SJC28, and hsCRP) were assessed at this visit; otherwise, DAS28-hsCRP at Week 12 was considered as missing. The differences in DAS28-hsCRP LS Means were not statistically significant between any of the SKI-O-703 treatment groups and the placebo group.

End point type	Primary

End point timeframe:

At week 12

End point values	SKI-O-703 100 mg	SKI-O-703 200 mg	SKI-O-703 400 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	40	41	41
Units: percent				
arithmetic mean (standard deviation)				
Baseline	5.52 (± 0.627)	5.31 (± 0.819)	5.38 (± 0.833)	5.47 (± 0.874)
Actual Value at Week 12	4.56 (± 1.006)	4.30 (± 0.940)	4.25 (± 1.191)	4.50 (± 0.847)
Change from Baseline at Week 12	-0.96 (± 0.892)	-1.01 (± 1.030)	-1.13 (± 1.074)	-0.98 (± 0.892)

Statistical analyses

Statistical analysis title	Statistical Analysis Plan - 100 mg vs Placebo

Statistical analysis description:

The change from baseline in DAS28-hsCRP at Week 12 was analyzed using an ANCOVA model. The model included treatment groups as a factor and DAS28-hsCRP at baseline as a covariate.

Comparison groups	Placebo v SKI-O-703 100 mg
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.846
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.217

Statistical analysis title	Statistical Analysis Plan - 200 mg vs Placebo

Statistical analysis description:

The change from baseline in DAS28-hsCRP at Week 12 was analyzed using an ANCOVA model. The model included treatment groups as a factor and DAS28-hsCRP at baseline as a covariate.

Comparison groups	Placebo v SKI-O-703 200 mg

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.616
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.32
Variability estimate	Standard error of the mean
Dispersion value	0.218

Statistical analysis title	Statistical Analysis Plan - 400 mg vs Placebo

Statistical analysis description:

The change from baseline in DAS28-hsCRP at Week 12 was analyzed using an ANCOVA model. The model included treatment groups as a factor and DAS28-hsCRP at baseline as a covariate.

Comparison groups	Placebo v SKI-O-703 400 mg
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.368
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.217

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) have been measured during the 12 week Treatment Period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	SKI-O-703 100 mg

Reporting group description:

SKI-O-703 capsules were provided as Swedish orange capsules and contained the active ingredient SKI-O-703 (100 mg). SKI-O-703 100 mg was administered BID, orally, no later than 30 minutes after food.

Reporting group title	SKI-O-703 200 mg

Reporting group description:

SKI-O-703 capsules were provided as Swedish orange capsules and contained the active ingredient SKIO-703 (100 mg). SKI-O-703 200 mg was administered BID, orally, no later than 30 minutes after food.

Reporting group title	SKI-O-703 400 mg

Reporting group description:

SKI-O-703 capsules were provided as Swedish orange capsules and contained the active ingredient SKIO-703 (100 mg). SKI-O-703 400 mg was administered BID, orally, no later than 30 minutes after food.

Reporting group title	Placebo

Reporting group description:

Placebo capsules were identical in appearance and weight to the SKI-O-703 capsules and contained microcrystalline cellulose and magnesium stearate. Placebo was administered BID, orally, no later than 30 minutes after food.

Serious adverse events	SKI-O-703 100 mg	SKI-O-703 200 mg	SKI-O-703 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	1 / 41 (2.44%)
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)			
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocarditis			

subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (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
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
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			
Pneumonia viral			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (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	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 41 (2.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Pneumonia viral			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	SKI-O-703 100 mg	SKI-O-703 200 mg	SKI-O-703 400 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 41 (39.02%)	23 / 40 (57.50%)	25 / 41 (60.98%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Allergy to plants			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0

Metrorrhagia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 41 (4.88%)	0 / 40 (0.00%)	4 / 41 (9.76%)
occurrences (all)	2	0	4
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	3 / 41 (7.32%)
occurrences (all)	1	0	3
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Blood pressure increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Neutrophil count decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Platelet count increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Left ventricular hypertrophy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Ventricular extrasystoles			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Myocarditis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 41 (2.44%)	6 / 40 (15.00%)	6 / 41 (14.63%)
occurrences (all)	1	6	6
Somnolence			

subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Neutropenia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Hypochromic anaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Microcytic anaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	3 / 40 (7.50%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Constipation			
subjects affected / exposed	3 / 41 (7.32%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	3	0	1
Dyspepsia			
subjects affected / exposed	0 / 41 (0.00%)	3 / 40 (7.50%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Diarrhoea			

subjects affected / exposed	2 / 41 (4.88%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	2	1	1
Flatulence			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Epigastric discomfort			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Periodontal disease			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Hepatic function abnormal			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Rosacea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Urethral syndrome			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Leukocyturia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Rheumatoid arthritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Joint range of motion decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Synovitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Bursitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	2 / 41 (4.88%)
occurrences (all)	0	1	2
Bronchitis			

subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	2 / 40 (5.00%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Cystitis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Genital infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Pneumonia viral			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Hyperkalaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Vitamin D deficiency			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 41 (0.00%)	0 / 40 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 41 (46.34%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Allergy to plants			

subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Metrorrhagia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Blood pressure increased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Blood potassium decreased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Platelet count increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Cardiac disorders			
Left ventricular hypertrophy			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Sinus tachycardia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Ventricular extrasystoles			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Myocarditis			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hypochromic anaemia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Microcytic anaemia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Constipation			

subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Epigastric discomfort			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Periodontal disease			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Hepatic function abnormal			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Rosacea			

subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Urethral syndrome			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Leukocyturia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Rheumatoid arthritis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Joint range of motion decreased			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Synovitis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Bursitis			

subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Genital infection			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

Pneumonia viral subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1 1 / 41 (2.44%) 1		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all) Vitamin D deficiency subjects affected / exposed occurrences (all) Hypercholesterolaemia subjects affected / exposed occurrences (all) Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0 0 / 41 (0.00%) 0 1 / 41 (2.44%) 1 1 / 41 (2.44%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2018	• The word "patient" was replaced with "subject" throughout the protocol. • Added EudraCT number on protocol title page. • Added food effect rationale from recently completed food effect study following single oral administration of 400 mg SKI-O-703 (Study OSCO-P1203). • Added justification for use of placebo in the study as per the request from regulatory group. • Provided detailed information of procedures and assessments to be done during each period (at screening and randomization [Day 1], 12-week treatment period, and 4-week follow-up period). Also added details of subject error. Details of randomization visit (Study Day 1) has been updated and provided clarification for PK/PD subsets. • The following sections were updated for better clarity: - Inclusion criteria. - Exclusion criteria. - Schedule of Events. - PK assessment. - PD assessment - Study Treatments: Updated dosage strength, deleted 50 mg and 200 mg strength capsules, now only 100 mg capsules will be used. Accordingly, dosing scheme also updated. • Updated some definitions. • Added 'Grade 5 Fatal' intensity under section for assessment of severity of AEs. • Subgroup of geographic region has been added. • Appendices were updated or added (eg, to provide details of list of excluded drugs, to provide details regarding efficacy assessments, etc).
08 February 2019	• Exclusion criteria related to TB was updated. • Local urine pregnancy test was added for Visits 2 to 7 for WOCBP. • Pregnancy-related text was updated to clarify that if a female subject became pregnant, she must discontinue study drug immediately. Also, it was clarified that subjects must be counseled during the informed consent process to inform the investigator of any pregnancy that occurred during study participation and for 6 months after the last dose of study drug. • On Day 1, the physical examination was updated from brief to complete. • Text related to PK and PD blood sample processing was updated. • Oracle™ Clinical Remote Data Capture was deleted throughout and Medidata Rave was added for consistency. • Appendices were updated.

03 April 2020	• Updated Inclusion and exclusion criteria • Study Design: As per request from Serbian authority, additional language has been added in Section 3.1.Updated safety variables to include tympanic temperature measurement for Korean subjects. Details of randomization visit (Study Day 1) has been updated and provided clarification for PK/PD subsets. • Updated guidelines for dose interruption and reduction. • Updated content of placebo capsules. • Removed the requirement about promptly reporting any overdose with or without associated AEs to the PPD Drug Safety Center. • csDMARDs dose stability during wash-out is not applicable. • Known CYP1A2 and UGT1A1 inhibitors and inducers must be prohibited for 4 weeks or 5 half-lives (whichever is longer), prior to Day 1 dosing. • Updates Schedule of Events. • Removed assessment of carbon dioxide in serum chemistry. Updated urinalysis to remove turbidity assessment. • The requirements to be an Independent Joint Assessor were expanded. • Defined the 8 categories that will be assessed by the HAQ-DI. • All statistical tests will be 2-sided and performed using a 5% significance level, leading to 95% CIs (2-sided). • A mixed model repeat measure (MMRM) analysis will be used instead of ANCOVA for analysis of secondary endpoints. • Appendices were updated. There is also Protocol Amendment 04, Version 5.0 dated 19 Oct 2020.

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.

None reported.

Notes: