



Clinical trial results:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects With Non-Segmental Vitiligo

Summary

EudraCT number	2021-000081-15
Trial protocol	FR
Global end of trial date	29 August 2023

Results information

Result version number	v1 (current)
This version publication date	12 September 2024
First version publication date	12 September 2024

Trial information

Trial identification

Sponsor protocol code	M19-051
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04927975
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 August 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and efficacy of upadacitinib for the treatment of adult subjects with non-segmental vitiligo.

Protection of trial subjects:

Subjects signed and dated an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2021
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: 15
Country: Number of subjects enrolled	United States: 94
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	France: 44
Worldwide total number of subjects	185
EEA total number of subjects	44

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)	180

From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who met eligibility criteria at Baseline were randomized in a 2:2:2:1:1 ratio to one of the five treatment groups. At Week 24, subjects who were randomized to placebo at Baseline were switched to either 22 mg (Group 4) or 11 mg (Group 5) upadacitinib in a blinded fashion per pre-specified randomization assignments.

Period 1

Period 1 title	Period 1 (Baseline-Week 24)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Period 1

Arm description:

Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral tablets

Arm title	Upa 6 mg Period 1
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Arm description:

Participants received upadacitinib 6 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1.

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

Dosage and administration details:

Oral tablets

Arm title	Upa 11 mg Period 1
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Arm description:

Participants received upadacitinib 11 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1.

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

Dosage and administration details:

Oral tablets

Arm title	Upa 22 mg Period 1
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Arm description:

Participants received upadacitinib 22 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1.

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

Dosage and administration details:

Oral tablets

Number of subjects in period 1	Placebo Period 1	Upa 6 mg Period 1	Upa 11 mg Period 1
Started	46	49	47
Completed	44	46	45
Not completed	2	3	2
Death	-	-	-
Lost to follow-up	-	2	1
Withdrawal by subject	2	1	1

Number of subjects in period 1	Upa 22 mg Period 1
Started	43
Completed	38
Not completed	5
Death	1
Lost to follow-up	-
Withdrawal by subject	4

Period 2

Period 2 title	Period 2 (Week 24-52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo Period 1, Then Upa 11 mg Period 2
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Arm description:

Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 11 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.

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

Dosage and administration details:

Oral tablets

Arm title	Placebo Period 1, Then Upa 22 mg Period 2
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Arm description:

Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 22 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.

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

Dosage and administration details:

Oral tablets

Arm title	Upa 6 mg Period 1, Then Upa 6 mg Period 2
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Arm description:

Participants received upadacitinib 6 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 6 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.

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

Dosage and administration details:

Oral tablets

Arm title	Upa 11 mg Period 1, Then Upa 11 mg Period 2
Arm description: Participants received upadacitinib 11 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 11 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.	
Arm type	Experimental
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	ABT-494
Other name	RINVOQ
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral tablets

Arm title	Upa 22 mg Period 1, Then Upa 22 mg Period 2
Arm description: Participants received upadacitinib 22 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 22 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.	
Arm type	Experimental
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	ABT-494
Other name	RINVOQ
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral tablets

Number of subjects in period 2^[1]	Placebo Period 1, Then Upa 11 mg Period 2	Placebo Period 1, Then Upa 22 mg Period 2	Upa 6 mg Period 1, Then Upa 6 mg Period 2
Started	21	22	45
Completed	19	21	39
Not completed	2	1	6
Lost to follow-up	1	-	2
Withdrawal by subject	1	1	4

Number of subjects in period 2^[1]	Upa 11 mg Period 1, Then Upa 11 mg Period 2	Upa 22 mg Period 1, Then Upa 22 mg Period 2
Started	45	33
Completed	38	30
Not completed	7	3
Lost to follow-up	6	2
Withdrawal by subject	1	1

Notes:

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

Justification: A total of 185 subjects were randomized and received the study drug (placebo or upadacitinib) in Period 1. A total of 166 subjects completed study drug in Period 1. A total of 166 subjects entered Period 2 and received randomized study drug.

Baseline characteristics

Reporting groups

Reporting group title	Placebo Period 1
Reporting group description:	
Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1.	
Reporting group title	Upa 6 mg Period 1
Reporting group description:	
Participants received upadacitinib 6 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1.	
Reporting group title	Upa 11 mg Period 1
Reporting group description:	
Participants received upadacitinib 11 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1.	
Reporting group title	Upa 22 mg Period 1
Reporting group description:	
Participants received upadacitinib 22 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1.	

Reporting group values	Placebo Period 1	Upa 6 mg Period 1	Upa 11 mg Period 1
Number of subjects	46	49	47
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	46.8	45.1	45.5
standard deviation	± 10.48	± 11.68	± 11.90
Gender categorical			
Units: Subjects			
Female	29	26	34
Male	17	23	13
Ethnicity			
Units: Subjects			
Hispanic or Latino	5	6	4
Not Hispanic or Latino	41	43	43
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	6	7
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	4	3	3
White	34	35	36
More than one race	0	3	1
Unknown or Not Reported	2	1	0

Total Vitiligo Area Scoring Index (T-VASI)			
<p>The vitiligo area scoring index (VASI) is a validated scoring method used to assess the areas of depigmentation due to vitiligo. It is based on a composite estimate of the overall area of vitiligo patches, measured by the number of hand units (palm plus 5 digits = 1% body surface area [BSA]) multiplied by the degree of depigmentation within each affected area (0%, 10%, 25%, 50%, 75%, 90%, or 100%). The T-VASI is calculated using a formula that includes contributions from all body regions, with a possible range from 0 to 100, with higher scores indicating more severe disease.</p>			
Units: units on a scale			
arithmetic mean	21.014	20.993	22.322
standard deviation	± 16.9516	± 15.9672	± 18.1784
Facial Vitiligo Area Scoring Index (F-VASI)			
<p>The vitiligo area scoring index (VASI) is a validated scoring method used to assess the areas of depigmentation due to vitiligo. The F-VASI includes contributions from the face, with a possible range from 0 to 3, with higher scores indicating more severe disease.</p>			
Units: units on a scale			
arithmetic mean	1.043	1.154	1.021
standard deviation	± 0.6094	± 0.7655	± 0.5781

Reporting group values	Upa 22 mg Period 1	Total	
Number of subjects	43	185	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	48.2		
standard deviation	± 11.13	-	
Gender categorical			
Units: Subjects			
Female	26	115	
Male	17	70	
Ethnicity			
Units: Subjects			
Hispanic or Latino	5	20	
Not Hispanic or Latino	38	165	
Unknown or Not Reported	0	0	
Race			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	6	25	
Native Hawaiian or Other Pacific Islander	0	1	
Black or African American	1	11	
White	33	138	
More than one race	1	5	
Unknown or Not Reported	1	4	
Total Vitiligo Area Scoring Index (T-VASI)			
<p>The vitiligo area scoring index (VASI) is a validated scoring method used to assess the areas of depigmentation due to vitiligo. It is based on a composite estimate of the overall area of vitiligo patches, measured by the number of hand units (palm plus 5 digits = 1% body surface area [BSA]) multiplied by the degree of depigmentation within each affected area (0%, 10%, 25%, 50%, 75%, 90%, or 100%).</p>			

The T-VASI is calculated using a formula that includes contributions from all body regions, with a possible range from 0 to 100, with higher scores indicating more severe disease.			
Units: units on a scale			
arithmetic mean	21.843		
standard deviation	± 15.9324	-	
Facial Vitiligo Area Scoring Index (F-VASI)			
The vitiligo area scoring index (VASI) is a validated scoring method used to assess the areas of depigmentation due to vitiligo. The F-VASI includes contributions from the face, with a possible range from 0 to 3, with higher scores indicating more severe disease.			
Units: units on a scale			
arithmetic mean	1.159		
standard deviation	± 0.6585	-	

End points

End points reporting groups

Reporting group title	Placebo Period 1
Reporting group description: Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1.	
Reporting group title	Upa 6 mg Period 1
Reporting group description: Participants received upadacitinib 6 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1.	
Reporting group title	Upa 11 mg Period 1
Reporting group description: Participants received upadacitinib 11 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1.	
Reporting group title	Upa 22 mg Period 1
Reporting group description: Participants received upadacitinib 22 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1.	
Reporting group title	Placebo Period 1, Then Upa 11 mg Period 2
Reporting group description: Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 11 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.	
Reporting group title	Placebo Period 1, Then Upa 22 mg Period 2
Reporting group description: Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 22 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.	
Reporting group title	Upa 6 mg Period 1, Then Upa 6 mg Period 2
Reporting group description: Participants received upadacitinib 6 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 6 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.	
Reporting group title	Upa 11 mg Period 1, Then Upa 11 mg Period 2
Reporting group description: Participants received upadacitinib 11 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 11 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.	
Reporting group title	Upa 22 mg Period 1, Then Upa 22 mg Period 2
Reporting group description: Participants received upadacitinib 22 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 22 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2.	

Primary: Percent Change From Baseline in Facial-Vitiligo Area Scoring Index (F-VASI) at Week 24

End point title	Percent Change From Baseline in Facial-Vitiligo Area Scoring Index (F-VASI) at Week 24
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End point description:

The vitiligo area scoring index (VASI) is a validated scoring method used to assess the areas of depigmentation due to vitiligo. The F-VASI includes contributions from the face, with a possible range from 0 to 3, with higher scores indicating more severe disease. Negative changes from baseline indicate improvement.

Analysis population: ITT_1: all randomized participants in Period 1, analyzed according to the treatment groups that they were randomized to; mixed model repeated measures analysis (MMRM) including observed measurements at all visits

End point type	Primary
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End point timeframe:

Baseline, Week 24

End point values	Placebo Period 1	Upa 6 mg Period 1	Upa 11 mg Period 1	Upa 22 mg Period 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	45	43	33
Units: Percent change from baseline				
arithmetic mean (confidence interval 95%)	-14.36 (-24.86 to -3.85)	-21.96 (-32.18 to -11.75)	-35.63 (-46.11 to -25.14)	-33.96 (-45.41 to -22.50)

Statistical analyses

Statistical analysis title	Upa 6 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

Repeated measures analysis was conducted using a mixed model including observed measurements at all visits. The model included categorical fixed effects of treatment, visit and treatment-by-visit interaction, and stratification factors (age [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], active vitiligo [Yes/No]) derived from actual values, and the continuous fixed covariate of Baseline measurement. An unstructured variance covariance matrix was used.

Comparison groups	Placebo Period 1 v Upa 6 mg Period 1
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304
Method	Mixed-Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.18
upper limit	6.97

Statistical analysis title	Upa 11 mg Period 1 versus Placebo Period 1
Statistical analysis description:	
Repeated measures analysis was conducted using a mixed model including observed measurements at all visits. The model included categorical fixed effects of treatment, visit and treatment-by-visit interaction, and stratification factors (age [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], active vitiligo [Yes/No]) derived from actual values, and the continuous fixed covariate of Baseline measurement. An unstructured variance covariance matrix was used.	
Comparison groups	Placebo Period 1 v Upa 11 mg Period 1
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed-Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-21.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.02
upper limit	-6.52

Statistical analysis title	Upa 22 mg Period 1 versus Placebo Period 1
Statistical analysis description:	
Repeated measures analysis was conducted using a mixed model including observed measurements at all visits. The model included categorical fixed effects of treatment, visit and treatment-by-visit interaction, and stratification factors (age [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], active vitiligo [Yes/No]) derived from actual values, and the continuous fixed covariate of Baseline measurement. An unstructured variance covariance matrix was used.	
Comparison groups	Placebo Period 1 v Upa 22 mg Period 1
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Mixed-Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-19.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.04
upper limit	-4.16

Secondary: Percentage of Participants Achieving F-VASI 75 ($\geq 75\%$ Improvement in F-VASI From Baseline) at Week 24

End point title	Percentage of Participants Achieving F-VASI 75 ($\geq 75\%$ Improvement in F-VASI From Baseline) at Week 24
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End point description:

The vitiligo area scoring index (VASI) is a validated scoring method used to assess the areas of depigmentation due to vitiligo. The F-VASI includes contributions from the face, with a possible range from 0 to 3, with higher scores indicating more severe disease.

Analysis population: ITT_1: all randomized participants in Period 1, analyzed according to the treatment groups that they were randomized to; NRI-MI (non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random)

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo Period 1	Upa 6 mg Period 1	Upa 11 mg Period 1	Upa 22 mg Period 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	49	47	43
Units: percentage of participants				
number (confidence interval 95%)	2.2 (0.0 to 6.4)	8.2 (0.5 to 15.8)	19.1 (7.9 to 30.4)	14.0 (3.6 to 24.3)

Statistical analyses

Statistical analysis title	Upa 6 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

P-value calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (age group [≤ 50 and > 50], baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No])) for the comparison of two treatment groups. The calculations at each visit were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there were no missing data due to COVID-19.

Comparison groups	Placebo Period 1 v Upa 6 mg Period 1
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	15.2

Statistical analysis title	Upa 11 mg Period 1 versus Placebo Period 1
Statistical analysis description:	
P-value calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (age group [≤ 50 and > 50], baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No])) for the comparison of two treatment groups. The calculations at each visit were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there were no missing data due to COVID-19.	
Comparison groups	Placebo Period 1 v Upa 11 mg Period 1
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	17.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	29

Statistical analysis title	Upa 22 mg Period 1 versus Placebo Period 1
Statistical analysis description:	
P-value calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (age group [≤ 50 and > 50], baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No])) for the comparison of two treatment groups. The calculations at each visit were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there were no missing data due to COVID-19.	
Comparison groups	Placebo Period 1 v Upa 22 mg Period 1
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	21.9

Secondary: Percentage of Participants Achieving F-VASI 50 ($\geq 50\%$ Improvement in F-VASI From Baseline) at Week 24	
End point title	Percentage of Participants Achieving F-VASI 50 ($\geq 50\%$ Improvement in F-VASI From Baseline) at Week 24

End point description:

The vitiligo area scoring index (VASI) is a validated scoring method used to assess the areas of depigmentation due to vitiligo. The F-VASI includes contributions from the face, with a possible range from 0 to 3, with higher scores indicating more severe disease.

Analysis population: ITT_1: all randomized participants in Period 1, analyzed according to the treatment groups that they were randomized to; NRI-MI (non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random)

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo Period 1	Upa 6 mg Period 1	Upa 11 mg Period 1	Upa 22 mg Period 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	49	47	43
Units: percentage of participants				
number (confidence interval 95%)	10.9 (1.9 to 19.9)	16.3 (6.0 to 26.7)	38.3 (24.4 to 52.2)	39.5 (24.9 to 54.1)

Statistical analyses

Statistical analysis title	Upa 6 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

P-value calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (age group [≤ 50 and > 50], baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No])) for the comparison of two treatment groups. The calculations at each visit were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there were no missing data due to COVID-19.

Comparison groups	Placebo Period 1 v Upa 6 mg Period 1
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.327
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	19.7

Statistical analysis title	Upa 11 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

P-value calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (age group [≤ 50 and > 50], baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No])) for the comparison of two treatment groups. The calculations at each visit were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there were no missing data due to COVID-19.

Comparison groups	Placebo Period 1 v Upa 11 mg Period 1
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	29.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.8
upper limit	44.9

Statistical analysis title

Upa 22 mg Period 1 versus Placebo Period 1

Statistical analysis description:

P-value calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (age group [≤ 50 and > 50], baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No])) for the comparison of two treatment groups. The calculations at each visit were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there were no missing data due to COVID-19.

Comparison groups	Placebo Period 1 v Upa 22 mg Period 1
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	28.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.6
upper limit	44.7

Secondary: Percentage of Participants Achieving Total Vitiligo Area Scoring Index (T-VASI) 50 ($\geq 50\%$ Improvement in T-VASI From Baseline) at Week 24

End point title	Percentage of Participants Achieving Total Vitiligo Area Scoring Index (T-VASI) 50 ($\geq 50\%$ Improvement in T-VASI From Baseline) at Week 24
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End point description:

The vitiligo area scoring index (VASI) is a validated scoring method used to assess the areas of

depigmentation due to vitiligo. It is based on a composite estimate of the overall area of vitiligo patches, measured by the number of hand units (palm plus 5 digits = 1% body surface area [BSA]) multiplied by the degree of depigmentation within each affected area (0%, 10%, 25%, 50%, 75%, 90%, or 100%). The T-VASI is calculated using a formula that includes contributions from all body regions, with a possible range from 0 to 100, with higher scores indicating more severe disease.

Analysis population: ITT_1: all randomized participants in Period 1, analyzed according to the treatment groups that they were randomized to; NRI-MI (non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random)

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo Period 1	Upa 6 mg Period 1	Upa 11 mg Period 1	Upa 22 mg Period 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	49	47	43
Units: percentage of participants				
number (confidence interval 95%)	2.2 (0.0 to 6.4)	6.1 (0.0 to 12.8)	6.4 (0.0 to 13.4)	11.6 (2.0 to 21.2)

Statistical analyses

Statistical analysis title	Upa 6 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

P-value calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (age group [≤ 50 and > 50], baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No])) for the comparison of two treatment groups. The calculations at each visit were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there were no missing data due to COVID-19.

Comparison groups	Placebo Period 1 v Upa 6 mg Period 1
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	11.2

Statistical analysis title	Upa 11 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

P-value calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (age group [≤ 50 and > 50], baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No])) for the comparison of two treatment groups. The calculations at each visit were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there were no missing data due to COVID-19.

Comparison groups	Placebo Period 1 v Upa 11 mg Period 1
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	11.8

Statistical analysis title

Upa 22 mg Period 1 versus Placebo Period 1

Statistical analysis description:

P-value calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (age group [≤ 50 and > 50], baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No])) for the comparison of two treatment groups. The calculations at each visit were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there were no missing data due to COVID-19.

Comparison groups	Placebo Period 1 v Upa 22 mg Period 1
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	17.2

Secondary: Percent Change From Baseline in T-VASI at Week 24

End point title	Percent Change From Baseline in T-VASI at Week 24
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End point description:

The vitiligo area scoring index (VASI) is a validated scoring method used to assess the areas of depigmentation due to vitiligo. It is based on a composite estimate of the overall area of vitiligo patches, measured by the number of hand units (palm plus 5 digits = 1% body surface area [BSA]) multiplied by the degree of depigmentation within each affected area (0%, 10%, 25%, 50%, 75%, 90%, or 100%).

The T-VASI is calculated using a formula that includes contributions from all body regions, with a possible range from 0 to 100, with higher scores indicating more severe disease. Negative changes from baseline indicate improvement.

Analysis population: ITT_1: all randomized participants in Period 1, analyzed according to the treatment groups that they were randomized to; mixed model repeated measures analysis (MMRM) including observed measurements at all visits.

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo Period 1	Upa 6 mg Period 1	Upa 11 mg Period 1	Upa 22 mg Period 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	45	43	33
Units: Percent change from baseline				
least squares mean (confidence interval 95%)	-6.42 (-13.17 to 0.34)	-13.87 (-20.45 to -7.29)	-17.26 (-24.00 to -10.52)	-20.69 (-28.05 to -13.32)

Statistical analyses

Statistical analysis title	Upa 6 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

Repeated measures analysis was conducted using a mixed model including observed measurements at all visits. The model included categorical fixed effects of treatment, visit and treatment-by-visit interaction, and stratification factors (age [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], active vitiligo [Yes/No]) derived from actual values, and the continuous fixed covariate of Baseline measurement. An unstructured variance covariance matrix was used.

Comparison groups	Placebo Period 1 v Upa 6 mg Period 1
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Mixed-Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-7.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.86
upper limit	1.96

Statistical analysis title	Upa 11 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

Repeated measures analysis was conducted using a mixed model including observed measurements at all visits. The model included categorical fixed effects of treatment, visit and treatment-by-visit interaction, and stratification factors (age [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], active vitiligo [Yes/No]) derived from actual values, and the continuous fixed covariate of Baseline measurement. An unstructured variance covariance matrix was used.

Comparison groups	Placebo Period 1 v Upa 11 mg Period 1
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Mixed-Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-10.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.37
upper limit	-1.32

Statistical analysis title

Upa 22 mg Period 1 versus Placebo Period 1

Statistical analysis description:

Repeated measures analysis was conducted using a mixed model including observed measurements at all visits. The model included categorical fixed effects of treatment, visit and treatment-by-visit interaction, and stratification factors (age [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], active vitiligo [Yes/No]) derived from actual values, and the continuous fixed covariate of Baseline measurement. An unstructured variance covariance matrix was used.

Comparison groups	Placebo Period 1 v Upa 22 mg Period 1
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed-Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-14.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.24
upper limit	-4.3

Secondary: Change From Baseline in the Vitiligo Quality-of-Life (VitiQoL) Instrument Total Score at Week 24

End point title	Change From Baseline in the Vitiligo Quality-of-Life (VitiQoL) Instrument Total Score at Week 24
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End point description:

The VitiQoL is a validated questionnaire used in clinical trials to assess stigma-related vitiligo impacts. The VitiQoL uses subject-elicited social, affective, and behavior items, asking the subject's appraisal of

the vitiligo-related impacts over the last month. Fifteen items are scored on a 7-point scale ranging from 0 ("Not at all") to 6 ("All of the time"). Item scores (0 to 6) are summed to provide a total score range of 0 to 90; higher scores indicate greater impairment of quality of life (QoL). Negative changes from baseline indicate improvement.

Analysis population: ITT_1: all randomized participants in Period 1, analyzed according to the treatment groups that they were randomized to; mixed model repeated measures analysis (MMRM) including observed measurements at all visits.

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo Period 1	Upa 6 mg Period 1	Upa 11 mg Period 1	Upa 22 mg Period 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	44	44	34
Units: units on a scale				
least squares mean (confidence interval 95%)	-5.5 (-10.3 to -0.8)	-7.5 (-12.0 to -3.0)	-3.7 (-8.2 to 0.9)	-6.6 (-11.6 to -1.6)

Statistical analyses

Statistical analysis title	Upa 6 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

Repeated measures analysis was conducted using a mixed model including observed measurements at all visits. The model included categorical fixed effects of treatment, visit and treatment-by-visit interaction, and stratification factors (age [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], active vitiligo [Yes/No]) derived from actual values, and the continuous fixed covariate of Baseline measurement. An unstructured variance covariance matrix was used.

Comparison groups	Placebo Period 1 v Upa 6 mg Period 1
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.545
Method	Mixed-Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	4.4

Statistical analysis title	Upa 11 mg Period 1 versus Placebo Period 1
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Statistical analysis description:

Repeated measures analysis was conducted using a mixed model including observed measurements at all visits. The model included categorical fixed effects of treatment, visit and treatment-by-visit interaction, and stratification factors (age [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], active vitiligo [Yes/No]) derived from actual values, and the continuous fixed covariate of Baseline measurement. An unstructured variance covariance matrix was used.

Comparison groups	Placebo Period 1 v Upa 11 mg Period 1
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.565
Method	Mixed-Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	8.3

Statistical analysis title

Upa 22 mg Period 1 versus Placebo Period 1

Statistical analysis description:

Repeated measures analysis was conducted using a mixed model including observed measurements at all visits. The model included categorical fixed effects of treatment, visit and treatment-by-visit interaction, and stratification factors (age [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], active vitiligo [Yes/No]) derived from actual values, and the continuous fixed covariate of Baseline measurement. An unstructured variance covariance matrix was used.

Comparison groups	Placebo Period 1 v Upa 22 mg Period 1
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.754
Method	Mixed-Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	5.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality/adverse events were collected from informed consent through the end of the study. Median time on follow-up was 168 days for all groups in Period 1.

Adverse event reporting additional description:

Median time on follow-up for Period 2 was as follows: Placebo Period 1, Then Upa 11 mg Period 2 (198 days); Placebo Period 1, Then Upa 22 mg Period 2 and Upa 22 mg Period 1, Then Upa 22 mg Period 2 (212 days); Upa 6 mg Period 1, Then Upa 6 mg Period 2 (204 days); and Upa 11 mg Period 1, Then Upa 11 mg Period 2 (207 days).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Placebo Period 1
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Reporting group description:

Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1. AEs and SAEs were collected from the time of informed consent and during Period 1, as long as it did not exceed the start date of Period 2.

Reporting group title	Upa 11 mg Period 1
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Reporting group description:

Participants received upadacitinib 11 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. AEs and SAEs were collected from the time of informed consent and during Period 1, as long as it did not exceed the start date of Period 2.

Reporting group title	Upa 22 mg Period 1
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Reporting group description:

Participants received upadacitinib 22 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. AEs and SAEs were collected from the time of informed consent and during Period 1, as long as it did not exceed the start date of Period 2.

Reporting group title	Upa 22 mg Period 1, Then Upa 22 mg Period 2
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Reporting group description:

Participants received upadacitinib 22 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 22 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2. AEs and SAEs were collected from the start date of Period 2 to the end of the study.

Reporting group title	Placebo Period 1, Then Upa 22 mg Period 2
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Reporting group description:

Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 22 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2. AEs and SAEs were collected from the start date of Period 2 to the end of the study.

Reporting group title	Upa 6 mg Period 1, Then Upa 6 mg Period 2
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Reporting group description:

Participants received upadacitinib 6 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 6 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2. AEs and SAEs were collected from the start date of Period 2 to the end of the study.

Reporting group title	Upa 11 mg Period 1, Then Upa 11 mg Period 2
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Reporting group description:

Participants received upadacitinib 11 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 11 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2. AEs and SAEs were collected from the start date of Period 2 to the end of the study.

Reporting group title	Upa 6 mg Period 1
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Reporting group description:

Participants received upadacitinib 6 mg administered orally once a day (QD) as tablets for 24 weeks during Period 1. AEs and SAEs were collected from the time of informed consent and during Period 1, as long as it did not exceed the start date of Period 2.

Reporting group title	Placebo Period 1, Then Upa 11 mg Period 2
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Reporting group description:

Participants received Placebo for upadacitinib administered orally once a day (QD) as tablets for 24 weeks during Period 1. Participants then received upadacitinib 11 mg administered orally once a day (QD) as tablets for 28 weeks during Period 2. AEs and SAEs were collected from the start date of Period 2 to the end of the study.

Serious adverse events	Placebo Period 1	Upa 11 mg Period 1	Upa 22 mg Period 1
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	3 / 43 (6.98%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) INVASIVE LOBULAR BREAST CARCINOMA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications CLAVICLE FRACTURE			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders ARTERIOSCLEROSIS CORONARY ARTERY			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders ISCHAEMIC STROKE			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

DEATH			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PAIN			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 43 (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
Infections and infestations			
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	1 / 43 (2.33%)
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	Upa 22 mg Period 1, Then Upa 22 mg Period 2	Placebo Period 1, Then Upa 22 mg Period 2	Upa 6 mg Period 1, Then Upa 6 mg Period 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (0.00%)
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)			
INVASIVE LOBULAR BREAST CARCINOMA			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
ARTERIOSCLEROSIS CORONARY ARTERY			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DEATH			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (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
PAIN			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (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
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (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	Upa 11 mg Period 1, Then Upa 11 mg Period 2	Upa 6 mg Period 1	Placebo Period 1, Then Upa 11 mg Period 2
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 45 (4.44%)	1 / 49 (2.04%)	1 / 21 (4.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) INVASIVE LOBULAR BREAST CARCINOMA			
subjects affected / exposed	1 / 45 (2.22%)	0 / 49 (0.00%)	0 / 21 (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
Injury, poisoning and procedural complications CLAVICLE FRACTURE			
subjects affected / exposed	0 / 45 (0.00%)	0 / 49 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders ARTERIOSCLEROSIS CORONARY ARTERY			
subjects affected / exposed	0 / 45 (0.00%)	1 / 49 (2.04%)	0 / 21 (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
Nervous system disorders ISCHAEMIC STROKE			
subjects affected / exposed	1 / 45 (2.22%)	0 / 49 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions DEATH			
subjects affected / exposed	0 / 45 (0.00%)	0 / 49 (0.00%)	0 / 21 (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
PAIN			
subjects affected / exposed	0 / 45 (0.00%)	0 / 49 (0.00%)	0 / 21 (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
Renal and urinary disorders NEPHROLITHIASIS			

subjects affected / exposed	0 / 45 (0.00%)	0 / 49 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 45 (0.00%)	0 / 49 (0.00%)	0 / 21 (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

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

Non-serious adverse events	Placebo Period 1	Upa 11 mg Period 1	Upa 22 mg Period 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 46 (56.52%)	28 / 47 (59.57%)	23 / 43 (53.49%)
Investigations			
WEIGHT INCREASED			
subjects affected / exposed	1 / 46 (2.17%)	1 / 47 (2.13%)	3 / 43 (6.98%)
occurrences (all)	1	1	3
BLOOD THYROID STIMULATING HORMONE DECREASED			
subjects affected / exposed	1 / 46 (2.17%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
SKIN LACERATION			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	4 / 46 (8.70%)	9 / 47 (19.15%)	2 / 43 (4.65%)
occurrences (all)	4	11	3
General disorders and administration site conditions			
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	3 / 46 (6.52%)	0 / 47 (0.00%)	1 / 43 (2.33%)
occurrences (all)	3	0	1
FATIGUE			

subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1	2 / 47 (4.26%) 2	5 / 43 (11.63%) 5
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	4 / 46 (8.70%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	5	0	0
DIARRHOEA			
subjects affected / exposed	1 / 46 (2.17%)	3 / 47 (6.38%)	1 / 43 (2.33%)
occurrences (all)	1	3	1
VOMITING			
subjects affected / exposed	0 / 46 (0.00%)	2 / 47 (4.26%)	3 / 43 (6.98%)
occurrences (all)	0	2	3
NAUSEA			
subjects affected / exposed	3 / 46 (6.52%)	2 / 47 (4.26%)	4 / 43 (9.30%)
occurrences (all)	3	2	4
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	1 / 46 (2.17%)	4 / 47 (8.51%)	2 / 43 (4.65%)
occurrences (all)	1	4	2
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	1 / 46 (2.17%)	4 / 47 (8.51%)	6 / 43 (13.95%)
occurrences (all)	4	4	7
DYSHIDROTIC ECZEMA			
subjects affected / exposed	0 / 46 (0.00%)	0 / 47 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	1 / 46 (2.17%)	3 / 47 (6.38%)	0 / 43 (0.00%)
occurrences (all)	1	3	0
INSOMNIA			
subjects affected / exposed	0 / 46 (0.00%)	3 / 47 (6.38%)	0 / 43 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
NASOPHARYNGITIS			

subjects affected / exposed	3 / 46 (6.52%)	2 / 47 (4.26%)	4 / 43 (9.30%)
occurrences (all)	5	2	4
COVID-19			
subjects affected / exposed	8 / 46 (17.39%)	9 / 47 (19.15%)	9 / 43 (20.93%)
occurrences (all)	8	9	9
GASTROENTERITIS			
subjects affected / exposed	3 / 46 (6.52%)	1 / 47 (2.13%)	1 / 43 (2.33%)
occurrences (all)	3	1	1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 46 (2.17%)	2 / 47 (4.26%)	0 / 43 (0.00%)
occurrences (all)	1	2	0
URINARY TRACT INFECTION			
subjects affected / exposed	3 / 46 (6.52%)	4 / 47 (8.51%)	2 / 43 (4.65%)
occurrences (all)	3	7	3

Non-serious adverse events	Upa 22 mg Period 1, Then Upa 22 mg Period 2	Placebo Period 1, Then Upa 22 mg Period 2	Upa 6 mg Period 1, Then Upa 6 mg Period 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 33 (51.52%)	11 / 22 (50.00%)	12 / 45 (26.67%)
Investigations			
WEIGHT INCREASED			
subjects affected / exposed	2 / 33 (6.06%)	0 / 22 (0.00%)	0 / 45 (0.00%)
occurrences (all)	2	0	0
BLOOD THYROID STIMULATING HORMONE DECREASED			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
SKIN LACERATION			
subjects affected / exposed	0 / 33 (0.00%)	0 / 22 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	2 / 33 (6.06%)	1 / 22 (4.55%)	2 / 45 (4.44%)
occurrences (all)	2	1	2
General disorders and administration site conditions			

INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3	0 / 22 (0.00%) 0	0 / 45 (0.00%) 0
FATIGUE subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 22 (0.00%) 0	2 / 45 (4.44%) 2
Gastrointestinal disorders ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 22 (0.00%) 0	0 / 45 (0.00%) 0
DIARRHOEA subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 22 (0.00%) 0	1 / 45 (2.22%) 1
VOMITING subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 22 (0.00%) 0	0 / 45 (0.00%) 0
NAUSEA subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 22 (0.00%) 0	0 / 45 (0.00%) 0
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	1 / 22 (4.55%) 1	0 / 45 (0.00%) 0
Skin and subcutaneous tissue disorders ACNE subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	2 / 22 (9.09%) 3	1 / 45 (2.22%) 2
DYSHIDROTIC ECZEMA subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 22 (4.55%) 1	0 / 45 (0.00%) 0
Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 22 (0.00%) 0	0 / 45 (0.00%) 0
INSOMNIA			

subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 22 (0.00%) 0	0 / 45 (0.00%) 0
Infections and infestations NASOPHARYNGITIS subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 22 (13.64%) 3	1 / 45 (2.22%) 1
COVID-19 subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 5	5 / 22 (22.73%) 5	7 / 45 (15.56%) 7
GASTROENTERITIS subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 22 (0.00%) 0	0 / 45 (0.00%) 0
UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	0 / 22 (0.00%) 0	1 / 45 (2.22%) 2
URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	3 / 22 (13.64%) 3	2 / 45 (4.44%) 2

Non-serious adverse events	Upa 11 mg Period 1, Then Upa 11 mg Period 2	Upa 6 mg Period 1	Placebo Period 1, Then Upa 11 mg Period 2
Total subjects affected by non-serious adverse events subjects affected / exposed	22 / 45 (48.89%)	19 / 49 (38.78%)	9 / 21 (42.86%)
Investigations WEIGHT INCREASED subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 49 (0.00%) 0	0 / 21 (0.00%) 0
BLOOD THYROID STIMULATING HORMONE DECREASED subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	0 / 49 (0.00%) 0	0 / 21 (0.00%) 0
Injury, poisoning and procedural complications SKIN LACERATION subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	0 / 49 (0.00%) 0	2 / 21 (9.52%) 2
Nervous system disorders			

HEADACHE subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 5	0 / 49 (0.00%) 0	2 / 21 (9.52%) 2
General disorders and administration site conditions INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all) FATIGUE subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1 0 / 45 (0.00%) 0	1 / 49 (2.04%) 1 2 / 49 (4.08%) 2	0 / 21 (0.00%) 0 1 / 21 (4.76%) 1
Gastrointestinal disorders ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0 1 / 45 (2.22%) 1 0 / 45 (0.00%) 0 1 / 45 (2.22%) 1	0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 1 / 49 (2.04%) 1 0 / 49 (0.00%) 0	0 / 21 (0.00%) 0 1 / 21 (4.76%) 1 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	2 / 49 (4.08%) 2	0 / 21 (0.00%) 0
Skin and subcutaneous tissue disorders ACNE subjects affected / exposed occurrences (all) DYSHIDROTIC ECZEMA subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2 0 / 45 (0.00%) 0	3 / 49 (6.12%) 3 0 / 49 (0.00%) 0	1 / 21 (4.76%) 1 0 / 21 (0.00%) 0
Psychiatric disorders			

ANXIETY			
subjects affected / exposed	0 / 45 (0.00%)	1 / 49 (2.04%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
INSOMNIA			
subjects affected / exposed	0 / 45 (0.00%)	0 / 49 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	2 / 45 (4.44%)	4 / 49 (8.16%)	3 / 21 (14.29%)
occurrences (all)	2	4	4
COVID-19			
subjects affected / exposed	12 / 45 (26.67%)	7 / 49 (14.29%)	1 / 21 (4.76%)
occurrences (all)	12	7	1
GASTROENTERITIS			
subjects affected / exposed	0 / 45 (0.00%)	0 / 49 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	4 / 45 (8.89%)	3 / 49 (6.12%)	3 / 21 (14.29%)
occurrences (all)	4	3	3
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 45 (2.22%)	1 / 49 (2.04%)	0 / 21 (0.00%)
occurrences (all)	2	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2021	<p>Protocol Version 2.0</p> <ul style="list-style-type: none">• Updated Synopsis and Section 2.1 to add "in some countries" to clarify the approval status of upadacitinib for the treatment of RA, PsA, and AS• Clarified that previous treatment with permanent skin bleaching agents to treat vitiligo is prohibited.• Clarified the approximate number of sites that will be selected and that subjects at participating sites will be required to participate after digital imaging platform is available for implementation at the site• Updated Section 5.3 to revise the dose for systemic corticosteroids from 1 mg/kg to 1 mg/kg/day• Updated Section 5.3 to change the wording regarding natural daily light exposure from "encouraged" to "allowed"• Updated Section 5.3 to add language prohibiting use throughout the study of any drugs considered to be strong CYP3A inhibitors or inducers, or herbal supplements or traditional medicines with unknown effects on CYP3A• Updated Section 5.5 to condense the wording regarding subject non-compliance with study procedures• Updated Section 5.5 to add "beginning at Week 8" to the discontinuation criterion regarding worsening vitiligo as defined by an increase of 25% or higher in T-VASI from Baseline• Updated Section 7.4 to clarify that categorical stratification factors will be adjusted in the models• Updated Appendix D to add respiratory rate and body temperature to vital signs

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported