Clinical trial results:
Moderate to Severe Atopic Dermatitis: Evaluation of Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects in Japan

Summary

EudraCT number	2022-002777-29
Trial protocol	Outside EU/EEA
Global end of trial date	19 August 2022

Results information

Result version number	v1 (current)
This version publication date	23 February 2023
First version publication date	23 February 2023

Trial information

Trial identification

Sponsor protocol code	M17-377

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03661138
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	1 North Waukegan Road, North Chicago, IL, United States, 60064
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to assess the safety of upadacitinib combined with topical corticosteroids (TCS) in adolescent and adult subjects in Japan with moderate to severe atopic dermatitis (AD) who are candidates for systemic therapy.

Protection of trial subjects:

The study was conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Prior to the initiation of any screening or study-specific procedures, the investigator or his or her representative explained the nature of the study to the subject or his or her representative and answered all questions regarding this study. The informed consent statement was reviewed and signed and dated by the subject and/or the subject's parent or legal guardian and the person who administered the informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 272
Worldwide total number of subjects	272
EEA total number of subjects	0

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)	25

Adults (18-64 years)	245
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a 35-day screening period.

Period 1

Period 1 title	Double Blind (DB) Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Study sites and subjects remained blinded for the duration of the study. To maintain integrity of the trial and avoid introduction of bias, the study team only had access to unblinded subject level data for adverse events adverse events of special interest (AESIs) and serious adverse events (SAEs) for regulatory submissions. In order to maintain the blind, the upadacitinib tablets and placebo tablets provided for the study were identical in appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + TCS

Arm description:

Placebo administered once daily (QD) along with TCS for 16 weeks.

Arm type	Placebo
Investigational medicinal product name	placebo for upadacitinib (ABT-494)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug was taken QD beginning on Day 1 (Baseline) at approximately the same time each day, with or without food.

Investigational medicinal product name	topical corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment, Cream
Routes of administration	Topical use

Dosage and administration details:

A TCS regimen in combination with study drug was mandatory until Week 16. After Week 16, the use of any concomitant topical medication for AD could be administered per investigator discretion and was no longer required.

Arm title	Upadacitinib 15 mg + TCS

Arm description:

Upadacitinib 15 mg administered QD along with TCS for 16 weeks.

Arm type	Experimental

Investigational medicinal product name	upadacitinib
Investigational medicinal product code	ABT-494
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug was taken QD beginning on Day 1 (Baseline) at approximately the same time each day, with or without food.

Investigational medicinal product name	topical corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream, Ointment
Routes of administration	Topical use

Dosage and administration details:

A TCS regimen in combination with study drug was mandatory until Week 16. After Week 16, the use of any concomitant topical medication for AD could be administered per investigator discretion and was no longer required.

Arm title	Upadacitinib 30 mg + TCS

Arm description:

Upadacitinib 30 mg administered QD along with TCS for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	upadacitinib
Investigational medicinal product code	ABT-494
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug was taken QD beginning on Day 1 (Baseline) at approximately the same time each day, with or without food.

Investigational medicinal product name	topical corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream, Ointment
Routes of administration	Topical use

Dosage and administration details:

A TCS regimen in combination with study drug was mandatory until Week 16. After Week 16, the use of any concomitant topical medication for AD could be administered per investigator discretion and was no longer required.

Number of subjects in period 1	Placebo + TCS	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg + TCS
Started	90	91	91
Completed	87	89	88
Not completed	3	2	3
Consent withdrawn by subject	2	-	2
Other, not specified	1	-	1
Adverse event	-	2	-

Period 2

Period 2 title	Blind Extension/Open Label Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Investigator

Blinding implementation details:

Single-blinded and then open label after Week 52.
Study sites and subjects will remain blinded for the duration of the study. To maintain integrity of the trial and avoid introduction of bias, the study team will only have access to unblinded subject level data for AESIs and SAEs for regulatory submissions.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + TCS / Upadacitinib 15 mg +TCS

Arm description:

Subjects in the double blind Placebo + TCS arm (Week 1 to 16) received upadacitinib 15 mg QD in the 36-week blind extension period (Week 16 to 52), and the open label long-term extension Period (Week 52 to Week 160 or permanent withdrawal of the marketing application).

Arm type	Experimental
Investigational medicinal product name	upadacitinib
Investigational medicinal product code	ABT-494
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug was taken QD beginning on Day 1 (Baseline) at approximately the same time each day, with or without food.

Arm title	Placebo + TCS / Upadacitinib 30 mg +TCS

Arm description:

Subjects in the double blind Placebo + TCS arm (Week 1 to 16) received upadacitinib 30 mg QD in the 36-week blind extension period (Week 16 to 52), and the open label long-term extension Period (Week 52 to Week 160 or permanent withdrawal of the marketing application).

Arm type	Experimental
Investigational medicinal product name	upadacitinib
Investigational medicinal product code	ABT-494
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug was taken QD beginning on Day 1 (Baseline) at approximately the same time each day, with or without food.

Arm title	Upadacitinib 15 mg +TCS / Upadacitinib 15 mg +TCS

Arm description:

Subjects in the double blind Upadacitinib 15 mg + TCS arm (Week 1 to 16) received upadacitinib 15 mg QD in the 36-week blind extension period (Week 16 to 52), and the open label long-term extension Period (Week 52 to Week 160 or permanent withdrawal of the marketing application).

Arm type	Experimental

Investigational medicinal product name	upadacitinib
Investigational medicinal product code	ABT-494
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug was taken QD beginning on Day 1 (Baseline) at approximately the same time each day, with or without food.

Arm title	Upadacitinib 30 mg +TCS / Upadacitinib 30 mg +TCS

Arm description:

Subjects in the double blind Upadacitinib 30 mg + TCS arm (Week 1 to 16) received upadacitinib 30 mg QD in the 36-week blind extension period (Week 16 to 52), and the open label long-term extension Period (Week 52 to Week 160 or permanent withdrawal of the marketing application).

Arm type	Experimental
Investigational medicinal product name	upadacitinib
Investigational medicinal product code	ABT-494
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug was taken QD beginning on Day 1 (Baseline) at approximately the same time each day, with or without food.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Study sites and subjects will remain blinded for the duration of the study. To maintain integrity of the trial and avoid introduction of bias, the study team will only have access to unblinded subject level data for AESIs and SAEs for regulatory submissions.

Number of subjects in period 2	Placebo + TCS / Upadacitinib 15 mg +TCS	Placebo + TCS / Upadacitinib 30 mg +TCS	Upadacitinib 15 mg +TCS / Upadacitinib 15 mg +TCS
Started	42	45	89
Completed	36	40	80
Not completed	6	5	9
Consent withdrawn by subject	6	3	5
Other, not specified	-	1	2
Adverse event	-	-	1
Lost to follow-up	-	1	1

Number of subjects in period 2	Upadacitinib 30 mg +TCS / Upadacitinib 30 mg +TCS
Started	88
Completed	74
Not completed	14
Consent withdrawn by subject	8
Other, not specified	3
Adverse event	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + TCS
Reporting group description:	
Placebo administered once daily (QD) along with TCS for 16 weeks.	
Reporting group title	Upadacitinib 15 mg + TCS
Reporting group description:	
Upadacitinib 15 mg administered QD along with TCS for 16 weeks.	
Reporting group title	Upadacitinib 30 mg + TCS
Reporting group description:	
Upadacitinib 30 mg administered QD along with TCS for 16 weeks.	

Reporting group values	Placebo + TCS	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg + TCS
Number of subjects	90	91	91
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 36.3 ± 12.64	 35.9 ± 13.22	 34.7 ± 12.74
Gender categorical Units: Subjects			
Female	16	23	22
Male	74	68	69
Race Units: Subjects			
Asian	90	91	91
Ethnicity Units: Subjects			
Not Hispanic or Latino	90	91	91

Reporting group values	Total		
Number of subjects	272		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	61		
Male	211		

Race Units: Subjects			
Asian	272		
Ethnicity Units: Subjects			
Not Hispanic or Latino	272		

End points

End points reporting groups

Reporting group title	Placebo + TCS
Reporting group description:	
Placebo administered once daily (QD) along with TCS for 16 weeks.	
Reporting group title	Upadacitinib 15 mg + TCS
Reporting group description:	
Upadacitinib 15 mg administered QD along with TCS for 16 weeks.	
Reporting group title	Upadacitinib 30 mg + TCS
Reporting group description:	
Upadacitinib 30 mg administered QD along with TCS for 16 weeks.	
Reporting group title	Placebo + TCS / Upadacitinib 15 mg +TCS
Reporting group description:	
Subjects in the double blind Placebo + TCS arm (Week 1 to 16) received upadacitinib 15 mg QD in the 36-week blind extension period (Week 16 to 52), and the open label long-term extension Period (Week 52 to Week 160 or permanent withdrawal of the marketing application).	
Reporting group title	Placebo + TCS / Upadacitinib 30 mg +TCS
Reporting group description:	
Subjects in the double blind Placebo + TCS arm (Week 1 to 16) received upadacitinib 30 mg QD in the 36-week blind extension period (Week 16 to 52), and the open label long-term extension Period (Week 52 to Week 160 or permanent withdrawal of the marketing application).	
Reporting group title	Upadacitinib 15 mg +TCS / Upadacitinib 15 mg +TCS
Reporting group description:	
Subjects in the double blind Upadacitinib 15 mg + TCS arm (Week 1 to 16) received upadacitinib 15 mg QD in the 36-week blind extension period (Week 16 to 52), and the open label long-term extension Period (Week 52 to Week 160 or permanent withdrawal of the marketing application).	
Reporting group title	Upadacitinib 30 mg +TCS / Upadacitinib 30 mg +TCS
Reporting group description:	
Subjects in the double blind Upadacitinib 30 mg + TCS arm (Week 1 to 16) received upadacitinib 30 mg QD in the 36-week blind extension period (Week 16 to 52), and the open label long-term extension Period (Week 52 to Week 160 or permanent withdrawal of the marketing application).	
Subject analysis set title	Safety Double Blind Population: Placebo + TCS
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who were randomized to placebo + TCS at baseline and received at least one dose of study drug in the double blind period.	
Subject analysis set title	Safety Double Blind Population: Upadacitinib 15 mg + TCS
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who were randomized to upadacitinib 15 mg + TCS at baseline and received at least one dose of study drug in the double blind period.	
Subject analysis set title	Safety Double Blind Population: Upadacitinib 30 mg + TCS
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who were randomized to upadacitinib 30 mg + TCS at baseline and received at least one dose of study drug in the double blind period.	
Subject analysis set title	All Upadacitinib Treated Population: Upadacitinib 15 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects randomized to upadacitinib 15 mg who received at least one dose of upadacitinib in the study.	
Subject analysis set title	All Upadacitinib Treated Population: Upadacitinib 30 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects randomized to upadacitinib 30 mg who received at least one dose of upadacitinib in the study.

Primary: Number of Subjects With TEAEs, SAEs, and Discontinuations Due to AEs in the Double Blind Treatment Period

End point title	Number of Subjects With TEAEs, SAEs, and Discontinuations Due to AEs in the Double Blind Treatment Period[1]

End point description:

An AE is defined as any untoward medical occurrence which does not necessarily have a causal relationship with treatment. An SAE is any event that results in the death of a subject, is life-threatening, results in hospitalization or prolongation of hospitalization, is a congenital anomaly, results in persistent or significant disability/incapacity, is an important medical event requiring medical or surgical intervention to prevent a serious outcome. The severity of each AE was rated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
IP=investigational product

End point type	Primary

End point timeframe:

From 1st dose of study drug and before the 1st dose of study drug in extension (Week 16), or after the last dose of double blind study drug + 30 days (for subjects not entering the blind extension period). Median treatment duration was 112 days.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	Safety Double Blind Population: Placebo + TCS	Safety Double Blind Population: Upadacitinib 15 mg + TCS	Safety Double Blind Population: Upadacitinib 30 mg + TCS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	90	91	91	
Units: subjects				
TEAE	38	51	58	
TEAE with reasonably possible relationship to IP	11	12	25	
Severe TEAE	0	2	4	
Serious TEAE (STEAE)	1	1	1	
STEAE with reasonably possible relationship to IP	0	1	1	
TEAE leading to discontinuation of study drug	1	2	1	
TEAE leading to death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With TEAEs, SAEs, and Discontinuations Due to AEs During Administration of Upadacitinib

End point title	Number of Subjects With TEAEs, SAEs, and Discontinuations Due to AEs During Administration of Upadacitinib[2]

End point description:

An AE is defined as any untoward medical occurrence which does not necessarily have a causal relationship with treatment. An SAE is any event that results in the death of a subject, is life-

threatening, results in hospitalization or prolongation of hospitalization, is a congenital anomaly, results in persistent or significant disability/incapacity, is an important medical event requiring medical or surgical intervention to prevent a serious outcome. The severity of each AE was rated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
IP=investigational product

End point type	Primary

End point timeframe:

From first dose of upadacitinib up to the last dose of upadacitinib + 30 days. Median treatment duration was 1114 days.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	All Upadacitinib Treated Population: Upadacitinib 15 mg	All Upadacitinib Treated Population: Upadacitinib 30 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	136		
Units: subjects				
TEAE	121	124		
TEAE with reasonably possible relationship to IP	70	74		
Severe TEAE	18	19		
Serious TEAE (STEAE)	15	13		
STEAE with reasonably possible relationship to IP	6	6		
TEAE leading to discontinuation of study drug	8	7		
TEAE leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With TEAEs of Special Interest in the Double Blind Period

End point title	Number of Subjects With TEAEs of Special Interest in the Double Blind Period[3]

End point description:

"Opportunistic Infection" excludes tuberculosis and herpes zoster. "Major Adverse Cardiovascular Events" are defined as cardiovascular (CV) death, non-fatal myocardial infarction and non-fatal stroke. CV death includes acute myocardial Infarction, sudden cardiac death, death due to heart failure, CV Procedure-Related death, death due to CV hemorrhage, fatal stroke, pulmonary embolism and other CV causes. "Venous Thromboembolic Events" include deep vein thrombosis (DVT) and pulmonary embolism (PE).

End point type	Primary

End point timeframe:

From 1st dose of study drug and before the 1st dose of study drug in extension (Week 16), or after the last dose of double blind study drug + 30 days (for subjects not entering the blind extension period). Median treatment duration was 112 days.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	Safety Double Blind Population: Placebo + TCS	Safety Double Blind Population: Upadacitinib 15 mg + TCS	Safety Double Blind Population: Upadacitinib 30 mg + TCS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	90	91	91	
Units: subjects				
Serious Infections	0	0	1	
Opportunistic Infection	0	3	1	
Possible Malignancy	0	0	0	
Malignancy	0	0	0	
Non-Melanoma Skin Cancer (NMSC)	0	0	0	
Malignancy excluding NMSC	0	0	0	
Lymphoma	0	0	0	
Hepatic Disorder	0	1	1	
Gastrointestinal Perforations	0	0	0	
Anemia	0	0	1	
Neutropenia	0	1	4	
Lymphopenia	0	0	0	
Herpes Zoster	0	0	4	
Creatine Phosphokinase (CPK) Elevation	0	1	3	
Renal Dysfunction	0	0	0	
Active Tuberculosis	0	0	0	
Adjudicated Major Adverse Cardiovascular Events	0	1	0	
Adjudicated Venous Thromboembolic Events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With TEAEs of Special Interest During Administration of Upadacitinib

End point title	Number of Subjects With TEAEs of Special Interest During Administration of Upadacitinib[4]

End point description:

"Opportunistic Infection" excludes tuberculosis and herpes zoster. "Major Adverse Cardiovascular Events" are defined as CV death, non-fatal myocardial infarction and non-fatal stroke. CV death includes acute myocardial Infarction, sudden cardiac death, death due to heart failure, CV Procedure-Related death, death due to CV hemorrhage, fatal stroke, pulmonary embolism and other CV causes. "Venous Thromboembolic Events" include DVT and PE.

End point type	Primary

End point timeframe:

From first dose of upadacitinib up to the last dose of upadacitinib + 30 days. Median treatment duration was 1114 days.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	All Upadacitinib Treated Population: Upadacitinib 15 mg	All Upadacitinib Treated Population: Upadacitinib 30 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	136		
Units: subjects				
Serious Infections	7	9		
Opportunistic Infection	13	6		
Possible Malignancy	1	0		
Malignancy	1	0		
Non-Melanoma Skin Cancer (NMSC)	0	0		
Malignancy excluding NMSC	1	0		
Lymphoma	0	1		
Hepatic Disorder	14	16		
Gastrointestinal Perforations	0	0		
Anemia	4	8		
Neutropenia	3	8		
Lymphopenia	0	4		
Herpes Zoster	29	39		
Creatine Phosphokinase (CPK) Elevation	8	15		
Renal Dysfunction	0	0		
Active Tuberculosis	0	0		
Adjudicated Major Adverse Cardiovascular Events	1	0		
Adjudicated Venous Thromboembolic Events	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Important Hematology During the Double Blind Period

End point title	Number of Subjects With Potentially Clinically Important Hematology During the Double Blind Period[5]

End point description:

End point type	Primary

End point timeframe:

From 1st dose of study drug and before the 1st dose of study drug in extension (Week 16), or after the last dose of double blind study drug + 30 days (for subjects not entering the blind extension period). Median treatment duration was 112 days.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	Safety Double Blind Population: Placebo + TCS	Safety Double Blind Population: Upadacitinib 15 mg + TCS	Safety Double Blind Population: Upadacitinib 30 mg + TCS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	90	91	91	
Units: subjects				
Hemoglobin < 80 g/L	0	0	0	
Leukocytes < 2.0 10^9/L	0	0	0	
Lymphocytes < 0.5 10^9/L	0	1	0	
Neutrophils < 1.0 10^9/L	0	2	0	
Platelets < 50 10^9/L	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Important Hematology During Administration of Upadacitinib

End point title	Number of Subjects With Potentially Clinically Important Hematology During Administration of Upadacitinib[6]

End point description:

End point type	Primary

End point timeframe:

From first dose of upadacitinib up to the last dose of upadacitinib + 30 days. Median treatment duration was 1114 days.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	All Upadacitinib Treated Population: Upadacitinib 15 mg	All Upadacitinib Treated Population: Upadacitinib 30 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	136		
Units: subjects				
Hemoglobin < 80 g/L	0	0		
Leukocytes < 2.0 10^9/L	0	0		
Lymphocytes < 0.5 10^9/L	1	6		
Neutrophils < 1.0 10^9/L	2	3		
Platelets < 50 10^9/L	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Important Chemistry During the Double Blind Period

End point title	Number of Subjects With Potentially Clinically Important Chemistry During the Double Blind Period[7]

End point description:

ULN=upper limit of normal

End point type	Primary

End point timeframe:

From 1st dose of study drug and before the 1st dose of study drug in extension (Week 16), or after the last dose of double blind study drug + 30 days (for subjects not entering the blind extension period). Median treatment duration was 112 days.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	Safety Double Blind Population: Placebo + TCS	Safety Double Blind Population: Upadacitinib 15 mg + TCS	Safety Double Blind Population: Upadacitinib 30 mg + TCS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	90	91	91	
Units: subjects				
Alanine Aminotransferase > 5.0 x ULN	1	0	0	
Albumin < 20 g/L	0	0	0	
Alkaline Phosphatase > 5.0 x ULN	0	0	0	
Aspartate Aminotransferase > 5.0 x ULN	0	0	0	
Calcium Hyper > 3.1 mmol/L	0	0	0	
Calcium Hypo < 1.75 mmol/L	0	0	0	
Cholesterol > 10.34 mmol/L	0	0	2	
Creatine Kinase >5.0 x ULN	0	0	2	
Creatinine > 3.0 x ULN	0	0	0	
Glucose Hyper > 13.9 mmol/L	0	0	0	
Glucose Hypo < 2.2 mmol/L	0	0	0	
Phosphate < 0.6 mmol/L	0	0	0	
Potassium Hyper > 6.0 mmol/L	0	0	0	
Potassium Hypo < 3.0 mmol/L	0	0	0	
Sodium Hyper > 155 mmol/L	0	0	0	
Sodium Hypo < 130 mmol/L	0	0	0	
Triglycerides > 5.7 mmol/L	3	1	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Important Chemistry During Administration of Upadacitinib

End point title	Number of Subjects With Potentially Clinically Important

	Chemistry During Administration of Upadacitinib[8]
End point description:	
ULN=upper limit of normal	
End point type	Primary
End point timeframe:	
From first dose of upadacitinib up to the last dose of upadacitinib + 30 days. Median treatment duration was 1114 days.	
Notes:	
[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Descriptive statistics are presented per protocol.	

End point values	All Upadacitinib Treated Population: Upadacitinib 15 mg	All Upadacitinib Treated Population: Upadacitinib 30 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	136		
Units: subjects				
Alanine Aminotransferase > 5.0 x ULN	3	1		
Albumin < 20 g/L	0	0		
Alkaline Phosphatase > 5.0 x ULN	0	0		
Aspartate Aminotransferase > 5.0 x ULN	2	0		
Calcium Hyper > 3.1 mmol/L	0	0		
Calcium Hypo < 1.75 mmol/L	0	0		
Cholesterol > 10.34 mmol/L	0	3		
Creatine Kinase >5.0 x ULN	6	11		
Creatinine > 3.0 x ULN	0	0		
Glucose Hyper > 13.9 mmol/L	0	0		
Glucose Hypo < 2.2 mmol/L	0	0		
Phosphate < 0.6 mmol/L	1	1		
Potassium Hyper > 6.0 mmol/L	0	0		
Potassium Hypo < 3.0 mmol/L	1	0		
Sodium Hyper > 155 mmol/L	0	0		
Sodium Hypo < 130 mmol/L	0	0		
Triglycerides > 5.7 mmol/L	8	13		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Important Vital Signs During the Double Blind Period

End point title	Number of Subjects With Potentially Clinically Important Vital Signs During the Double Blind Period[9]
End point description:	
Vitals signs included increases () and decreases () from baseline (BL) in sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP), and weight (for adult subjects).	
End point type	Primary
End point timeframe:	
From 1st dose of study drug and before the 1st dose of study drug in extension (Week 16), or after the	

last dose of double blind study drug + 30 days (for subjects not entering the blind extension period). Median treatment duration was 112 days.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	Safety Double Blind Population: Placebo + TCS	Safety Double Blind Population: Upadacitinib 15 mg + TCS	Safety Double Blind Population: Upadacitinib 30 mg + TCS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	90[10]	91[11]	91[12]	
Units: subjects				
SBP ≤ 90 mmHg + ≥ 20 mmHg from BL; n=90, 91, 91	1	2	2	
SBP ≥ 160 mmHg + ≥ 20 mmHg from BL; n=90, 91, 91	1	2	0	
DBP ≤ 50 mmHg + ≥ 10 mmHg from BL; n=90, 91, 91	2	3	2	
DBP ≥ 100 mmHg + ≥ 10 mmHg from BL; n=90, 91, 91	3	4	2	
Weight (Adults Only) > 7% from BL; n=80, 80, 81	2	1	0	
Weight (Adults Only) > 7% from BL; n=80, 80, 81	2	6	13	

Notes:

[10] - n=subjects with an assessment

[11] - n=subjects with an assessment

[12] - n=subjects with an assessment

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Important Vital Signs During Administration of Upadacitinib

End point title	Number of Subjects With Potentially Clinically Important Vital Signs During Administration of Upadacitinib[13]

End point description:

Vitals signs included increases () and decreases () from BL in sitting SBP, sitting DBP, and weight (for adult subjects).

End point type	Primary

End point timeframe:

From first dose of upadacitinib up to the last dose of upadacitinib + 30 days. Median treatment duration was 1114 days.

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	All Upadacitinib Treated Population: Upadacitinib 15 mg	All Upadacitinib Treated Population: Upadacitinib 30 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133[14]	136[15]		
Units: subjects				
SBP ≤ 90 mmHg + ≥ 20 mmHg from BL; n=133, 136	3	3		
SBP ≥ 160 mmHg + ≥ 20 mmHg from BL; n=133, 136	8	4		
DBP ≤ 50 mmHg + ≥ 10 mmHg from BL; n=133, 136	6	4		
DBP ≥ 100 mmHg + ≥ 10 mmHg from BL; n=133, 136	18	12		
Weight (Adults Only) > 7% from BL; n=117, 121	21	17		
Weight (Adults Only) > 7% from BL; n=117, 121	57	57		

Notes:

[14] - n=subjects with an assessment

[15] - n=subjects with an assessment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DB Period: From 1st dose of study drug and before the 1st dose of study drug in extension (Week 16), or after the last dose of double blind study drug + 30 days (for subjects not entering the blind extension period). Median treatment duration = 112 days.

Adverse event reporting additional description:

All Upadacitinib Groups: From first dose of upadacitinib up to the last dose of upadacitinib + 30 days. Median treatment duration = 1114 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Safety Double Blind Population: Placebo + TCS

Reporting group description:

Subjects who were randomized to placebo + TCS at baseline and received at least one dose of study drug in the double blind period.

Reporting group title	All Upadacitinib Treated Population: Upadacitinib 30 mg + TCS

Reporting group description:

Randomized subjects who received at least one dose of upadacitinib 30 mg in the study.

Reporting group title	All Upadacitinib Treated Population: Upadacitinib 15 mg + TCS

Reporting group description:

Randomized subjects who received at least one dose of upadacitinib 15 mg in the study.

Reporting group title	Safety Double Blind Population: Upadacitinib 15 mg + TCS

Reporting group description:

Subjects who were randomized to upadacitinib 15 mg + TCS at baseline and received at least one dose of study drug in the double blind period.

Reporting group title	Safety Double Blind Population: Upadacitinib 30 mg + TCS

Reporting group description:

Subjects who were randomized to upadacitinib 30 mg + TCS at baseline and received at least one dose of study drug in the double blind period.

Serious adverse events	Safety Double Blind Population: Placebo + TCS	All Upadacitinib Treated Population: Upadacitinib 30 mg + TCS	All Upadacitinib Treated Population: Upadacitinib 15 mg + TCS
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 90 (1.11%)	13 / 136 (9.56%)	15 / 133 (11.28%)
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)			
OSTEOMA			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (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

Injury, poisoning and procedural complications			
CONCUSSION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENISCUS INJURY			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (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
RADIUS FRACTURE			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (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
SKIN LACERATION			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
HYDROCELE			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (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
Nervous system disorders			
CEREBELLAR HAEMORRHAGE			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CYST			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

CATARACT DIABETIC			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL DETACHMENT			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ALCOHOLIC PANCREATITIS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INGUINAL HERNIA			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IRRITABLE BOWEL SYNDROME			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINE POLYP			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	1 / 90 (1.11%)	0 / 136 (0.00%)	0 / 133 (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
Respiratory, thoracic and mediastinal disorders			
PNEUMOTHORAX			

subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX SPONTANEOUS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
SOMATIC SYMPTOM DISORDER			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (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
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 90 (0.00%)	3 / 136 (2.21%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ECZEMA HERPETICUM			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ENTERITIS INFECTIOUS			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES SIMPLEX			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	0 / 90 (0.00%)	2 / 136 (1.47%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER CUTANEOUS DISSEMINATED			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER DISSEMINATED			
subjects affected / exposed	0 / 90 (0.00%)	1 / 136 (0.74%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	0 / 90 (0.00%)	0 / 136 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Safety Double Blind Population: Upadacitinib 15 mg + TCS	Safety Double Blind Population: Upadacitinib 30 mg + TCS	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 91 (1.10%)	1 / 91 (1.10%)	

number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
OSTEOMA			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
CONCUSSION			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENISCUS INJURY			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN LACERATION			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
HYDROCELE			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBELLAR HAEMORRHAGE			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
CYST			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CATARACT DIABETIC			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL DETACHMENT			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ALCOHOLIC PANCREATITIS			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IRRITABLE BOWEL SYNDROME			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE POLYP			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLELITHIASIS			

subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PNEUMOTHORAX			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX SPONTANEOUS			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
SOMATIC SYMPTOM DISORDER			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ECZEMA HERPETICUM			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS INFECTIOUS			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES SIMPLEX			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER CUTANEOUS DISSEMINATED			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER DISSEMINATED			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			

subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety Double Blind Population: Placebo + TCS	All Upadacitinib Treated Population: Upadacitinib 30 mg + TCS	All Upadacitinib Treated Population: Upadacitinib 15 mg + TCS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 90 (32.22%)	114 / 136 (83.82%)	108 / 133 (81.20%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 90 (0.00%)	11 / 136 (8.09%)	9 / 133 (6.77%)
occurrences (all)	0	13	13
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 90 (0.00%)	15 / 136 (11.03%)	8 / 133 (6.02%)
occurrences (all)	0	16	8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
SKIN PAPILLOMA			
subjects affected / exposed	0 / 90 (0.00%)	8 / 136 (5.88%)	14 / 133 (10.53%)
occurrences (all)	0	8	17
Nervous system disorders			
HEADACHE			
subjects affected / exposed	2 / 90 (2.22%)	12 / 136 (8.82%)	6 / 133 (4.51%)
occurrences (all)	3	16	11
General disorders and administration site conditions			
INJECTION SITE PAIN			
subjects affected / exposed	0 / 90 (0.00%)	11 / 136 (8.09%)	3 / 133 (2.26%)
occurrences (all)	0	19	4
PYREXIA			
subjects affected / exposed	1 / 90 (1.11%)	28 / 136 (20.59%)	20 / 133 (15.04%)
occurrences (all)	1	33	25
Eye disorders			

CONJUNCTIVITIS ALLERGIC			
subjects affected / exposed	0 / 90 (0.00%)	5 / 136 (3.68%)	8 / 133 (6.02%)
occurrences (all)	0	6	10
Gastrointestinal disorders			
DENTAL CARIES			
subjects affected / exposed	0 / 90 (0.00%)	4 / 136 (2.94%)	8 / 133 (6.02%)
occurrences (all)	0	4	8
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	1 / 90 (1.11%)	8 / 136 (5.88%)	1 / 133 (0.75%)
occurrences (all)	1	10	1
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	5 / 90 (5.56%)	53 / 136 (38.97%)	34 / 133 (25.56%)
occurrences (all)	5	64	43
DERMATITIS ATOPIC			
subjects affected / exposed	3 / 90 (3.33%)	16 / 136 (11.76%)	19 / 133 (14.29%)
occurrences (all)	3	18	20
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 90 (0.00%)	11 / 136 (8.09%)	2 / 133 (1.50%)
occurrences (all)	0	15	2
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 90 (0.00%)	4 / 136 (2.94%)	8 / 133 (6.02%)
occurrences (all)	0	4	8
ECZEMA HERPETICUM			
subjects affected / exposed	0 / 90 (0.00%)	5 / 136 (3.68%)	11 / 133 (8.27%)
occurrences (all)	0	9	16
FOLLICULITIS			
subjects affected / exposed	2 / 90 (2.22%)	7 / 136 (5.15%)	13 / 133 (9.77%)
occurrences (all)	3	8	18
FURUNCLE			
subjects affected / exposed	2 / 90 (2.22%)	3 / 136 (2.21%)	7 / 133 (5.26%)
occurrences (all)	2	4	9
GASTROENTERITIS			

subjects affected / exposed	1 / 90 (1.11%)	5 / 136 (3.68%)	8 / 133 (6.02%)
occurrences (all)	1	5	9
HERPES SIMPLEX			
subjects affected / exposed	2 / 90 (2.22%)	7 / 136 (5.15%)	14 / 133 (10.53%)
occurrences (all)	2	12	32
HERPES ZOSTER			
subjects affected / exposed	0 / 90 (0.00%)	35 / 136 (25.74%)	26 / 133 (19.55%)
occurrences (all)	0	38	26
INFLUENZA			
subjects affected / exposed	1 / 90 (1.11%)	11 / 136 (8.09%)	7 / 133 (5.26%)
occurrences (all)	1	11	7
NASOPHARYNGITIS			
subjects affected / exposed	14 / 90 (15.56%)	44 / 136 (32.35%)	36 / 133 (27.07%)
occurrences (all)	15	68	55
PARONYCHIA			
subjects affected / exposed	0 / 90 (0.00%)	10 / 136 (7.35%)	1 / 133 (0.75%)
occurrences (all)	0	12	1
ORAL HERPES			
subjects affected / exposed	0 / 90 (0.00%)	8 / 136 (5.88%)	12 / 133 (9.02%)
occurrences (all)	0	14	19
PHARYNGITIS			
subjects affected / exposed	1 / 90 (1.11%)	7 / 136 (5.15%)	6 / 133 (4.51%)
occurrences (all)	1	8	6
TINEA PEDIS			
subjects affected / exposed	2 / 90 (2.22%)	13 / 136 (9.56%)	3 / 133 (2.26%)
occurrences (all)	2	13	3

Non-serious adverse events	Safety Double Blind Population: Upadacitinib 15 mg + TCS	Safety Double Blind Population: Upadacitinib 30 mg + TCS	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 91 (43.96%)	44 / 91 (48.35%)	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 91 (1.10%)	1 / 91 (1.10%)	
occurrences (all)	1	1	
BLOOD CREATINE PHOSPHOKINASE			

INCREASED			
subjects affected / exposed	1 / 91 (1.10%)	3 / 91 (3.30%)	
occurrences (all)	1	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
SKIN PAPILLOMA			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	1 / 91 (1.10%)	1 / 91 (1.10%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
INJECTION SITE PAIN			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences (all)	0	0	
PYREXIA			
subjects affected / exposed	4 / 91 (4.40%)	3 / 91 (3.30%)	
occurrences (all)	5	3	
Eye disorders			
CONJUNCTIVITIS ALLERGIC			
subjects affected / exposed	1 / 91 (1.10%)	1 / 91 (1.10%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
DENTAL CARIES			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	0 / 91 (0.00%)	2 / 91 (2.20%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	12 / 91 (13.19%)	18 / 91 (19.78%)	
occurrences (all)	14	18	
DERMATITIS ATOPIC			

subjects affected / exposed	3 / 91 (3.30%)	0 / 91 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 91 (0.00%)	5 / 91 (5.49%)	
occurrences (all)	0	5	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences (all)	0	0	
ECZEMA HERPETICUM			
subjects affected / exposed	3 / 91 (3.30%)	1 / 91 (1.10%)	
occurrences (all)	3	1	
FOLLICULITIS			
subjects affected / exposed	3 / 91 (3.30%)	2 / 91 (2.20%)	
occurrences (all)	4	2	
FURUNCLE			
subjects affected / exposed	2 / 91 (2.20%)	0 / 91 (0.00%)	
occurrences (all)	2	0	
GASTROENTERITIS			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences (all)	0	1	
HERPES SIMPLEX			
subjects affected / exposed	2 / 91 (2.20%)	1 / 91 (1.10%)	
occurrences (all)	2	1	
HERPES ZOSTER			
subjects affected / exposed	0 / 91 (0.00%)	4 / 91 (4.40%)	
occurrences (all)	0	4	
INFLUENZA			
subjects affected / exposed	1 / 91 (1.10%)	2 / 91 (2.20%)	
occurrences (all)	1	2	
NASOPHARYNGITIS			
subjects affected / exposed	12 / 91 (13.19%)	14 / 91 (15.38%)	
occurrences (all)	14	19	
PARONYCHIA			

subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences (all)	0	1	
ORAL HERPES			
subjects affected / exposed	1 / 91 (1.10%)	2 / 91 (2.20%)	
occurrences (all)	1	2	
PHARYNGITIS			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences (all)	0	1	
TINEA PEDIS			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2019	Updated to include safety results from the recent Phase 2b atopic dermatitis study and Phase 3 rheumatoid arthritis studies. Updated biomarker sample language for clarification. Added rationale for selection of doses for adolescents and recent efficacy and safety data from the Phase 2b study to justify dose selection. Updated Eligibility Criteria to specify method of glomerular filtration rate estimation for adult and adolescent subjects and to specify that topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) are not contraindicated. Updated contraception requirements to clarify age range of postmenopausal subjects and definition of childbearing potential to include female adolescents. Updated to allow prohibited medications and therapy after discontinuation of study drug and to clarify cannabis prohibition duration. Clarified required concomitant medication duration. Clarified the daily use of TCS and/or TCI during the study with step-down regimen, the restriction of wet wraps, and use after premature study drug discontinuation. Clarified that intentional/prospective deviations from withdrawal criteria are not permitted. Incorporated biomarker procedure for subjects after withdrawal from the study. Added clarification of treatment after end of study. Updated details on how the study drug was to be taken, packaged and labelled, stored and disposed of, dose randomization, selection and timing of study drug, treatment compliance, and blinding. Added proper detail of other study procedures originally found in the Operations Manual. Updated pregnancy language, methods and timing of safety assessment, recording data and analyses of safety findings, and reporting of AEs and intercurrent illnesses.
01 April 2019	(continued) Added clarifications for management of toxicity, serious infections, serious gastrointestinal (GI) events, cardiovascular and embolic/thrombotic events, malignancy, electrocardiogram (ECG) abnormality, and select laboratory abnormalities. Updated detail regarding the Data Monitoring Committee (DMC). Provided additional detail regarding safety data collection and Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting. Clarified timing of population pharmacokinetic (PK) reporting. Provided additional detail regarding subject consent. Updated Activity Schedule to include review of pregnancy avoidance recommendations, additional height measures for adolescents, additional procedures at the 30-Day Follow-Up Visit, additional 12-lead ECGs, chest x-ray clarification, and urine drug screen.

17 January 2020	Updated the benefits and risks to subjects to include safety language specifying that events of deep vein thrombosis and pulmonary embolism have been report in patients receiving Janus kinase (JAK) inhibitors including upadacitinib, and added text indicating that updating is not genotoxic but is teratogenic based on animal studies and there is no risk associated with administration in male partners of females of childbearing potential. Updated toxicity management instructions to include management of herpes zoster and muscle-related events, added recommendation for periodic skin examination for patients at increased risk for skin cancer. Instructions for the management of cardiovascular and embolic/thrombotic events were revised to make them specific to thrombosis events and included instructions that subjects must be discontinued if deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis is confirmed. Updated discontinuation criteria to include confirmed diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis. Added "Active" to tuberculosis (TB) and "adjudicated" to GI perforations in the list of reported AESIs.
01 December 2020	Stated that study drug shipments could be made from the study site to the subject and that there were no time limits for study drug interruption if no permanent study drug discontinuation criteria had been met. Updated to include details on how to perform specific activities/procedures that may be impacted by changes in global/local regulations due to the pandemic, provide guidance on delayed assessments due to the pandemic, and state which assessments may not be performed remotely. Provided instructions for completing supplemental study case report forms in the case of COVID-19-related missed/virtual visit, study drug discontinuations, or AEs; added instruction to interrupt study drug in subjects with confirmed diagnosis of COVID-19. Changed the last date of the open label (OL) long-term extension from Week 136 to Week 160. Updated the study drug discontinuation criteria for Eczema Area and Severity Index (EASI) worsening of 25% or more to include the following: "For example, permanent study drug discontinuation would apply at Week 8 if EASI score worsening criteria are met at Week 4 and Week 8 without rescue therapy given at Week 4. Permanent study drug discontinuation would apply at Week 12 if EASI score worsening criteria are met at Week 8 and Week 12 with rescue therapy given at Week 4. This rule applies similarly to later timepoints." In the safety section, added the supplemental electronic case report form for eczema herpeticum to the table of events that required a supplemental report, removed management of muscle-related events from toxicity management events, and updated guidelines for abnormal laboratory values for alanine aminotransferase (ALT) and aspartate transaminase (AST) in the toxicity management guidelines table.
01 December 2020	(continued) In the schedule of events, clarified that chest x-ray will be repeated annually (Weeks 100 and 148) starting at Week 52 if newly positive TB risk factor or results are obtained, added 12-lead ECG at Week 148 to accommodate extension to 160 weeks, clarified that blood samples for PK assay should not be taken at the Premature Discontinuation (PD) Visit if the PD Visit occurs after Week 16, and corrected the assessment time points for body surface area from every visit to only Screening, baseline, and Unscheduled Visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported