Clinical trial results:
Rheumatoid Arthritis: A Phase 2 Study to Investigate the Safety and Efficacy of ABBV-105 Given Alone or in Combination with Upadacitinib (ABBV-599 Combination) with a Background of Conventional Synthetic DMARDs in Subjects with Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs

Summary

EudraCT number	2018-000666-10
Trial protocol	GB HU BE ES
Global end of trial date	26 March 2020

Results information

Result version number	v2 (current)
This version publication date	20 May 2021
First version publication date	20 March 2021
Version creation reason	• Correction of full data set Edited endpoint description and the global end of trial date.

Trial information

Trial identification

Sponsor protocol code	M16-063

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03682705
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	26 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a 12-week, randomized, double-blind, parallel-group, Phase 2, dose exploratory, multicenter study. to evaluate the safety and efficacy of elsubrutinib (ELS) and ABBV-599 (ELS plus upadacitinib [UPA]) vs placebo on a background of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) for the treatment of signs and symptoms of rheumatoid arthritis (RA) in biological disease-modifying anti-rheumatic drugs (bDMARD)-inadequate response (bDMARD-IR) or bDMARD-intolerant participants with moderately to severely active RA and to define optimal dose for further development. Participants who met eligibility criteria were randomized in a 3:2:2:2:2:1 ratio to 1 of 6 treatment groups: ABBV-599 [UPA 15 mg/ ELS 60 mg]); ELS 60 mg/UPA placebo; ELS 20 mg/UPA placebo; ELS 5 mg/UPA placebo; UPA 15 mg/ELS placebo; and ELS placebo/UPA placebo. The study included a 35-day maximum screening period and a 12-week treatment period with 30-day follow-up.

Protection of trial subjects:

Subjects or their legally authorized representative must have voluntarily 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	08 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Puerto Rico: 6
Country: Number of subjects enrolled	United States: 131
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Czechia: 20
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	242
EEA total number of subjects	98

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)	162
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Full Analysis Set: all randomized participants who received at least 1 dose of randomized study drug

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ELS placebo/UPA placebo

Arm description:

Placebo capsule for elsubrutinib once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks

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

Dosage and administration details:

Placebo capsule for elsubrutinib will be administered orally.

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

Dosage and administration details:

Placebo tablet for upadacitinib will be administered orally.

Arm title	UPA 15 mg/ELS 60 mg

Arm description:

15 mg film-coated upadacitinib tablet once a day by mouth for 12 weeks; 60 mg elsubrutinib capsule once a day by mouth for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Elsubrutinib
Investigational medicinal product code	
Other name	ABBV-105
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Elsubrutinib capsule will be administered orally.

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

Dosage and administration details:

Upadacitinib tablet will be administered orally.

Arm title	ELS 60 mg/UPA placebo

Arm description:

60 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Elsubrutinib
Investigational medicinal product code	
Other name	ABBV-105
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Elsubrutinib capsule will be administered orally.

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

Dosage and administration details:

Placebo tablet for upadacitinib will be administered orally.

Arm title	ELS 20 mg/UPA placebo

Arm description:

20 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Elsubrutinib
Investigational medicinal product code	
Other name	ABBV-105
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Elsubrutinib capsule will be administered orally.

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

Dosage and administration details:

Placebo tablet for upadacitinib will be administered orally.

Arm title	ELS 5 mg/UPA placebo

Arm description:

5 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Elsubrutinib
Investigational medicinal product code	
Other name	ABBV-105
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Elsubrutinib capsule will be administered orally.

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

Dosage and administration details:

Placebo tablet for upadacitinib will be administered orally.

Arm title	UPA 15 mg/ELS placebo

Arm description:

15 mg film-coated upadacitinib tablet once a day by mouth for 12 weeks; placebo capsule for elsubrutinib once a day by mouth for 12 weeks

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

Dosage and administration details:

Upadacitinib tablet will be administered orally.

Investigational medicinal product name	Placebo for elsubrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule for elsubrutinib will be administered orally.

Number of subjects in period 1	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo
Started	19	62	41
Completed	17	58	38
Not completed	2	4	3
Adverse event, non-fatal	1	1	1
Other, not specified	-	-	-

Lost to follow-up	-	-	-
Withdrawal by subject	1	3	2

Number of subjects in period 1	ELS 20 mg/UPA placebo	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo
Started	39	41	40
Completed	34	35	38
Not completed	5	6	2
Adverse event, non-fatal	-	1	1
Other, not specified	1	2	-
Lost to follow-up	-	3	-
Withdrawal by subject	4	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ELS placebo/UPA placebo
Reporting group description:	
Placebo capsule for elsubrutinib once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks	
Reporting group title	UPA 15 mg/ELS 60 mg
Reporting group description:	
15 mg film-coated upadacitinib tablet once a day by mouth for 12 weeks; 60 mg elsubrutinib capsule once a day by mouth for 12 weeks	
Reporting group title	ELS 60 mg/UPA placebo
Reporting group description:	
60 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks	
Reporting group title	ELS 20 mg/UPA placebo
Reporting group description:	
20 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks	
Reporting group title	ELS 5 mg/UPA placebo
Reporting group description:	
5 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks	
Reporting group title	UPA 15 mg/ELS placebo
Reporting group description:	
15 mg film-coated upadacitinib tablet once a day by mouth for 12 weeks; placebo capsule for elsubrutinib once a day by mouth for 12 weeks	

Reporting group values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo
Number of subjects	19	62	41
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	57.6	56.2	59.2
standard deviation	± 9.12	± 12.82	± 11.11
Gender categorical			
Units: Subjects			
Female	17	48	36
Male	2	14	5

Reporting group values	ELS 20 mg/UPA placebo	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo
Number of subjects	39	41	40
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	59.7	58.1	57.7
standard deviation	± 10.95	± 11.01	± 10.60
Gender categorical			
Units: Subjects			
Female	35	33	35
Male	4	8	5

Reporting group values	Total		
Number of subjects	242		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	204		
Male	38		

End points

End points reporting groups

Reporting group title	ELS placebo/UPA placebo
Reporting group description:	
Placebo capsule for elsubrutinib once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks	
Reporting group title	UPA 15 mg/ELS 60 mg
Reporting group description:	
15 mg film-coated upadacitinib tablet once a day by mouth for 12 weeks; 60 mg elsubrutinib capsule once a day by mouth for 12 weeks	
Reporting group title	ELS 60 mg/UPA placebo
Reporting group description:	
60 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks	
Reporting group title	ELS 20 mg/UPA placebo
Reporting group description:	
20 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks	
Reporting group title	ELS 5 mg/UPA placebo
Reporting group description:	
5 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks	
Reporting group title	UPA 15 mg/ELS placebo
Reporting group description:	
15 mg film-coated upadacitinib tablet once a day by mouth for 12 weeks; placebo capsule for elsubrutinib once a day by mouth for 12 weeks	

Primary: Change From Baseline in Disease Activity Score 28 C-reactive Protein [DAS28-CRP]) at Week 12

End point title	Change From Baseline in Disease Activity Score 28 C-reactive Protein [DAS28-CRP]) at Week 12
End point description:	
The DAS28-CRP is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (0-100 mm), and high-sensitivity C-reactive protein (hsCRP; in mg/L). Scores on the DAS28-CRP range from 0 to approximately 10, where higher scores indicate more disease activity. Baseline is defined as the last non-missing value prior to the first dose of study drug. A negative change from baseline indicates improvement in disease activity.	

End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[1]	54[2]	35[3]	29[4]
Units: units on a scale				
least squares mean (confidence interval 90%)	-1.12 (-1.64 to -0.60)	-2.56 (-2.86 to -2.26)	-1.52 (-1.89 to -1.15)	-1.32 (-1.71 to -0.93)

Notes:

[1] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[2] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[3] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[4] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34[5]	37[6]		
Units: units on a scale				
least squares mean (confidence interval 90%)	-1.33 (-1.70 to -0.97)	-2.87 (-3.23 to -2.51)		

Notes:

[5] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[6] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

Statistical analysis title	UPA 15 mg/ELS 60 mg vs ELS Placebo/UPA Placebo

Statistical analysis description:

Mixed-Effect Model Repeated Measure (MMRM) analysis was conducted, testing the superiority of the combination of upadacitinib 15 mg and elsubrutinib 60 mg compared to placebo at Week 12. Data collected after a participant discontinued study drug was considered as missing. The mixed model included the categorical fixed effects of treatment, visit and treatment-by-visit interaction, prior bDMARD use, and baseline DAS28 (CRP) measurement.

Comparison groups	ELS placebo/UPA placebo v UPA 15 mg/ELS 60 mg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	LS Mean Difference
Point estimate	-1.44
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.03
upper limit	-0.85
Variability estimate	Standard error of the mean
Dispersion value	0.36

Secondary: Change from Baseline in Clinical Disease Activity Index (CDAI)

End point title	Change from Baseline in Clinical Disease Activity Index (CDAI)

End point description:

The CDAI is a composite index for assessing disease activity based on the summation of the total tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), patient global assessment of disease activity measured on a VAS from 0 to 10 cm, and physician global assessment of disease activity measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 78 with higher scores indicating higher disease activity. Baseline is defined as the last non-missing value prior to the first dose of study drug. A negative change from baseline indicates improvement in disease activity.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[7]	57[8]	38[9]	35[10]
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=17, 56, 38, 35, 35, 37)	-6.08 (-10.48 to -1.67)	-16.00 (-18.53 to -13.47)	-8.95 (-11.99 to -5.91)	-7.36 (-10.44 to -4.27)
Week 4 (n=17, 57, 37, 34, 37, 37)	-11.60 (-16.38 to -6.82)	-20.24 (-22.97 to -17.50)	-11.67 (-15.01 to -8.34)	-10.10 (-13.50 to -6.70)
Week 8 (n= 17, 56, 35, 31, 35, 37)	-12.46 (-17.52 to -7.40)	-24.95 (-27.86 to -22.05)	-15.07 (-18.65 to -11.49)	-17.10 (-20.83 to -13.38)
Week 12 (n= 18, 52, 35, 29, 33, 36))	-14.57 (-19.77 to -9.36)	-27.00 (-30.05 to -23.95)	-17.50 (-21.22 to -13.78)	-16.70 (-20.62 to -12.78)

Notes:

[7] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[8] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[9] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[10] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[11]	37[12]		
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=17, 56, 38, 35, 35, 37)	-8.38 (-11.48 to -5.28)	-14.03 (-17.04 to -11.02)		
Week 4 (n=17, 57, 37, 34, 37, 37)	-12.90 (-16.22 to -9.58)	-20.30 (-23.57 to -17.03)		

Week 8 (n= 17, 56, 35, 31, 35, 37)	-14.84 (-18.42 to -11.26)	-23.72 (-27.20 to -20.24)		
Week 12 (n= 18, 52, 35, 29, 33, 36))	-16.51 (-20.27 to -12.75)	-28.85 (-32.48 to -25.21)		

Notes:

[11] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[12] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Clinical Remission (CR) Based on Disease Activity Score 28 C-reactive Protein [DAS28-CRP]) at Week 12

End point title	Percentage of Participants Achieving Clinical Remission (CR) Based on Disease Activity Score 28 C-reactive Protein [DAS28-CRP]) at Week 12

End point description:

The DAS28-CRP is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (0-100 mm), and high-sensitivity C-reactive protein (hsCRP; in mg/L). Scores on the DAS28-CRP range from 0 to approximately 10, where higher scores indicate more disease activity. Clinical remission (CR) based on DAS28 (CRP) is defined as achieving a DAS28 (CRP) of less than 2.6.

End point type	Secondary

End point timeframe:

At Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[13]	62[14]	41[15]	39[16]
Units: percentage of participants				
number (confidence interval 90%)	10.5 (3.55 to 27.35)	32.3 (23.41 to 42.59)	19.5 (11.36 to 31.44)	7.7 (3.12 to 17.76)

Notes:

[13] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[14] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[15] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[16] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[17]	40[18]		
Units: percentage of participants				
number (confidence interval 90%)	9.8 (4.46 to 20.04)	42.5 (30.52 to 55.43)		

Notes:

[17] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[18] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Tender Joint Count 68 (TJC68)

End point title	Change From Baseline in Tender Joint Count 68 (TJC68)

End point description:

Sixty-eight joints were assessed for tenderness by physical examination. Pain or tenderness of each joint was classifiedas present (1) or absent (0), for a total possible score of 0 (0 joints with tenderness) to 68 (worst possible score/68 joints with tenderness). Baseline is defined as the last non-missing value prior to the first dose of study drug. Negative values indicate improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[19]	61[20]	39[21]	37[22]
Units: tender joint counts				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 61, 39, 37, 39, 40)	-2.47 (-6.10 to 1.16)	-8.42 (-10.53 to -6.31)	-3.65 (-6.23 to -1.07)	-3.86 (-6.46 to -1.26)
Week 4 (n=19, 61, 38, 36, 40, 39)	-9.21 (-13.08 to -5.34)	-11.86 (-14.10 to -9.62)	-5.16 (-7.93 to -2.39)	-5.39 (-8.18 to -2.60)
Week 8 (n=18, 59, 36, 33, 38, 38)	-8.82 (-12.85 to -4.79)	-15.44 (-17.75 to -13.12)	-8.43 (-11.31 to -5.55)	-10.83 (-13.78 to -7.88)
Week 12 (n=18, 56, 36, 31, 35, 37)	-8.47 (-12.81 to -4.12)	-16.33 (-18.84 to -13.83)	-9.14 (-12.23 to -6.05)	-9.33 (-12.55 to -6.12)

Notes:

[19] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[20] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[21] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[22] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[23]	40[24]		
Units: tender joint counts				

least squares mean (confidence interval 90%)				
Week 2 (n=19, 61, 39, 37, 39, 40)	-4.88 (-7.43 to -2.33)	-8.57 (-11.09 to -6.05)		
Week 4 (n=19, 61, 38, 36, 40, 39)	-8.08 (-10.77 to -5.39)	-12.76 (-15.46 to -10.06)		
Week 8 (n=18, 59, 36, 33, 38, 38)	-9.08 (-11.88 to -6.27)	-14.76 (-17.56 to -11.97)		
Week 12 (n=18, 56, 36, 31, 35, 37)	-12.58 (-15.64 to -9.52)	-17.56 (-20.58 to -14.53)		

Notes:

[23] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[24] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response

End point title	Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response

End point description:

Participants who met the following 3 conditions for improvement from baseline were classified as meeting the American College of Rheumatology 20% response (ACR20) criteria:
1. ≥ 20% improvement in 68-tender joint count
2. ≥ 20% improvement in 66-swollen joint count and
3. ≥ 20% improvement in at least 3 of the 5 following parameters:
- Patient's Assessment of Pain (Visual Analog Scale [VAS])
- Patient’s Global Assessment of Disease Activity (PtGA)
- Physician’s Global Assessment of Disease Activity (PhGA)
- Health Assessment Questionnaire Disability Index (HAQ-DI)
- High-sensitivity C-reactive protein (hsCRP)

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[25]	62[26]	41[27]	39[28]
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	21.1 (9.82 to 39.50)	45.2 (35.19 to 55.54)	24.4 (15.17 to 36.78)	12.8 (6.38 to 24.08)
Week 4	42.1 (25.63 to 60.55)	51.6 (41.33 to 61.76)	29.3 (19.16 to 41.94)	23.1 (13.95 to 35.70)
Week 8	36.8 (21.37 to 55.59)	64.5 (54.11 to 73.71)	39.0 (27.55 to 51.86)	30.8 (20.20 to 43.84)
Week 12	47.4 (30.07 to 65.33)	64.5 (54.11 to 73.71)	41.5 (29.72 to 54.26)	30.8 (20.20 to 43.84)

Notes:

[25] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[26] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[27] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[28] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	14.6 (7.76 to 25.89)	52.5 (39.77 to 64.91)		
Week 4	22.0 (13.24 to 34.13)	55.0 (42.16 to 67.21)		
Week 8	39.0 (27.55 to 51.86)	67.5 (54.55 to 78.23)		
Week 12	34.1 (23.29 to 46.97)	72.5 (59.75 to 82.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Low Disease Activity (LDA) Based on Disease Activity Score 28 C-reactive Protein [DAS28-CRP]) at Week 12

End point title	Percentage of Participants Achieving Low Disease Activity (LDA) Based on Disease Activity Score 28 C-reactive Protein [DAS28-CRP]) at Week 12

End point description:

The DAS28-CRP is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (0-100 mm), and high-sensitivity C-reactive protein (hsCRP; in mg/L). Scores on the DAS28-CRP range from 0 to approximately 10, where higher scores indicate more disease activity. Low Disease Activity (LDA) based on DAS28 (CRP) is defined as achieving a DAS28 (CRP) of less than or equal to 3.2.

End point type	Secondary

End point timeframe:

At Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[29]	62[30]	41[31]	39[32]
Units: percentage of participants				
least squares mean (confidence interval 90%)	21.1 (9.82 to 39.50)	41.9 (32.18 to 52.37)	22.0 (13.24 to 34.13)	10.3 (4.69 to 20.98)

Notes:

[29] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[30] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[31] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[32] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[33]	40[34]		
Units: percentage of participants				
least squares mean (confidence interval 90%)	14.6 (7.76 to 25.89)	55.0 (42.16 to 67.21)		

Notes:

[33] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[34] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Morning Stiffness Severity

End point title	Change From Baseline in Morning Stiffness Severity

End point description:

Morning stiffness severity was assessed by a numeric rating-scale (NRS). Participants rated the severity of morning stiffness during the past week from 0 to 10 with 0 representing "not severe" and 10 "very severe". Baseline is defined as the last non-missing value prior to the first dose of study drug. Negative values indicate improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[35]	59[36]	39[37]	35[38]
Units: units on a scale				
least squares mean (confidence interval				

90%)				
Week 2 (n=19, 59, 39, 35, 38, 38)	-1.76 (-2.54 to -0.98)	-2.02 (-2.48 to -1.56)	-0.91 (-1.47 to -0.35)	-0.68 (-1.26 to -0.11)
Week 4 (n=19, 59, 37, 34, 40, 38)	-1.76 (-2.63 to -0.90)	-2.71 (-3.22 to -2.21)	-0.82 (-1.45 to -0.20)	-0.83 (-1.47 to -0.19)
Week 8 (n=18, 57, 35, 31, 38, 37)	-1.67 (-2.56 to -0.77)	-3.07 (-3.59 to -2.55)	-1.30 (-1.94 to -0.65)	-0.97 (-1.64 to -0.30)
Week 12 (n=18, 54, 34, 29, 35, 36)	-1.61 (-2.60 to -0.63)	-3.23 (-3.81 to -2.65)	-1.27 (-1.99 to -0.56)	-1.30 (-2.06 to -0.55)

Notes:

[35] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[36] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[37] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[38] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[39]	38[40]		
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 35, 38, 38)	-0.59 (-1.15 to -0.04)	-1.84 (-2.40 to -1.29)		
Week 4 (n=19, 59, 37, 34, 40, 38)	-1.08 (-1.67 to -0.48)	-2.51 (-3.13 to -1.90)		
Week 8 (n=18, 57, 35, 31, 38, 37)	-1.50 (-2.11 to -0.88)	-3.07 (-3.70 to -2.44)		
Week 12 (n=18, 54, 34, 29, 35, 36)	-1.66 (-2.36 to -0.97)	-3.36 (-4.06 to -2.67)		

Notes:

[39] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[40] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Score 28 C-reactive Protein [DAS28-CRP])

End point title	Change From Baseline in Disease Activity Score 28 C-reactive Protein [DAS28-CRP])

End point description:

The DAS28-CRP is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (0-100 mm), and high-sensitivity C-reactive protein (hsCRP; in mg/L). Scores on the DAS28-CRP range from 0 to approximately 10, where higher scores indicate more disease activity. Baseline is defined as the last non-missing value prior to the first dose of study drug. A negative change from baseline indicates improvement in disease activity.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[41]	59[42]	39[43]	35[44]
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 35, 38, 39)	-0.46 (-0.83 to -0.10)	-1.53 (-1.75 to -1.31)	-0.63 (-0.89 to -0.36)	-0.44 (-0.71 to -0.18)
Week 4 (n=19, 59, 37, 34, 40, 39)	-0.90 (-1.33 to -0.47)	-1.96 (-2.21 to -1.71)	-0.87 (-1.18 to -0.56)	-0.68 (-1.00 to -0.36)
Week 8 (n=18, 57, 35, 30, 38, 38)	-0.78 (-1.27 to -0.29)	-2.40 (-2.68 to -2.11)	-1.21 (-1.56 to -0.86)	-1.24 (-1.61 to -0.87)
Week 12 (n=18, 54, 35, 29, 34, 37)	-1.12 (-1.64 to -0.60)	-2.56 (-2.86 to -2.26)	-1.52 (-1.89 to -1.15)	-1.32 (-1.71 to -0.93)

Notes:

[41] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[42] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[43] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[44] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[45]	39[46]		
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 35, 38, 39)	-0.56 (-0.82 to -0.30)	-1.43 (-1.69 to -1.17)		
Week 4 (n=19, 59, 37, 34, 40, 39)	-0.82 (-1.11 to -0.52)	-1.98 (-2.28 to -1.67)		
Week 8 (n=18, 57, 35, 30, 38, 38)	-1.11 (-1.45 to -0.77)	-2.34 (-2.68 to -2.00)		
Week 12 (n=18, 54, 35, 29, 34, 37)	-1.33 (-1.70 to -0.97)	-2.87 (-3.23 to -2.51)		

Notes:

[45] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[46] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

End point title	Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

End point description:

The Health Assessment Questionnaire - Disability Index is a patient-reported questionnaire that measures the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores) over the past week. Participants assessed their ability to do each task on a scale from 0 (without any difficulty) to 3 (unable to do). Scores were averaged to provide an overall score ranging from 0 to 3, where 0 represents no disability and 3 represents very severe, high-dependency disability. Baseline is defined as the last non-missing value prior to the first dose of study drug. A negative change from baseline in the overall score indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[47]	59[48]	39[49]	35[50]
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 35, 38, 38)	-0.22 (-0.37 to -0.06)	-0.34 (-0.43 to -0.25)	-0.13 (-0.24 to -0.02)	-0.06 (-0.17 to 0.05)
Week 4 (n=19, 59, 37, 34, 40, 38)	-0.36 (-0.53 to -0.18)	-0.39 (-0.49 to -0.29)	-0.11 (-0.23 to 0.02)	-0.14 (-0.27 to -0.02)
Week 8 (n=18, 57, 35, 31, 38, 37)	-0.24 (-0.44 to -0.05)	-0.47 (-0.59 to -0.36)	-0.29 (-0.43 to -0.15)	-0.15 (-0.30 to -0.00)
Week 12 (n=18, 54, 35, 29, 35, 36)	-0.30 (-0.52 to -0.08)	-0.52 (-0.65 to -0.39)	-0.31 (-0.46 to -0.15)	-0.12 (-0.28 to 0.05)

Notes:

[47] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[48] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[49] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[50] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[51]	38[52]		
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 35, 38, 38)	-0.16 (-0.27 to -0.05)	-0.22 (-0.33 to -0.11)		
Week 4 (n=19, 59, 37, 34, 40, 38)	-0.21 (-0.33 to -0.09)	-0.33 (-0.45 to -0.20)		
Week 8 (n=18, 57, 35, 31, 38, 37)	-0.15 (-0.29 to -0.02)	-0.47 (-0.61 to -0.33)		
Week 12 (n=18, 54, 35, 29, 35, 36)	-0.18 (-0.33 to -0.03)	-0.54 (-0.70 to -0.39)		

Notes:

[51] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[52] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving American College of Rheumatology/European League Against Rheumatism (EULAR) Boolean Remission

End point title	Percentage of Participants Achieving American College of Rheumatology/European League Against Rheumatism (EULAR) Boolean Remission

End point description:

The EULAR Boolean-based definition of remission is as follows: at any time point, a participant must satisfy all of the following: tender joint count ≤1, swollen joint count ≤1, C-reactive protein ≤1 mg/dl and Patient Global Assessment (PGA) ≤1 (on a 0–10 scale).

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[53]	62[54]	41[55]	39[56]
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	0 (0.00 to 12.46)	1.6 (0.36 to 6.91)	0 (0.00 to 6.19)	0 (0.00 to 6.49)
Week 4	0 (0.00 to 12.46)	6.5 (2.93 to 13.62)	2.4 (0.55 to 10.22)	0 (0.00 to 6.49)
Week 8	0 (0.00 to 12.46)	6.5 (2.93 to 13.62)	2.4 (0.55 to 10.22)	5.1 (1.71 to 14.37)
Week 12	0 (0.00 to 12.46)	11.3 (6.24 to 19.58)	9.8 (4.46 to 20.04)	2.6 (0.57 to 10.71)

Notes:

[53] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[54] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[55] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[56] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[57]	40[58]		

Units: percentage of participants				
number (confidence interval 90%)				
Week 2	0 (0.00 to 6.19)	0 (0.00 to 6.34)		
Week 4	0 (0.00 to 6.19)	2.5 (0.56 to 10.46)		
Week 8	0 (0.00 to 6.19)	12.5 (6.22 to 23.53)		
Week 12	2.4 (0.55 to 10.22)	10.0 (4.57 to 20.50)		

Notes:

[57] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[58] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Minimal Clinically Important Difference (MCID) in Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

End point title	Percentage of Participants Achieving Minimal Clinically Important Difference (MCID) in Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

End point description:

The Health Assessment Questionnaire - Disability Index is a patient-reported questionnaire that measures the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores) over the past week. Participants assessed their ability to do each task on a scale from 0 (without any difficulty) to 3 (unable to do). Scores were averaged to provide an overall score ranging from 0 to 3, where 0 represents no disability and 3 represents very severe, high-dependency disability. The minimal clinically important difference (MCID) in HAQ-DI is defined as change from Baseline ≤ -0.22 for rheumatoid arthritis.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[59]	62[60]	41[61]	39[62]
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	52.6 (34.67 to 69.93)	51.6 (41.33 to 61.76)	36.6 (25.40 to 49.43)	30.8 (20.20 to 43.84)
Week 4	68.4 (49.55 to 82.70)	54.8 (44.46 to 64.81)	34.1 (23.29 to 46.97)	41.0 (29.07 to 54.15)
Week 8	52.6 (34.67 to 69.93)	58.1 (47.63 to 67.82)	51.2 (38.71 to 63.58)	51.3 (38.47 to 63.93)
Week 12	47.4 (30.07 to 65.33)	58.1 (47.63 to 67.82)	53.7 (41.02 to 65.84)	43.6 (31.37 to 56.64)

Notes:

[59] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[60] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[61] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[62] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[63]	40[64]		
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	36.6 (25.40 to 49.43)	52.5 (39.77 to 64.91)		
Week 4	53.7 (41.02 to 65.84)	45.0 (32.79 to 57.84)		
Week 8	36.6 (25.40 to 49.43)	65.0 (52.01 to 76.09)		
Week 12	43.9 (31.93 to 56.63)	55.0 (42.16 to 67.21)		

Notes:

[63] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[64] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simplified Disease Activity Index (SDAI)

End point title	Change From Baseline in Simplified Disease Activity Index (SDAI)

End point description:

The SDAI is a validated measure of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, global disease activity assessed by the participant on a visual analogue scale from 0 to 10 (cm), global disease activity assessed by an investigator on a visual analogue scale from 0 to 10 (cm), and serum levels of C-reactive protein (CRP; mg/dL) were included in the SDAI score. Scores on the SDAI range from 0 to 86.with higher scores indicating higher disease activity. Baseline is defined as the last non-missing value prior to the first dose of study drug. A negative change from baseline indicates improvement in disease activity.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[65]	57[66]	38[67]	35[68]
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=17, 56, 38, 35, 35, 37)	-6.17 (-10.67 to -1.67)	-17.01 (-19.60 to -14.43)	-8.79 (-11.89 to -5.68)	-7.42 (-10.57 to -4.26)
Week 4 (n=17, 57, 37, 34, 37, 37)	-11.80 (-16.67 to -6.93)	-21.24 (-24.02 to -18.45)	-11.46 (-14.85 to -8.06)	-10.15 (-13.61 to -6.68)
Week 8 (n=17, 56, 35, 30, 35, 37)	-12.15 (-17.35 to -6.95)	-25.96 (-28.95 to -22.98)	-15.26 (-18.94 to -11.57)	-17.32 (-21.17 to -13.46)
Week 12 (n=18, 52, 35, 29, 32, 36)	-14.44 (-19.84 to -9.04)	-28.06 (-31.22 to -24.89)	-18.01 (-21.86 to -14.15)	-17.12 (-21.20 to -13.05)

Notes:

[65] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[66] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[67] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[68] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[69]	37[70]		
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=17, 56, 38, 35, 35, 37)	-8.54 (-11.71 to -5.38)	-15.30 (-18.37 to -12.22)		
Week 4 (n=17, 57, 37, 34, 37, 37)	-12.87 (-16.25 to -9.49)	-21.59 (-24.92 to -18.26)		
Week 8 (n=17, 56, 35, 30, 35, 37)	-15.21 (-18.89 to -11.53)	-25.07 (-28.65 to -21.49)		
Week 12 (n=18, 52, 35, 29, 32, 36)	-16.73 (-20.65 to -12.81)	-29.65 (-33.42 to -25.88)		

Notes:

[69] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[70] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response

End point title	Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response

End point description:

Participants who met the following 3 conditions for improvement from baseline were classified as meeting the American College of Rheumatology 50% response (ACR50) criteria:
1. ≥ 50% improvement in 68-tender joint count
2. ≥ 50% improvement in 66-swollen joint count and

3. ≥ 50% improvement in at least 3 of the 5 following parameters:
• Patient's Assessment of Pain (Visual Analog Scale [VAS])
• Patient’s Global Assessment of Disease Activity (PtGA)
• Physician’s Global Assessment of Disease Activity (PhGA)
• Health Assessment Questionnaire Disability Index (HAQ-DI)
• High-sensitivity C-reactive protein (hsCRP)

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[71]	62[72]	41[73]	39[74]
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	0 (0.00 to 12.46)	16.1 (9.89 to 25.20)	4.9 (1.63 to 13.71)	0 (0.00 to 6.49)
Week 4	10.5 (3.55 to 27.35)	19.4 (12.46 to 28.82)	17.1 (9.53 to 28.69)	2.6 (0.57 to 10.71)
Week 8	5.3 (1.18 to 20.50)	41.9 (32.18 to 52.37)	19.5 (11.36 to 31.44)	12.8 (6.38 to 24.08)
Week 12	21.1 (9.82 to 39.50)	45.2 (35.19 to 55.54)	29.3 (19.16 to 41.94)	12.8 (6.38 to 24.08)

Notes:

[71] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[72] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[73] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[74] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[75]	40[76]		
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	0 (0.00 to 6.19)	12.5 (6.22 to 23.53)		
Week 4	4.9 (1.63 to 13.71)	30.0 (19.66 to 42.87)		
Week 8	7.3 (2.96 to 16.96)	40.0 (28.29 to 52.98)		
Week 12	17.1 (9.53 to 28.69)	47.5 (35.09 to 60.23)		

Notes:

[75] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[76] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response

End point title	Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response

End point description:

Participants who met the following 3 conditions for improvement from baseline were classified as meeting the American College of Rheumatology 70% response (ACR70) criteria:
1. ≥ 70% improvement in 68-tender joint count
2. ≥ 70% improvement in 66-swollen joint count and
3. ≥ 70% improvement in at least 3 of the 5 following parameters:
• Patient's Assessment of Pain (Visual Analog Scale [VAS])
• Patient's Global Assessment of Disease Activity (PtGA)
• Physician's Global Assessment of Disease Activity (PhGA)
• Health Assessment Questionnaire Disability Index (HAQ-DI)
• High-sensitivity C-reactive protein (hsCRP)

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[77]	62[78]	41[79]	39[80]
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	0 (0.00 to 12.46)	8.1 (3.98 to 15.66)	2.4 (0.55 to 10.22)	0 (0.00 to 6.49)
Week 4	0 (0.00 to 12.46)	9.7 (5.09 to 17.64)	4.9 (1.63 to 13.71)	2.6 (0.57 to 10.71)
Week 8	0 (0.00 to 12.46)	17.7 (11.16 to 27.02)	4.9 (1.63 to 13.71)	2.6 (0.57 to 10.71)
Week 12	15.8 (6.49 to 33.62)	25.8 (17.81 to 35.82)	14.6 (7.76 to 25.89)	5.1 (1.71 to 14.37)

Notes:

[77] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[78] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[79] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[80] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[81]	40[82]		
Units: percentage of participants				
number (confidence interval 90%)				

Week 2	0 (0.00 to 6.19)	0 (0.00 to 6.34)		
Week 4	0 (0.00 to 6.19)	15.0 (7.96 to 26.47)		
Week 8	0 (0.00 to 6.19)	25.0 (15.57 to 37.60)		
Week 12	9.8 (4.46 to 20.04)	27.5 (17.60 to 40.25)		

Notes:

[81] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[82] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in High-Sensitivity C-reactive Protein (hsCRP)

End point title	Change From Baseline in High-Sensitivity C-reactive Protein (hsCRP)

End point description:

C-reactive protein is a blood test marker for inflammation in the body, and levels rise in response to inflammation. Baseline is defined as the last non-missing value prior to the first dose of study drug. A negative change from baseline in indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[83]	61[84]	39[85]	37[86]
Units: mg/L				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 61, 39, 37, 39, 40)	-0.51 (-4.82 to 3.81)	-9.29 (-11.79 to -6.80)	2.26 (-0.81 to 5.33)	-0.34 (-3.43 to 2.74)
Week 4 (n=19, 61, 38, 36, 40, 39)	1.54 (-3.72 to 6.79)	-10.08 (-13.08 to -7.08)	2.71 (-1.05 to 6.46)	-0.78 (-4.58 to 3.02)
Week 8 (n=18, 59, 36, 32, 38, 38)	3.23 (-1.56 to 8.03)	-9.97 (-12.70 to -7.24)	-1.39 (-4.83 to 2.05)	-2.58 (-6.15 to 1.00)
Week 12 (n=18, 56, 36, 31, 34, 37)	1.45 (-5.10 to 8.00)	-10.95 (-14.73 to -7.18)	-4.58 (-9.26 to 0.09)	-5.78 (-10.77 to -0.78)

Notes:

[83] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[84] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[85] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[86] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline

values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[87]	40[88]		
Units: mg/L				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 61, 39, 37, 39, 40)	-0.72 (-3.74 to 2.30)	-12.27 (-15.26 to -9.27)		
Week 4 (n=19, 61, 38, 36, 40, 39)	0.72 (-2.91 to 4.35)	-12.59 (-16.27 to -8.92)		
Week 8 (n=18, 59, 36, 32, 38, 38)	-2.93 (-6.26 to 0.39)	-13.13 (-16.46 to -9.81)		
Week 12 (n=18, 56, 36, 31, 34, 37)	-0.81 (-5.58 to 3.97)	-7.44 (-12.03 to -2.86)		

Notes:

[87] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[88] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28- ESR)

End point title	Change From Baseline in Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28- ESR)

End point description:

The DAS28-ESR is a validated index of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, the erythrocyte sedimentation rate (ESR; mm/hour), and the participant's assessment of global disease activity (on a visual analog scale [VAS] from 0 to 100 mm) are included in the DAS28 -ESR score. Scores on the DAS28-ESR range from 0 to 10; higher scores indicate more disease activity. Baseline is defined as the last non-missing value prior to the first dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[89]	59[90]	39[91]	34[92]
Units: units on a scale				
least squares mean (confidence interval 90%)				

Week 2 (n=19, 59, 39, 34, 38, 39)	-0.46 (-0.82 to -0.09)	-1.48 (-1.69 to -1.26)	-0.52 (-0.79 to -0.26)	-0.46 (-0.74 to -0.19)
Week 4 (n=19, 58, 37, 34, 40, 39)	-0.86 (-1.30 to -0.43)	-1.93 (-2.19 to -1.68)	-0.79 (-1.11 to -0.48)	-0.59 (-0.91 to -0.26)
Week 8 (n=18, 57, 35, 30, 37, 38)	-0.80 (-1.29 to -0.31)	-2.41 (-2.69 to -2.12)	-1.07 (-1.42 to -0.71)	-1.15 (-1.52 to -0.78)
Week 12 (n=18, 54, 35, 29, 35, 37)	-1.18 (-1.71 to -0.64)	-2.53 (-2.84 to -2.22)	-1.41 (-1.80 to -1.03)	-1.24 (-1.65 to -0.83)

Notes:

[89] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[90] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[91] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[92] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[93]	39[94]		
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 34, 38, 39)	-0.57 (-0.83 to -0.32)	-1.32 (-1.58 to -1.06)		
Week 4 (n=19, 58, 37, 34, 40, 39)	-0.92 (-1.23 to -0.62)	-1.90 (-2.20 to -1.59)		
Week 8 (n=18, 57, 35, 30, 37, 38)	-1.20 (-1.54 to -0.86)	-2.31 (-2.65 to -1.97)		
Week 12 (n=18, 54, 35, 29, 35, 37)	-1.44 (-1.82 to -1.06)	-2.88 (-3.25 to -2.50)		

Notes:

[93] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[94] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Low Disease Activity (LDA) Based on Clinical Disease Activity Index (CDAI) Criteria

End point title	Percentage of Participants Achieving Low Disease Activity (LDA) Based on Clinical Disease Activity Index (CDAI) Criteria

End point description:

The CDAI is a composite index for assessing disease activity based on the summation of the total tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), patient global assessment of disease activity measured on a VAS from 0 to 10 cm, and physician global assessment of disease activity measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 78 with higher scores indicating higher disease activity. Low Disease Activity (LDA) based on CDAI is defined as achieving a CDAI of less than or equal to 10.

End point type	Secondary

End point timeframe:

Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[95]	62[96]	41[97]	39[98]
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	10.5 (3.55 to 27.35)	16.1 (9.89 to 25.20)	9.8 (4.46 to 20.04)	0 (0.00 to 6.49)
Week 4	10.5 (3.55 to 27.35)	29.0 (20.59 to 39.23)	12.2 (6.06 to 23.01)	7.7 (3.12 to 17.76)
Week 8	5.3 (1.18 to 20.50)	46.8 (36.71 to 57.11)	17.1 (9.53 to 28.69)	20.5 (11.96 to 32.89)
Week 12	26.3 (13.44 to 45.09)	37.1 (27.74 to 47.53)	34.1 (23.29 to 46.97)	17.9 (10.03 to 30.02)

Notes:

[95] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[96] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[97] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[98] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[99]	40[100]		
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	2.4 (0.55 to 10.22)	12.5 (6.22 to 23.53)		
Week 4	12.2 (6.06 to 23.01)	22.5 (13.59 to 34.90)		
Week 8	24.4 (15.17 to 36.78)	35.0 (23.91 to 47.99)		
Week 12	17.1 (9.53 to 28.69)	57.5 (44.57 to 69.48)		

Notes:

[99] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data
[100] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Complete Remission (CR) Based on Clinical Disease Activity Index (CDAI) Criteria

End point title	Percentage of Participants Achieving Complete Remission (CR) Based on Clinical Disease Activity Index (CDAI) Criteria

End point description:

The CDAI is a composite index for assessing disease activity based on the summation of the total tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), patient global assessment of disease activity measured on a VAS from 0 to 10 cm, and physician global assessment of disease activity measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 78 with higher scores indicating higher disease activity. Complete Remission (CR) based on CDAI is defined as achieving a CDAI of less than or equal to 2.8.

End point type	Secondary

End point timeframe:

Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[101]	62[102]	41[103]	39[104]
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	0 (0.00 to 12.46)	3.2 (1.07 to 9.29)	0 (0.00 to 6.19)	0 (0.00 to 6.49)
Week 4	0 (0.00 to 12.46)	6.5 (2.93 to 13.62)	2.4 (0.55 to 10.22)	2.6 (0.57 to 10.71)
Week 8	0 (0.00 to 12.46)	12.9 (7.43 to 21.48)	7.3 (2.96 to 16.96)	2.6 (0.57 to 10.71)
Week 12	5.3 (1.18 to 20.50)	14.5 (8.65 to 23.35)	7.3 (2.96 to 16.96)	5.1 (1.71 to 14.37)

Notes:

[101] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[102] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[103] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[104] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[105]	40[106]		
Units: percentage of participants				
number (confidence interval 90%)				
Week 2	0 (0.00 to 6.19)	0 (0.00 to 6.34)		
Week 4	0 (0.00 to 6.19)	2.5 (0.56 to 10.46)		
Week 8	2.4 (0.55 to 10.22)	12.5 (6.22 to 23.53)		
Week 12	0 (0.00 to 6.19)	15.0 (7.96 to 26.47)		

Notes:

[105] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

[106] - FAS:randomized subjects rcvd ≥1 dose randomized study drug, nonresponder imputation for missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swollen Joint Count 66 (SJC66)

End point title	Change From Baseline in Swollen Joint Count 66 (SJC66)

End point description:

Sixty-six joints were assessed for swelling by physical examination. Swelling of each joint was classified as present (1) or absent (0), for a total possible score of 0 (0 joints with swelling) to 66 (worst possible score/66 joints with swelling). Baseline is defined as the last non-missing value prior to the first dose of study drug. Negative values indicate improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[107]	61[108]	39[109]	37[110]
Units: swollen joint counts				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 61, 39, 37, 39, 40)	-3.12 (-5.20 to -1.05)	-6.06 (-7.26 to -4.86)	-3.61 (-5.08 to -2.14)	-3.30 (-4.78 to -1.82)
Week 4 (n=19, 61, 38, 36, 40, 39)	-4.70 (-6.92 to -2.49)	-7.96 (-9.24 to -6.68)	-5.11 (-6.69 to -3.53)	-4.67 (-6.27 to -3.07)
Week 8 (n=18, 59, 36, 33, 38, 38)	-4.32 (-6.57 to -2.06)	-10.28 (-11.57 to -8.99)	-6.15 (-7.77 to -4.54)	-8.08 (-9.74 to -6.42)
Week 12 (n=18, 56, 36, 31, 35, 37)	-5.58 (-8.05 to -3.11)	-10.86 (-12.29 to -9.44)	-6.68 (-8.44 to -4.92)	-7.85 (-9.70 to -6.01)

Notes:

[107] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[108] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[109] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[110] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[111]	40[112]		
Units: swollen joint counts				

least squares mean (confidence interval 90%)				
Week 2 (n=19, 61, 39, 37, 39, 40)	-4.13 (-5.60 to -2.67)	-6.02 (-7.46 to -4.58)		
Week 4 (n=19, 61, 38, 36, 40, 39)	-6.05 (-7.60 to -4.51)	-8.81 (-10.35 to -7.26)		
Week 8 (n=18, 59, 36, 33, 38, 38)	-7.58 (-9.15 to -6.00)	-10.11 (-11.68 to -8.55)		
Week 12 (n=18, 56, 36, 31, 35, 37)	-8.59 (-10.35 to -6.83)	-11.14 (-12.86 to -9.42)		

Notes:

[111] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[112] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Participant's Assessment of Pain (Visual Analog Scale [VAS])

End point title	Change From Baseline in Participant's Assessment of Pain (Visual Analog Scale [VAS])

End point description:

Participants rated their pain on a visual analogue scale (VAS) of 0 to 100 (mm), with 0 representing no pain and 100 representing the worst possible pain. Baseline is defined as the last non-missing value prior to the first dose of study drug. Negative values indicate improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[113]	59[114]	39[115]	35[116]
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 35, 38, 39)	-14.97 (-22.80 to -7.14)	-24.02 (-28.63 to -19.41)	-10.22 (-15.81 to -4.63)	-8.78 (-14.49 to -3.07)
Week 4 (n=19, 59, 37, 34, 40, 39)	-20.87 (-29.60 to -12.14)	-28.17 (-33.28 to -23.07)	-12.95 (-19.27 to -6.63)	-8.41 (-14.85 to -1.97)
Week 8 (n=18, 57, 35, 31, 38, 38)	-16.21 (-25.97 to -6.45)	-31.86 (-37.50 to -26.22)	-20.92 (-27.96 to -13.88)	-11.12 (-18.46 to -3.79)
Week 12 (n=18, 54, 35, 29, 35, 37)	-23.37 (-33.74 to -13.01)	-32.27 (-38.32 to -26.23)	-19.52 (-26.97 to -12.06)	-10.46 (-18.38 to -2.55)

Notes:

[113] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[114] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[115] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-

baseline values

[116] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[117]	39[118]		
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 35, 38, 39)	-7.61 (-13.12 to -2.11)	-15.99 (-21.49 to -10.48)		
Week 4 (n=19, 59, 37, 34, 40, 39)	-9.91 (-15.93 to -3.88)	-25.58 (-31.69 to -19.48)		
Week 8 (n=18, 57, 35, 31, 38, 38)	-13.90 (-20.64 to -7.16)	-30.70 (-37.47 to -23.92)		
Week 12 (n=18, 54, 35, 29, 35, 37)	-17.84 (-25.13 to -10.55)	-38.34 (-45.57 to -31.12)		

Notes:

[117] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[118] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient's Global Assessment of Disease Activity (PGA)

End point title	Change From Baseline in Patient's Global Assessment of Disease Activity (PGA)

End point description:

Participants rated their disease activity for the past 24 hours using a Patient’s Global Assessment of Disease Activity Global visual analogue scale (VAS). The range is 0 to 100 mm, with 0 representing no disease activity and 100 representing severe disease activity. Negative values indicate improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[119]	59[120]	39[121]	35[122]
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 35, 38, 39)	-11.87 (-20.12 to -3.63)	-23.44 (-28.31 to -18.57)	-11.16 (-17.07 to -5.25)	-6.47 (-12.51 to -0.44)

Week 4 (n=19, 59, 37, 34, 40, 39)	-20.93 (-29.91 to -11.94)	-25.97 (-31.24 to -20.70)	-12.79 (-19.32 to -6.26)	-7.15 (-13.79 to -0.50)
Week 8 (n=18, 57, 35, 31, 38, 38)	-15.14 (-25.37 to -4.91)	-28.05 (-33.97 to -22.13)	-17.25 (-24.65 to -9.84)	-6.27 (-14.00 to 1.45)
Week 12 (n=18, 54, 35, 29, 35, 37)	-19.55 (-30.15 to -8.95)	-30.52 (-36.72 to -24.32)	-19.47 (-27.13 to -11.81)	-8.45 (-16.58 to -0.33)

Notes:

[119] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[120] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[121] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[122] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[123]	39[124]		
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=19, 59, 39, 35, 38, 39)	-5.95 (-11.76 to -0.14)	-14.76 (-20.56 to -8.95)		
Week 4 (n=19, 59, 37, 34, 40, 39)	-8.73 (-14.94 to -2.51)	-23.02 (-29.31 to -16.73)		
Week 8 (n=18, 57, 35, 31, 38, 38)	-14.25 (-21.34 to -7.17)	-26.79 (-33.90 to -19.69)		
Week 12 (n=18, 54, 35, 29, 35, 37)	-16.40 (-23.89 to -8.92)	-33.53 (-40.94 to -26.13)		

Notes:

[123] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values
[124] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physician's Global Assessment of Disease Activity (PhGA)

End point title	Change From Baseline in Physician's Global Assessment of Disease Activity (PhGA)

End point description:

The physician assessed a participant’s disease activity at the time of the visit using a Physician's Global Assessment of Disease visual analogue scale (VAS). The range is 0 to 100 mm, with 0 representing no disease activity and 100 representing severe disease activity. Negative values indicate improvement from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, and Week 12

End point values	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo	ELS 20 mg/UPA placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[125]	58[126]	38[127]	35[128]
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=17, 57, 38, 35, 36, 38)	-16.31 (-24.67 to -7.96)	-22.35 (-27.10 to -17.60)	-19.01 (-24.74 to -13.27)	-16.12 (-21.97 to -10.26)
Week 4 (n=17, 58, 37, 34, 37, 37)	-25.20 (-33.52 to -16.89)	-33.54 (-38.26 to -28.82)	-25.33 (-31.11 to -19.55)	-19.59 (-25.49 to -13.69)
Week 8 (n=17, 57, 35, 31, 35, 37)	-24.47 (-32.71 to -16.22)	-40.00 (-44.71 to -35.29)	-30.06 (-35.91 to -24.22)	-33.93 (-39.99 to -27.87)
Week 12 (n=18, 53, 35, 29, 33, 36)	-23.19 (-31.69 to -14.69)	-46.98 (-52.00 to -41.96)	-30.15 (-36.28 to -24.03)	-31.68 (-38.19 to -25.18)

Notes:

[125] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[126] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[127] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[128] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

End point values	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[129]	38[130]		
Units: units on a scale				
least squares mean (confidence interval 90%)				
Week 2 (n=17, 57, 38, 35, 36, 38)	-11.64 (-17.44 to -5.84)	-24.71 (-30.37 to -19.05)		
Week 4 (n=17, 58, 37, 34, 37, 37)	-18.31 (-24.05 to -12.56)	-34.17 (-39.86 to -28.49)		
Week 8 (n=17, 57, 35, 31, 35, 37)	-25.21 (-31.03 to -19.40)	-41.02 (-46.69 to -35.36)		
Week 12 (n=18, 53, 35, 29, 33, 36)	-24.55 (-30.75 to -18.36)	-50.89 (-56.87 to -44.91)		

Notes:

[129] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

[130] - FAS: randomized, rcvd ≥ 1 dose randomized study drug, non-missing baseline, ≥ 1 post-baseline values

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) collected from 1st dose of study drug until 30 d after last dose, up to 16 wks. SAEs and protocol-related nonserious AEs were collected from the time the subject signed consent.

Adverse event reporting additional description:

TEAEs and SAEs are defined as any AE or SAE with onset or worsening reported by a participant from the time that the first dose of study drug is administered until 30 days have elapsed following discontinuation of study drug. TEAEs were collected whether elicited or spontaneously reported by the participant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	ELS placebo/UPA placebo

Reporting group description:

Placebo capsule for elsubrutinib once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks

Reporting group title	UPA 15 mg/ELS 60 mg

Reporting group description:

15 mg film-coated upadacitinib tablet once a day by mouth for 12 weeks; 60 mg elsubrutinib capsule once a day by mouth for 12 weeks

Reporting group title	ELS 60 mg/UPA placebo

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks

Reporting group title	ELS 20 mg/UPA placebo

Reporting group description:

20 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks

Reporting group title	ELS 5 mg/UPA placebo

Reporting group description:

5 mg elsubrutinib capsule once a day by mouth for 12 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for 12 weeks

Reporting group title	UPA 15 mg/ELS placebo

Reporting group description:

15 mg film-coated upadacitinib tablet once a day by mouth for 12 weeks; placebo capsule for elsubrutinib once a day by mouth for 12 weeks

Serious adverse events	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	0 / 41 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			

PROSTATIC SPECIFIC ANTIGEN INCREASED			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RIB FRACTURE			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
CARDIAC ARREST			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
LUMBAR RADICULOPATHY			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
PYELONEPHRITIS			

subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ELS 20 mg/UPA placebo	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 39 (5.13%)	3 / 41 (7.32%)	0 / 40 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Investigations			
PROSTATIC SPECIFIC ANTIGEN INCREASED			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (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 / 39 (0.00%)	1 / 41 (2.44%)	0 / 40 (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
RIB FRACTURE			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 40 (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
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 40 (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
Cardiac disorders			
CARDIAC ARREST			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CORONARY ARTERY DISEASE			

subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 40 (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
Nervous system disorders			
LUMBAR RADICULOPATHY			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 40 (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			
PYELONEPHRITIS			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 40 (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

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

Non-serious adverse events	ELS placebo/UPA placebo	UPA 15 mg/ELS 60 mg	ELS 60 mg/UPA placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 19 (52.63%)	7 / 62 (11.29%)	17 / 41 (41.46%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
BLOOD GLUCOSE INCREASED			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ENDOMETRIAL ADENOCARCINOMA			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
ANIMAL BITE			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
General disorders and administration			

site conditions			
PERIPHERAL SWELLING			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 19 (0.00%)	1 / 62 (1.61%)	2 / 41 (4.88%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
ERYTHEMA			
subjects affected / exposed	1 / 19 (5.26%)	1 / 62 (1.61%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 19 (5.26%)	1 / 62 (1.61%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
ARTHRITIS			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
BONE DEFORMITY			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
RHEUMATOID ARTHRITIS			
subjects affected / exposed	2 / 19 (10.53%)	0 / 62 (0.00%)	3 / 41 (7.32%)
occurrences (all)	2	0	3
Infections and infestations			

BRONCHITIS			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
SINUSITIS			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
TOOTH INFECTION			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 19 (5.26%)	4 / 62 (6.45%)	2 / 41 (4.88%)
occurrences (all)	1	4	2
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 19 (0.00%)	0 / 62 (0.00%)	4 / 41 (9.76%)
occurrences (all)	0	0	5
Metabolism and nutrition disorders			
VITAMIN D DEFICIENCY			
subjects affected / exposed	1 / 19 (5.26%)	0 / 62 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	ELS 20 mg/UPA placebo	ELS 5 mg/UPA placebo	UPA 15 mg/ELS placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 39 (25.64%)	8 / 41 (19.51%)	9 / 40 (22.50%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
BLOOD GLUCOSE INCREASED			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ENDOMETRIAL ADENOCARCINOMA			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			

ANIMAL BITE			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
PERIPHERAL SWELLING			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
ERYTHEMA			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
ARTHRITIS			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
BONE DEFORMITY			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
RHEUMATOID ARTHRITIS			

subjects affected / exposed	3 / 39 (7.69%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	3	3	0
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
SINUSITIS			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
TOOTH INFECTION			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 39 (7.69%)	2 / 41 (4.88%)	2 / 40 (5.00%)
occurrences (all)	3	2	2
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 39 (5.13%)	2 / 41 (4.88%)	3 / 40 (7.50%)
occurrences (all)	2	2	4
Metabolism and nutrition disorders			
VITAMIN D DEFICIENCY			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2018	Version 2.0 • Modified categorization of PhGA assessment (from patient-reported outcome to exam) • Clarified PK sample collection and creatine phosphokinase (CPK) laboratory test requirements • Updated biomarker collection requirements • Added respiratory rate to vital signs collected and abnormal labs to the list of potential reasons for study drug discontinuation
05 October 2018	Version 3.0 • Added a 12-lead ECG to Weeks 2, 4, and 8 • Added information on subject at-home weekly temperature monitoring for assessment of serious infections
11 March 2019	Version 4.0 • Reduced the washout period from ≥ 10 weeks to ≥ 4 weeks for adalimumab, infliximab, certolizumab, golimumab, tocilizumab, and abatacept • Prior exposure to JAK inhibitors changed from not allowed to not greater than 2 weeks with the addition of a washout period ≥ 30 days required prior to first dose of study drug • Added clarification that nonsteroidal anti-inflammatory drugs, acetaminophen/paracetamol, oral corticosteroids (equivalent to prednisone ≤ 10 mg/day), or inhaled corticosteroids, if not taken at Baseline, should not be initiated. • Added TBNK cell testing may be completed at Screening (rather than Baseline) if indicated • Added footnote regarding pre-dose collection for biomarker samples at Baseline to the Activity Schedule • Added information on dispensing the subject dosing diary and at-home temperature monitoring log at Baseline and a reminder to review the at-home temperature monitoring log during weekly at-home temperature monitoring • Added T or T SPOT®.TB test language from the Canada-specific amendment • Added an unblinded administrative interim assessment of efficacy when 80% of subjects have completed the Week 12 visit (to be performed in addition to the previously planned unblinded safety assessments)
15 October 2019	Version 5.0 • Updated Sponsor/Emergency Medical Contact info

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported