Clinical trial results:
A Phase 2 Study to Investigate the Safety and Efficacy of Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599 Combination) in Subjects With Moderately to Severely Active Systemic Lupus Erythematosus

Summary

EudraCT number	2019-000638-20
Trial protocol	DE ES HU NL BG IT
Global end of trial date	14 July 2022

Results information

Result version number	v1 (current)
This version publication date	13 July 2023
First version publication date	13 July 2023

Trial information

Trial identification

Sponsor protocol code	M19-130

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03978520
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	14 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety and efficacy of elsubrutinib, upadacitinib (UPA), and ABBV-599 (elsubrutinib/upadacitinib) High Dose and Low Dose combinations vs placebo for the treatment of signs and symptoms of Systemic Lupus Erythematosus (SLE) in participants with moderately to severely active SLE and to define doses for further development.

Protection of trial subjects:

Subjects or their legally authorized representative (if required per local regulations) must have understood and personally, 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. In Japan, subjects under 20 years of age must have voluntarily signed and dated an informed consent, in addition to their parent or legal guardian. Legally authorized representation did not apply in the case of Germany and France, and protected persons such as minors, adults under guardianship, pregnant women, persons deprived of their liberty and persons incapable or unable to express their consent were not included in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 July 2019
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	Argentina: 39
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	China: 20
Country: Number of subjects enrolled	Colombia: 19
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 22
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Mexico: 24
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Poland: 11

Country: Number of subjects enrolled	Puerto Rico: 19
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Taiwan: 20
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 96
Worldwide total number of subjects	341
EEA total number of subjects	52

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)	337
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects or their legally authorized representative (if required per local regulations) must have understood and personally, 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.

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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Elsubrutinib placebo/upadacitinib placebo

Arm description:

Placebo capsule for elsubrutinib once a day by mouth for up to 48 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for up to 48 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:

Capsule; Oral

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:

Film-coated tablet; Oral

Arm title	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)

Arm description:

60 mg elsubrutinib capsule once a day by mouth for up to 48 weeks; 30 mg upadacitinib film-coated tablet once a day by mouth for up to 48 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:	
Capsule; Oral	
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	
Other name	RINVOQ
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Film-coated tablet; Oral	
Arm title	Elsubrutinib Placebo/Upadacitinib 30 mg

Arm description:

Placebo capsule for elsubrutinib once a day by mouth for up to 48 weeks; 30 mg upadacitinib film-coated tablet once a day by mouth for up to 48 weeks

Arm type	Experimental
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:	
Capsule; Oral	

Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	
Other name	RINVOQ
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Film-coated tablet; Oral	
Arm title	ABBV-599 Low Dose (Elsubrutinib 60 mg/Upadacitinib 15 mg)

Arm description:

60 mg elsubrutinib capsule once a day by mouth for up to 24 weeks; 15 mg upadacitinib film-coated tablet once a day by mouth for up to 24 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:	
Capsule; Oral	
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	
Other name	RINVOQ
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Film-coated tablet; Oral	
Arm title	Elsubrutinib 60 mg/Upadacitinib Placebo

Arm description:

60 mg elsubrutinib capsule once a day by mouth for up to 24 weeks; placebo film-coated tablet for

upadacitinib once a day by mouth for up to 24 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: Capsule; Oral	
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: Film-coated tablet; Oral	

Number of subjects in period 1	Elsubrutinib placebo/upadacitinib placebo	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)	Elsubrutinib Placebo/Upadacitinib 30 mg
Started	75	68	62
Completed	52	52	51
Not completed	23	16	11
Adverse event, non-fatal	2	5	3
Other, not specified	9	4	1
Sponsor decision: interim analysis data review	-	-	-
Lost to follow-up	2	2	2
COVID-19 infection	-	1	-
Withdrawal by subject	10	4	5

Number of subjects in period 1	ABBV-599 Low Dose (Elsubrutinib 60 mg/Upadacitinib 15 mg)	Elsubrutinib 60 mg/Upadacitinib Placebo
Started	69	67
Completed	24	29
Not completed	45	38
Adverse event, non-fatal	5	6
Other, not specified	1	2
Sponsor decision: interim analysis data review	33	24
Lost to follow-up	-	1
COVID-19 infection	-	-
Withdrawal by subject	6	5

Baseline characteristics

Reporting groups

Reporting group title	Elsubrutinib placebo/upadacitinib placebo

Reporting group description:

Placebo capsule for elsubrutinib once a day by mouth for up to 48 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for up to 48 weeks

Reporting group title	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for up to 48 weeks; 30 mg upadacitinib film-coated tablet once a day by mouth for up to 48 weeks

Reporting group title	Elsubrutinib Placebo/Upadacitinib 30 mg

Reporting group description:

Placebo capsule for elsubrutinib once a day by mouth for up to 48 weeks; 30 mg upadacitinib film-coated tablet once a day by mouth for up to 48 weeks

Reporting group title	ABBV-599 Low Dose (Elsubrutinib 60 mg/Upadacitinib 15 mg)

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for up to 24 weeks; 15 mg upadacitinib film-coated tablet once a day by mouth for up to 24 weeks

Reporting group title	Elsubrutinib 60 mg/Upadacitinib Placebo

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for up to 24 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for up to 24 weeks

Reporting group values	Elsubrutinib placebo/upadacitinib placebo	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)	Elsubrutinib Placebo/Upadacitinib 30 mg
Number of subjects	75	68	62
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	41.7	42.7	42.5
standard deviation	± 12.05	± 11.27	± 11.89
Gender categorical Units: Subjects			
Female	75	62	57
Male	0	6	5
Race Units: Subjects			
American Indian or Alaska Native	3	3	0
Asian	23	14	13
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	4	9
White	43	45	34

More than one race	2	2	6
Unknown or Not Reported	0	0	0

Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score			
The SLEDAI-2K is a global SLE disease activity index that focuses on high-impact disease manifestations across 9 organ systems. It includes 24 clinical and laboratory variables with manifestations weighted by the affected organ system. Scores range from 0 to 105, with higher scores indicating more severe disease.			
Units: units on a scale			
arithmetic mean	9.1	8.9	9.0
standard deviation	± 3.88	± 2.75	± 2.75
Physician's Global Assessment (PhGA) score			
Physician's assessment of patient's overall disease activity due to Systemic Lupus Erythematosus (SLE), as compared with all possible participants with SLE. The benchmarks of the visual analog scale are 0, 1, 2, and 3 on the line corresponding to no, mild, moderate, and severe SLE disease activity, respectively.			
Units: units on a scale			
arithmetic mean	1.75	1.80	1.70
standard deviation	± 0.440	± 0.417	± 0.438
Daily dose of corticosteroid			
Units: mg/day			
arithmetic mean	7.937	6.743	6.242
standard deviation	± 7.1270	± 6.3736	± 6.0920

Reporting group values	ABBV-599 Low Dose (Elsubrutinib 60 mg/Upadacitinib 15 mg)	Elsubrutinib 60 mg/Upadacitinib Placebo	Total
Number of subjects	69	67	341
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	41.4	42.0	
standard deviation	± 11.85	± 11.84	-
Gender categorical			
Units: Subjects			
Female	63	62	319
Male	6	5	22
Race			
Units: Subjects			
American Indian or Alaska Native	1	4	11
Asian	13	9	72
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	6	31
White	45	44	211
More than one race	2	4	16
Unknown or Not Reported	0	0	0

Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score			
The SLEDAI-2K is a global SLE disease activity index that focuses on high-impact disease manifestations across 9 organ systems. It includes 24 clinical and laboratory variables with manifestations weighted by the affected organ system. Scores range from 0 to 105, with higher scores indicating more severe disease.			
Units: units on a scale			
arithmetic mean	8.8	9.2	
standard deviation	± 2.86	± 3.18	-
Physician's Global Assessment (PhGA) score			
Physician's assessment of patient's overall disease activity due to Systemic Lupus Erythematosus (SLE), as compared with all possible participants with SLE. The benchmarks of the visual analog scale are 0, 1, 2, and 3 on the line corresponding to no, mild, moderate, and severe SLE disease activity, respectively.			
Units: units on a scale			
arithmetic mean	1.77	1.77	
standard deviation	± 0.422	± 0.392	-
Daily dose of corticosteroid			
Units: mg/day			
arithmetic mean	6.891	6.291	
standard deviation	± 6.1056	± 6.1096	-

End points

End points reporting groups

Reporting group title	Elsubrutinib placebo/upadacitinib placebo

Reporting group description:

Placebo capsule for elsubrutinib once a day by mouth for up to 48 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for up to 48 weeks

Reporting group title	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for up to 48 weeks; 30 mg upadacitinib film-coated tablet once a day by mouth for up to 48 weeks

Reporting group title	Elsubrutinib Placebo/Upadacitinib 30 mg

Reporting group description:

Placebo capsule for elsubrutinib once a day by mouth for up to 48 weeks; 30 mg upadacitinib film-coated tablet once a day by mouth for up to 48 weeks

Reporting group title	ABBV-599 Low Dose (Elsubrutinib 60 mg/Upadacitinib 15 mg)

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for up to 24 weeks; 15 mg upadacitinib film-coated tablet once a day by mouth for up to 24 weeks

Reporting group title	Elsubrutinib 60 mg/Upadacitinib Placebo

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for up to 24 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for up to 24 weeks

Primary: Percentage of Participants Achieving SLE Responder Index (SRI)-4 and Steroid Dose ≤10 mg Prednisone Equivalent Once a Day (QD) at Week 24

End point title	Percentage of Participants Achieving SLE Responder Index (SRI)-4 and Steroid Dose ≤10 mg Prednisone Equivalent Once a Day (QD) at Week 24[1]

End point description:

SLE Responder Index (SRI)-4 is defined as follows with all criteria compared to Baseline:
• ≥4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score
• No worsening of the overall condition (< 0.3 point increase in Physician's Global Assessment [PhGA])
• No new British Isles Lupus Assessment Group (BILAG) A or more than 1 new BILAG B disease activity scores (i.e., no organ system changes from baseline B/C/D/E to A and no more than 1 organ system changes from baseline C/D/E to B). A letter score is assigned to each organ system with following indications: A = severe, B = moderate, C = mild, D = inactive with prior history, and E = inactive with no history.

End point type	Primary

End point timeframe:

Baseline, Week 24

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: When 50% of planned participants had completed Week 24 or withdrawn from the study, the ABBV-599 Low Dose and elsubrutinib 60 mg treatment groups were terminated as these groups did not meet projected efficacy. Per protocol, terminated groups were removed from the efficacy analyses.

End point values	Elsubrutinib placebo/upadacitinib placebo	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)	Elsubrutinib Placebo/Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75[2]	68[3]	62[4]	
Units: percentage of participants				
number (confidence interval 95%)	37.3 (26.4 to 48.3)	48.5 (36.7 to 60.4)	54.8 (42.5 to 67.2)	

Notes:

[2] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)

[3] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)

[4] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)

Statistical analyses

Statistical analysis title	ABBV-599 High Dose vs elsubrutinib/Upa placebo

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	27.1

Statistical analysis title	Elsubrutinib/Upa Placebo, Elsubrutinib placebo/Upa

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v Elsubrutinib Placebo/Upadacitinib 30 mg

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	16.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	31.9

Statistical analysis title	ABBV-599 High Dose vs Elsubrutinib placebo/Upa

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib Placebo/Upadacitinib 30 mg v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.566
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.8
upper limit	11.4

Secondary: Percentage of Participants Achieving SLE Responder Index (SRI)-4 at Week 24

End point title	Percentage of Participants Achieving SLE Responder Index (SRI)-4 at Week 24[5]

End point description:

SLE Responder Index (SRI)-4 is defined as follows with all criteria compared to Baseline:
• ≥4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score
• No worsening of the overall condition (< 0.3 point increase in Physician's Global Assessment [PhGA])
• No new British Isles Lupus Assessment Group (BILAG) A or more than 1 new BILAG B disease activity scores (i.e., no organ system changes from baseline B/C/D/E to A and no more than 1 organ system changes from baseline C/D/E to B). A letter score is assigned to each organ system with following indications: A = severe, B = moderate, C = mild, D = inactive with prior history, and E = inactive with no history.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: When 50% of planned participants had completed Week 24 or withdrawn from the study, the ABBV-599 Low Dose and elsubrutinib 60 mg treatment groups were terminated as these groups did not meet projected efficacy. Per protocol, terminated groups were removed from the efficacy analyses.

End point values	Elsubrutinib placebo/upadacitinib placebo	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)	Elsubrutinib Placebo/Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75[6]	68[7]	62[8]	
Units: percentage of participants				
number (confidence interval 95%)	38.7 (27.6 to 49.7)	54.4 (42.6 to 66.2)	56.5 (44.1 to 68.8)	

Notes:

[6] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)

[7] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)

[8] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)

Statistical analyses

Statistical analysis title	ABBV-599 High Dose vs elsubrutinib/Upa placebo

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg) v Elsubrutinib placebo/upadacitinib placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	18.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	32.6

Statistical analysis title	Elsubrutinib/Upa Placebo, Elsubrutinib placebo/Upa

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline

immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v Elsubrutinib Placebo/Upadacitinib 30 mg
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	33.2

Statistical analysis title	ABBV-599 High Dose vs Elsubrutinib placebo/Upa

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib Placebo/Upadacitinib 30 mg v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.882
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	15.2

Secondary: Percentage of Participants Achieving British Isles Lupus Assessment Group (BILAG) Based Combined Lupus Assessment (BICLA) Response at Week 24

End point title	Percentage of Participants Achieving British Isles Lupus Assessment Group (BILAG) Based Combined Lupus Assessment (BICLA) Response at Week 24[9]

End point description:

BICLA is a composite responder index. Achievement of BICLA response is defined as improvement in all initial A and B BILAG scores, with no more than one new BILAG B score without worsening of the overall condition (no worsening in Physician's Global Assessment [PhGA], < 0.3 point increase) and no worsening of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: When 50% of planned participants had completed Week 24 or withdrawn from the study, the ABBV-599 Low Dose and elsubrutinib 60 mg treatment groups were terminated as these groups did not meet projected efficacy. Per protocol, terminated groups were removed from the efficacy analyses.

End point values	Elsubrutinib placebo/upadacitinib placebo	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)	Elsubrutinib Placebo/Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75[10]	68[11]	62[12]	
Units: percentage of participants				
number (confidence interval 95%)	42.7 (31.5 to 53.9)	54.4 (42.6 to 66.2)	58.1 (45.8 to 70.3)	

Notes:

[10] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)
[11] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)
[12] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)

Statistical analyses

Statistical analysis title	ABBV-599 High Dose vs elsubrutinib/Upa placebo

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	29.4

Statistical analysis title	Elsubrutinib/Upa Placebo, Elsubrutinib placebo/Upa

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v Elsubrutinib Placebo/Upadacitinib 30 mg
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.091
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	13.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	30.1

Statistical analysis title	ABBV-599 High Dose vs Elsubrutinib placebo/Upa

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib Placebo/Upadacitinib 30 mg v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.447
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	-6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.5
upper limit	9.9

Secondary: Percentage of Participants Achieving Lupus Low Disease Activity State (LLDAS) at Week 24

End point title	Percentage of Participants Achieving Lupus Low Disease Activity State (LLDAS) at Week 24[13]

End point description:

LLDAS is a state of low disease activity based on Systemic Lupus Erythematosus Disease Activity Index 2000 score (SLEDAI-2K score ≤4 excluding SLEDAI-2K activity in major organ systems), absence of SLE disease activity in major organ systems and new disease activity, Physician's Global Assessment (PhGA ≤1), and concomitant medication usage (steroid dose ≤7.5 mg QD and toleration of immunosuppressive drugs at standard maintenance doses).

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: When 50% of planned participants had completed Week 24 or withdrawn from the study, the ABBV-599 Low Dose and elsubrutinib 60 mg treatment groups were terminated as these groups did not meet projected efficacy. Per protocol, terminated groups were removed from the efficacy analyses.

End point values	Elsubrutinib placebo/upadacitinib placebo	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)	Elsubrutinib Placebo/Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75[14]	68[15]	62[16]	
Units: percentage of participants				
number (confidence interval 95%)	13.3 (5.6 to 21.0)	30.9 (19.9 to 41.9)	45.2 (32.8 to 57.5)	

Notes:

[14] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)
[15] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)
[16] - Subjects rcvd ≥ 1 study drug dose; NRI-C (multiple imputation for missing data due to COVID-19)

Statistical analyses

Statistical analysis title	ABBV-599 High Dose vs elsubrutinib/Upa placebo

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	16.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.5
upper limit	28.9

Statistical analysis title	Elsubrutinib/Upa Placebo, Elsubrutinib placebo/Upa

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v Elsubrutinib Placebo/Upadacitinib 30 mg
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	31
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.1
upper limit	44

Statistical analysis title	ABBV-599 High Dose vs Elsubrutinib placebo/Upa

Statistical analysis description:

The difference between the groups was assessed using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline corticosteroid dose above 10 mg prednisone-equivalent (≤10 mg or > 10 mg), screening SLEDAI-2K (< 10 or ≥10), baseline interferon score (high or low or NA), baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate) (yes or no).

Comparison groups	Elsubrutinib Placebo/Upadacitinib 30 mg v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	-13.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.4
upper limit	1

Secondary: Change From Baseline in Daily Prednisone Dose at Week 24

End point title	Change From Baseline in Daily Prednisone Dose at Week 24[17]

End point description:

Participants'current use of steroid therapy was assessed at each study visit, and the amount of daily prednisone was documented.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: When 50% of planned participants had completed Week 24 or withdrawn from the study, the ABBV-599 Low Dose and elsubrutinib 60 mg treatment groups were terminated as these groups did not meet projected efficacy. Per protocol, terminated groups were removed from the efficacy analyses.

End point values	Elsubrutinib placebo/upadacitinib placebo	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)	Elsubrutinib Placebo/Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56[18]	54[19]	48[20]	
Units: mg				
least squares mean (confidence interval 95%)	-0.65 (-1.57 to 0.28)	-0.45 (-1.38 to 0.48)	-0.62 (-1.60 to 0.36)	

Notes:

[18] - Subjects who rcvd ≥ 1 study drug dose w/ available data; Mixed-Effect Model Repeat Measurement used
[19] - Subjects who rcvd ≥ 1 study drug dose w/ available data; Mixed-Effect Model Repeat Measurement used
[20] - Subjects who rcvd ≥ 1 study drug dose w/ available data; Mixed-Effect Model Repeat Measurement used

Statistical analyses

Statistical analysis title	ABBV-599 High Dose vs elsubrutinib/Upa placebo

Statistical analysis description:

The Mixed-Effect Model Repeat Measurement model included fixed effects of Tx, visit and Tx-by-visit interaction, stratification factors (Baseline corticosteroid dose > 10 mg prednisone-equivalent (≤10 mg or >10 mg), screening SLEDAI-2K (<10 or ≥10), baseline interferon score (high/low/NA, baseline immunosuppressant (yes/no)), and continuous fixed covariates of measurements at Baseline.

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Mixed-effect model repeat measurement
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	1.23
Variability estimate	Standard error of the mean
Dispersion value	0.527

Statistical analysis title	Elsubrutinib/Upa Placebo, Elsubrutinib placebo/Upa

Statistical analysis description:

The Mixed-Effect Model Repeat Measurement model included fixed effects of Tx, visit and Tx-by-visit interaction, stratification factors (Baseline corticosteroid dose > 10 mg prednisone-equivalent (≤10 mg or >10 mg), screening SLEDAI-2K (<10 or ≥10), baseline interferon score (high/low/NA, baseline immunosuppressant (yes/no)), and continuous fixed covariates of measurements at Baseline.

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v Elsubrutinib Placebo/Upadacitinib 30 mg
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.963
Method	Mixed-effect model repeat measurement
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.545

Statistical analysis title	ABBV-599 High Dose vs Elsubrutinib placebo/Upa

Statistical analysis description:

The Mixed-Effect Model Repeat Measurement model included fixed effects of Tx, visit and Tx-by-visit interaction, stratification factors (Baseline corticosteroid dose > 10 mg prednisone-equivalent (≤10 mg or >10 mg), screening SLEDAI-2K (<10 or ≥10), baseline interferon score (high/low/NA, baseline immunosuppressant (yes/no)), and continuous fixed covariates of measurements at Baseline.

Comparison groups	Elsubrutinib Placebo/Upadacitinib 30 mg v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.754
Method	Mixed-effect model repeat measurement
Parameter estimate	LS Mean Difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.25
Variability estimate	Standard error of the mean
Dispersion value	0.547

Secondary: Number of Flares Per Patient-year by Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLEDAI Flare Index Through Week 24

End point title	Number of Flares Per Patient-year by Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLEDAI Flare Index Through Week 24[21]

End point description:

The SELENA SLEDAI flare index defines mild/moderate or severe SLE flares using the SLEDAI score, definitions of worsening signs and symptoms, treatment changes, and Physician's Global Assessment of Disease Activity.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: When 50% of planned participants had completed Week 24 or withdrawn from the study, the ABBV-599 Low Dose and elsubrutinib 60 mg treatment groups were terminated as these groups did not meet projected efficacy. Per protocol, terminated groups were removed from the efficacy analyses.

End point values	Elsubrutinib placebo/upadacitinib placebo	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)	Elsubrutinib Placebo/Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75[22]	68[23]	62[24]	
Units: Events per patient-year				
number (confidence interval 95%)				
Mild/Moderate	2.45 (1.92 to 2.99)	1.39 (0.97 to 1.81)	1.76 (1.28 to 2.25)	
Severe	0.36 (0.16 to 0.56)	0.26 (0.08 to 0.44)	0.10 (-0.01 to 0.22)	
Overall	2.81 (2.24 to 3.38)	1.65 (1.20 to 2.10)	1.87 (1.37 to 2.36)	

Notes:
[22] - Subjects who rcvd ≥ 1 study drug dose w/ available data; data as observed
[23] - Subjects who rcvd ≥ 1 study drug dose w/ available data; data as observed
[24] - Subjects who rcvd ≥ 1 study drug dose w/ available data; data as observed

Statistical analyses

Statistical analysis title	ABBV-599 High Dose vs elsubrutinib/Upa placebo

Statistical analysis description:
Mild/Moderate

A negative binomial regression model was used to assess treatment effect with treatment, visit, and stratification factors as covariates.

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Binomial regression
Parameter estimate	Rate difference
Point estimate	-1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	-0.39

Statistical analysis title	Elsubrutinib/Upa Placebo, Elsubrutinib placebo/Upa

Statistical analysis description:
Mild/Moderate

A negative binomial regression model was used to assess treatment effect with treatment, visit, and stratification factors as covariates.

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v Elsubrutinib Placebo/Upadacitinib 30 mg
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	Binomial regression
Parameter estimate	Rate difference
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.41
upper limit	0.03

Statistical analysis title	ABBV-599 High Dose vs Elsubrutinib placebo/Upa

Statistical analysis description:

Mild/Moderate

A negative binomial regression model was used to assess treatment effect with treatment, visit, and stratification factors as covariates.

Comparison groups	Elsubrutinib Placebo/Upadacitinib 30 mg v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.252
Method	Binomial regression
Parameter estimate	Rate difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.27

Statistical analysis title	ABBV-599 High Dose vs elsubrutinib/Upa placebo

Statistical analysis description:

SEVERE

A negative binomial regression model was used to assess treatment effect with treatment, visit, and stratification factors as covariates.

Comparison groups	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg) v Elsubrutinib placebo/upadacitinib placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.467
Method	Binomial regression
Parameter estimate	Rate difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.17

Statistical analysis title	Elsubrutinib/Upa Placebo, Elsubrutinib placebo/Upa

Statistical analysis description:

SEVERE

A negative binomial regression model was used to assess treatment effect with treatment, visit, and stratification factors as covariates.

Comparison groups	Elsubrutinib Placebo/Upadacitinib 30 mg v Elsubrutinib placebo/upadacitinib placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Binomial regression
Parameter estimate	Rate difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	-0.02

Statistical analysis title	ABBV-599 High Dose vs Elsubrutinib placebo/Upa

Statistical analysis description:

SEVERE

A negative binomial regression model was used to assess treatment effect with treatment, visit, and stratification factors as covariates.

Comparison groups	Elsubrutinib Placebo/Upadacitinib 30 mg v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156
Method	Binomial regression
Parameter estimate	Rate difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.37

Statistical analysis title	ABBV-599 High Dose vs elsubrutinib/Upa placebo

Statistical analysis description:

OVERALL

A negative binomial regression model was used to assess treatment effect with treatment, visit, and stratification factors as covariates.

Comparison groups	ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg) v Elsubrutinib placebo/upadacitinib placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Binomial regression
Parameter estimate	Rate difference
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.89
upper limit	-0.44

Statistical analysis title	Elsubrutinib/Upa Placebo, Elsubrutinib placebo/Upa

Statistical analysis description:

OVERALL

A negative binomial regression model was used to assess treatment effect with treatment, visit, and stratification factors as covariates.

Comparison groups	Elsubrutinib placebo/upadacitinib placebo v Elsubrutinib Placebo/Upadacitinib 30 mg
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Binomial regression
Parameter estimate	Rate difference
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.19

Statistical analysis title	ABBV-599 High Dose vs Elsubrutinib placebo/Upa

Statistical analysis description:

OVERALL

A negative binomial regression model was used to assess treatment effect with treatment, visit, and stratification factors as covariates.

Comparison groups	Elsubrutinib Placebo/Upadacitinib 30 mg v ABBV-599 High Dose (Elsubrutinib 60 mg/upadacitinib 30 mg)

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.526
Method	Binomial regression
Parameter estimate	Rate difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	0.46

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality is reported from enrollment to end of study; median time on follow-up was 337.0, 337.0, 338.5, 281.0, and 295.0 days for the placebo, ABBV-599 High Dose, upadacitinib, ABBV-599 Low Dose, and elsubrutinib groups, respectively.

Adverse event reporting additional description:

TEAEs and SAEs were collected from first dose of study drug until 30 days after last dose of study drug; mean time on treatment was 286.1 days, 289.8 days, 297.7 days, 226.4 days, and 228.6 days, for the placebo, ABBV-599 High Dose, upadacitinib, ABBV-599 Low Dose, and elsubrutinib groups, respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Elsubrutinib Placebo/Upadacitinib Placebo

Reporting group description:

Placebo capsule for elsubrutinib once a day by mouth for up to 48 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for up to 48 weeks

Reporting group title	Elsubrutinib Placebo/Upadacitinib 30 mg

Reporting group description:

Placebo capsule for elsubrutinib once a day by mouth for up to 48 weeks; 30 mg upadacitinib film-coated tablet once a day by mouth for up to 48 weeks

Reporting group title	ABBV-599 High Dose (Elsubrutinib 60 mg/Upadacitinib 30 mg)

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for up to 48 weeks; 30 mg upadacitinib film-coated tablet once a day by mouth for up to 48 weeks

Reporting group title	ABBV-599 Low Dose (Elsubrutinib 60 mg/Upadacitinib 15 mg)

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for up to 24 weeks; 15 mg upadacitinib film-coated tablet once a day by mouth for up to 24 weeks

Reporting group title	Elsubrutinib 60 mg/Upadacitinib Placebo

Reporting group description:

60 mg elsubrutinib capsule once a day by mouth for up to 24 weeks; placebo film-coated tablet for upadacitinib once a day by mouth for up to 24 weeks

Serious adverse events	Elsubrutinib Placebo/Upadacitinib Placebo	Elsubrutinib Placebo/Upadacitinib 30 mg	ABBV-599 High Dose (Elsubrutinib 60 mg/Upadacitinib 30 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 75 (17.33%)	13 / 62 (20.97%)	7 / 68 (10.29%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	1
Vascular disorders			
VENOUS THROMBOSIS LIMB			

subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSIVE URGENCY			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	2 / 75 (2.67%)	0 / 62 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ACCIDENTAL DEATH			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
Reproductive system and breast disorders			
BREAST MASS			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PNEUMONITIS			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPISTAXIS			

subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
BIPOLAR DISORDER			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
Investigations			
SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX INCREASED			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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			
JOINT INJURY			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
FALL			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
TIBIA FRACTURE			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
PERICARDIAL EFFUSION			

subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
STRESS CARDIOMYOPATHY			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CENTRAL NERVOUS SYSTEM LUPUS			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (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
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MIGRAINE			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (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
RUPTURED CEREBRAL ANEURYSM			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (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
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (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
Blood and lymphatic system disorders			

NEUTROPENIA			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
DYSPHAGIA			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
GASTRITIS			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
OESOPHAGITIS			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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			
LUPUS NEPHRITIS			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (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
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETEROLITHIASIS			
subjects affected / exposed	2 / 75 (2.67%)	0 / 62 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

NEPHROLITHIASIS			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
OSTEONECROSIS			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
SYSTEMIC LUPUS ERYTHEMATOSUS			
subjects affected / exposed	1 / 75 (1.33%)	1 / 62 (1.61%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABSCESS LIMB			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DISSEMINATED VARICELLA ZOSTER VIRUS INFECTION			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (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
DIVERTICULITIS			

subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (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
GASTROENTERITIS			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (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
ESCHERICHIA SEPSIS			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
ENDOCARDITIS BACTERIAL			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC ABSCESS			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
MYCOPLASMA INFECTION			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
MENINGITIS TUBERCULOUS			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
OESOPHAGEAL CANDIDIASIS			

subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	0 / 68 (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
HERPES ZOSTER			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 75 (0.00%)	1 / 62 (1.61%)	0 / 68 (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
PNEUMONIA			
subjects affected / exposed	0 / 75 (0.00%)	2 / 62 (3.23%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
PNEUMONIA FUNGAL			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA RESPIRATORY SYNCYTIAL VIRAL			
subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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
SEPSIS			

subjects affected / exposed	0 / 75 (0.00%)	0 / 62 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DIABETES MELLITUS			
subjects affected / exposed	1 / 75 (1.33%)	0 / 62 (0.00%)	0 / 68 (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

Serious adverse events	ABBV-599 Low Dose (Elsubrutinib 60 mg/Upadacitinib 15 mg)	Elsubrutinib 60 mg/Upadacitinib Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 69 (13.04%)	7 / 67 (10.45%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Vascular disorders			
VENOUS THROMBOSIS LIMB			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE URGENCY			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ACCIDENTAL DEATH			
subjects affected / exposed	0 / 69 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			

BREAST MASS			
subjects affected / exposed	1 / 69 (1.45%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
BIPOLAR DISORDER			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX INCREASED			
subjects affected / exposed	1 / 69 (1.45%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
JOINT INJURY			
subjects affected / exposed	0 / 69 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			

subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TIBIA FRACTURE			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STRESS CARDIOMYOPATHY			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CENTRAL NERVOUS SYSTEM LUPUS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MIGRAINE			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RUPTURED CEREBRAL ANEURYSM			

subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed	1 / 69 (1.45%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
DYSPHAGIA			
subjects affected / exposed	1 / 69 (1.45%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGITIS			
subjects affected / exposed	1 / 69 (1.45%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

LUPUS NEPHRITIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETEROLITHIASIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
OSTEONECROSIS			
subjects affected / exposed	1 / 69 (1.45%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC LUPUS ERYTHEMATOSUS			
subjects affected / exposed	2 / 69 (2.90%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCESS LIMB			
subjects affected / exposed	0 / 69 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

COVID-19			
subjects affected / exposed	0 / 69 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
DISSEMINATED VARICELLA ZOSTER VIRUS INFECTION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	1 / 69 (1.45%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA SEPSIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCARDITIS BACTERIAL			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC ABSCESS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYCOPLASMA INFECTION			

subjects affected / exposed	0 / 69 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS TUBERCULOUS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL CANDIDIASIS			
subjects affected / exposed	0 / 69 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 69 (1.45%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA FUNGAL			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA RESPIRATORY SYNCYTIAL VIRAL			

subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 69 (1.45%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DIABETES MELLITUS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Elsubrutinib Placebo/Upadacitinib Placebo	Elsubrutinib Placebo/Upadacitinib 30 mg	ABBV-599 High Dose (Elsubrutinib 60 mg/Upadacitinib 30 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 75 (52.00%)	35 / 62 (56.45%)	38 / 68 (55.88%)
Investigations			
WEIGHT INCREASED			
subjects affected / exposed	1 / 75 (1.33%)	1 / 62 (1.61%)	4 / 68 (5.88%)
occurrences (all)	1	2	8
Nervous system disorders			
HEADACHE			
subjects affected / exposed	9 / 75 (12.00%)	2 / 62 (3.23%)	4 / 68 (5.88%)
occurrences (all)	13	2	4
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	6 / 75 (8.00%)	3 / 62 (4.84%)	3 / 68 (4.41%)
occurrences (all)	6	3	3

FATIGUE			
subjects affected / exposed	2 / 75 (2.67%)	0 / 62 (0.00%)	4 / 68 (5.88%)
occurrences (all)	2	0	4
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	6 / 75 (8.00%)	4 / 62 (6.45%)	4 / 68 (5.88%)
occurrences (all)	11	4	4
GASTRITIS			
subjects affected / exposed	0 / 75 (0.00%)	2 / 62 (3.23%)	0 / 68 (0.00%)
occurrences (all)	0	2	0
DIARRHOEA			
subjects affected / exposed	6 / 75 (8.00%)	4 / 62 (6.45%)	3 / 68 (4.41%)
occurrences (all)	6	5	4
CONSTIPATION			
subjects affected / exposed	4 / 75 (5.33%)	1 / 62 (1.61%)	1 / 68 (1.47%)
occurrences (all)	4	1	1
VOMITING			
subjects affected / exposed	3 / 75 (4.00%)	4 / 62 (6.45%)	2 / 68 (2.94%)
occurrences (all)	3	6	3
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	1 / 75 (1.33%)	2 / 62 (3.23%)	4 / 68 (5.88%)
occurrences (all)	2	2	4
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	2 / 75 (2.67%)	4 / 62 (6.45%)	2 / 68 (2.94%)
occurrences (all)	2	4	2
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	5 / 75 (6.67%)	1 / 62 (1.61%)	3 / 68 (4.41%)
occurrences (all)	5	1	3
BACK PAIN			
subjects affected / exposed	4 / 75 (5.33%)	1 / 62 (1.61%)	3 / 68 (4.41%)
occurrences (all)	5	1	3
Infections and infestations			

COVID-19			
subjects affected / exposed	8 / 75 (10.67%)	7 / 62 (11.29%)	3 / 68 (4.41%)
occurrences (all)	8	7	3
BRONCHITIS			
subjects affected / exposed	1 / 75 (1.33%)	4 / 62 (6.45%)	1 / 68 (1.47%)
occurrences (all)	1	4	1
HERPES ZOSTER			
subjects affected / exposed	3 / 75 (4.00%)	3 / 62 (4.84%)	7 / 68 (10.29%)
occurrences (all)	3	3	7
ORAL HERPES			
subjects affected / exposed	1 / 75 (1.33%)	3 / 62 (4.84%)	5 / 68 (7.35%)
occurrences (all)	1	4	11
NASOPHARYNGITIS			
subjects affected / exposed	3 / 75 (4.00%)	1 / 62 (1.61%)	6 / 68 (8.82%)
occurrences (all)	3	1	6
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 75 (10.67%)	5 / 62 (8.06%)	7 / 68 (10.29%)
occurrences (all)	10	6	13
URINARY TRACT INFECTION			
subjects affected / exposed	9 / 75 (12.00%)	11 / 62 (17.74%)	8 / 68 (11.76%)
occurrences (all)	10	15	14

Non-serious adverse events	ABBV-599 Low Dose (Elsubrutinib 60 mg/Upadacitinib 15 mg)	Elsubrutinib 60 mg/Upadacitinib Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 69 (40.58%)	36 / 67 (53.73%)	
Investigations			
WEIGHT INCREASED			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	7 / 69 (10.14%)	10 / 67 (14.93%)	
occurrences (all)	8	12	
General disorders and administration site conditions			

PYREXIA			
subjects affected / exposed	2 / 69 (2.90%)	1 / 67 (1.49%)	
occurrences (all)	2	1	
FATIGUE			
subjects affected / exposed	1 / 69 (1.45%)	3 / 67 (4.48%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	2 / 69 (2.90%)	6 / 67 (8.96%)	
occurrences (all)	2	6	
GASTRITIS			
subjects affected / exposed	0 / 69 (0.00%)	4 / 67 (5.97%)	
occurrences (all)	0	4	
DIARRHOEA			
subjects affected / exposed	3 / 69 (4.35%)	2 / 67 (2.99%)	
occurrences (all)	4	3	
CONSTIPATION			
subjects affected / exposed	4 / 69 (5.80%)	1 / 67 (1.49%)	
occurrences (all)	4	1	
VOMITING			
subjects affected / exposed	2 / 69 (2.90%)	2 / 67 (2.99%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	4 / 69 (5.80%)	0 / 67 (0.00%)	
occurrences (all)	7	0	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 67 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 69 (2.90%)	5 / 67 (7.46%)	
occurrences (all)	3	5	
BACK PAIN			

subjects affected / exposed	2 / 69 (2.90%)	2 / 67 (2.99%)	
occurrences (all)	2	2	
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 69 (2.90%)	8 / 67 (11.94%)	
occurrences (all)	2	8	
BRONCHITIS			
subjects affected / exposed	0 / 69 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
HERPES ZOSTER			
subjects affected / exposed	3 / 69 (4.35%)	1 / 67 (1.49%)	
occurrences (all)	3	1	
ORAL HERPES			
subjects affected / exposed	3 / 69 (4.35%)	0 / 67 (0.00%)	
occurrences (all)	3	0	
NASOPHARYNGITIS			
subjects affected / exposed	5 / 69 (7.25%)	0 / 67 (0.00%)	
occurrences (all)	6	0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	5 / 69 (7.25%)	5 / 67 (7.46%)	
occurrences (all)	5	6	
URINARY TRACT INFECTION			
subjects affected / exposed	5 / 69 (7.25%)	4 / 67 (5.97%)	
occurrences (all)	9	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2019	Protocol Amendment 1 Clarified eligibility criteria Introduction of certain prohibited medications as a result of the development or worsening of lupus manifestation was prioritized by moving to the top of the list Clarified that subjects must be discontinued from study drug for an ECG change considered clinically significant and with reasonable possibility of relationship to study drug OR a confirmed absolute QTcF value > 500 msec or confirmed increase of ≥60 msec from baseline Added 12-lead ECG at Week 36
25 July 2019	Protocol Amendment 2 Clarified that if different national regulations exist for TB testing, those regulations should be applied Clarified consent criterion with respect to legally authorized representation with respect to Germany Clarified that at Week 24 the investigator should assess if continuing in the study is in the best interest of the patient

12 December 2019	Protocol Amendment 3 Added text about approval of upadacitinib in US and EU Added deep vein thrombosis and pulmonary embolism as events reported in patients receiving JAK inhibitors Provided preclinical information indicating that upadacitinib is not genotoxic but is teratogenic Added definition of SLE Responder Index (SRI)-4 Revised wording for secondary endpoints 8, 9, and 10 Removed CPK elevation as an adverse event area of safety interest Clarified that optionality of collection/analysis is given through ICF Included footnote clarifying that study will go from double-blind to single-blind when the Study Team is unblinded after Week 24 primary efficacy endpoint analysis is completed SLEDAI-2K ≥6 score at Screening must be re-confirmed at Baseline Visit Clarified that subjects must be on background treatment, stable for 30 days prior to Baseline, and background treatment may include prednisone equivalent Updated Eligibility #9, #18, #30, #32, #33, and #36 Clarified wording for the following contraceptive guideline: Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure). Added Traditional Chinese Medicines as prohibited medication while on study drug Clarified that, at Week 24, the Investigator must assess and document in source that continuing in the study is in the best interest of the subject Clarified that subject may request withdrawal from study drug/study Noted that a subject will be discontinued from study drug immediately if diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis is confirmed Clarified that worsening SLE including flares will be captured and analyzed by the 4 disease activity forms and will not be captured as AEs unless they result in serious outcomes Elevated CPK removed as an AESI Updated Toxicity Management Updated Activity Schedule
04 June 2020	Protocol Amendment 4 Updated synopsis Updated text to indicate that BTK is expressed in multiple immune cell types associated with the pathogenesis of SLE (in addition to RA and other autoimmune diseases). Deleted text describing the comparative selectivity of elsubrutinib. Added text regarding approval of upadacitinib for the treatment of adults with RA in the US, EU, and Japan. Deleted text describing the total number of subjects who have received upadacitinib and in the respective indications. Updated Background and Rationale and Benefits and Risks to Subjects Updated Contraception Recommendations Updated Secondary Endpoints Updated Safety and Complaints and Adverse Events and Toxicity Management Updated Biomarker Research Clarified that the sites and subjects will remain blinded throughout the remainder of the study. Updated Overall Study Design and Plan and Discussion of Study Design Updated Eligibility Criteria #1, #4, #10, #11, #24, #30, and #31 Updated Prohibited Medications and Therapy and Concomitant Therapy Updated Withdrawal of Subjects and Discontinuation of Study Updated Follow-Up After Subject Discontinuation of Study Drug or from Study Updated Randomization/Drug Assignment Updated Protocol Deviations Updated Statistical and Analytical Plans and Statistical Analyses for Efficacy Updated Activity Schedule Updated Completion of the Study and References sections Updated Appendix E

15 October 2020	Protocol Amendment 5 Made COVID-19 pandemic-related changes Updated Synopsis Updated Background and Rationale Updated Objectives and Hypotheses Updated Primary, Secondary, and Additional Efficacy Endpoints Updated Safety and Data Monitoring Committee Updated Biomarker Research Updated Overall Study Design and Plan and Randomization/Drug Assignment Updated Discussion of Study Design Updated Eligibility Criteria #8, #14, #15 and #32 Updated Prohibited Medications and Therapy and Concomitant Therapy Updated Withdrawal of Subjects and Discontinuation of Study Updated Follow-Up After Subject Discontinuation of Study Drug or from Study Updated Data Monitoring Committee Updated Complaints and Adverse Events and Toxicity Management Updated Statistical and Analytical Plans and Statistical Analyses for Efficacy (Added text to indicate that the unblinded interim analysis will be performed by an independent team at AbbVie after 50% of subjects have completed Week 24 assessments, and that the study team will remain blinded.) Added a new section, Section 7.5, with details regarding the conduct of the unblinded interim analysis. These details were also added to the Synopsis. Created a new section, Section 7.6, with details regarding the statistical tests to be used for this study and clarified that no multiplicity adjustment will be applied because this is a Phase 2 study Updated the version number and date of issue of the upadacitinib Investigator's Brochure Updated Activity Schedule
25 October 2021	Protocol Amendment 6 Clarified the adjustment of treatment groups in Study M19-130 as a result of the completed 50% interim analysis at Week 24 If the study is partially terminated (i.e., only certain groups are discontinued), details for follow-up of subjects were provided

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported