Clinical trial results:
A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Branebrutinib Treatment in Subjects with Active Systemic Lupus Erythematosus or Primary Sjögren's Syndrome, or Branebrutinib Treatment Followed by Open-label Abatacept Treatment in Subjects with Active Rheumatoid Arthritis

Summary

EudraCT number	2019-002205-22
Trial protocol	GB FR BE ES PL NL DE
Global end of trial date	05 December 2022

Results information

Result version number	v1 (current)
This version publication date	24 December 2023
First version publication date	24 December 2023

Trial information

Trial identification

Sponsor protocol code	IM014-029

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04186871
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Organization Name: Bristol-Myers Squibb, Clinical.Trials@bms.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	21 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2022
Global end of trial reached?	Yes
Global end of trial date	05 December 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To compare the efficacy of branebrutinib with PBO at Week 24 in the treatment of subjects with SLE and pSS.

- To compare the efficacy of branebrutinib with PBO at Week 12 in the treatment of subjects with moderate to severe RA on a stable background of MTX who have had an inadequate response to MTX

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 January 2020
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: 4
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Poland: 62
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	119
EEA total number of subjects	75

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)	113
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were enrolled concurrently for the RA, SLE, and pSS sub-studies.119 Participants were treated.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	SLE- Placebo

Arm description:

Participants with systemic lupus erythematosus (SLE) receive placebo once daily (QD) during a 24-week double-blind placebo-controlled treatment period.

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

Dosage and administration details:

PBO matching Branebrutinib oral capsule

Arm title	SLE- Branebrutinib

Arm description:

Participants with systemic lupus erythematosus (SLE) receive branebrutinib 9mg once daily (QD) during a 24-week double-blind placebo-controlled treatment period.

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

Dosage and administration details:

3 mg dose × 3 capsules (9 mg total dose)

Arm title	pSS- Placebo

Arm description:

Participants with primary Sjögren’s syndrome (pSS) receive placebo once daily (QD) during a 24-week double-blind placebo-controlled treatment period.

Arm type	Placebo

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

Dosage and administration details:

PBO matching Branebrutinib oral capsule

Arm title	pSS- Branebrutinib

Arm description:

Participants with primary Sjögren's syndrome (pSS) receive branebrutinib 9mg once daily (QD) during a 24-week double-blind placebo-controlled treatment period.

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

Dosage and administration details:

3 mg dose × 3 capsules (9 mg total dose)

Arm title	RA- Placebo

Arm description:

Participants with rheumatoid arthritis (RA) receive placebo once daily (QD) during a 12-week double-blind placebo-controlled treatment period, followed by an additional 12 weeks of treatment with open-label abatacept.

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

Dosage and administration details:

PBO matching Branebrutinib oral capsule

Arm title	RA- Branebrutinib

Arm description:

Participants with rheumatoid arthritis (RA) receive branebrutinib 9mg once daily (QD) during a 12-week double-blind placebo-controlled treatment period, followed by an additional 12 weeks of treatment with open-label abatacept.

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

Dosage and administration details:

3 mg dose × 3 capsules (9 mg total dose)

Number of subjects in period 1	SLE- Placebo	SLE- Branebrutinib	pSS- Placebo
Started	5	15	4
Double Blind Period	5	15	4
Open Label Period	0 [1]	0 [2]	0 [3]
Completed	3	11	4
Not completed	2	4	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	1	1	-
Study terminated by sponsor	1	2	-
Other reasons	-	-	-
Lost to follow-up	-	-	-
Lack of efficacy	-	1	-

Number of subjects in period 1	pSS- Branebrutinib	RA- Placebo	RA- Branebrutinib
Started	10	21	64
Double Blind Period	10	21	64
Open Label Period	0 [4]	20	61
Completed	9	20	58
Not completed	1	1	6
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	-	2
Study terminated by sponsor	1	-	-
Other reasons	-	-	1
Lost to follow-up	-	-	1
Lack of efficacy	-	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only RA participants had the Open-Label option.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only RA participants had the Open-Label option.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only RA participants had the Open-Label option.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only RA participants had the Open-Label option.

Baseline characteristics

Reporting groups	
Reporting group title	SLE- Placebo
Reporting group description:	
Participants with systemic lupus erythematosus (SLE) receive placebo once daily (QD) during a 24-week double-blind placebo-controlled treatment period.	
Reporting group title	SLE- Branebrutinib
Reporting group description:	
Participants with systemic lupus erythematosus (SLE) receive branebrutinib 9mg once daily (QD) during a 24-week double-blind placebo-controlled treatment period.	
Reporting group title	pSS- Placebo
Reporting group description:	
Participants with primary Sjögren's syndrome (pSS) receive placebo once daily (QD) during a 24-week double-blind placebo-controlled treatment period.	
Reporting group title	pSS- Branebrutinib
Reporting group description:	
Participants with primary Sjögren's syndrome (pSS) receive branebrutinib 9mg once daily (QD) during a 24-week double-blind placebo-controlled treatment period.	
Reporting group title	RA- Placebo
Reporting group description:	
Participants with rheumatoid arthritis (RA) receive placebo once daily (QD) during a 12-week double-blind placebo-controlled treatment period, followed by an additional 12 weeks of treatment with open-label abatacept.	
Reporting group title	RA- Branebrutinib
Reporting group description:	
Participants with rheumatoid arthritis (RA) receive branebrutinib 9mg once daily (QD) during a 12-week double-blind placebo-controlled treatment period, followed by an additional 12 weeks of treatment with open-label abatacept.	

Reporting group values	SLE- Placebo	SLE- Branebrutinib	pSS- Placebo
Number of subjects	5	15	4
Age categorical Units: Subjects			
Adults (18-64 years)	5	14	4
From 65-84 years	0	1	0
Age Continuous Units: Years			
arithmetic mean	47.6	44.2	47.8
standard deviation	± 10.99	± 12.91	± 4.19
Sex: Female, Male Units: Participants			
Female	5	14	4
Male	0	1	0
Race/Ethnicity, Customized Units: Subjects			
Asian - Non-Japanese	0	0	0
Black or African American	1	3	0
White	2	6	4
Not Reported	0	0	0
American Indian or Alaska Native	2	6	0

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	9	0
Not Hispanic or Latino	2	6	4
Unknown or Not Reported	0	0	0

Reporting group values	pSS- Branebrutinib	RA- Placebo	RA- Branebrutinib
Number of subjects	10	21	64
Age categorical Units: Subjects			
Adults (18-64 years)	10	21	59
From 65-84 years	0	0	5
Age Continuous Units: Years			
arithmetic mean	46.6	46.0	50.1
standard deviation	± 9.28	± 12.95	± 11.62
Sex: Female, Male Units: Participants			
Female	7	18	45
Male	3	3	19
Race/Ethnicity, Customized Units: Subjects			
Asian - Non-Japanese	0	0	2
Black or African American	0	0	2
White	9	21	59
Not Reported	1	0	1
American Indian or Alaska Native	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	7
Not Hispanic or Latino	8	20	57
Unknown or Not Reported	1	0	0

Reporting group values	Total		
Number of subjects	119		
Age categorical Units: Subjects			
Adults (18-64 years)	113		
From 65-84 years	6		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	93		
Male	26		
Race/Ethnicity, Customized Units: Subjects			
Asian - Non-Japanese	2		
Black or African American	6		

White	101		
Not Reported	2		
American Indian or Alaska Native	8		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	21		
Not Hispanic or Latino	97		
Unknown or Not Reported	1		

End points

End points reporting groups

Reporting group title	SLE- Placebo
Reporting group description:	
Participants with systemic lupus erythematosus (SLE) receive placebo once daily (QD) during a 24-week double-blind placebo-controlled treatment period.	
Reporting group title	SLE- Branebrutinib
Reporting group description:	
Participants with systemic lupus erythematosus (SLE) receive branebrutinib 9mg once daily (QD) during a 24-week double-blind placebo-controlled treatment period.	
Reporting group title	pSS- Placebo
Reporting group description:	
Participants with primary Sjögren's syndrome (pSS) receive placebo once daily (QD) during a 24-week double-blind placebo-controlled treatment period.	
Reporting group title	pSS- Branebrutinib
Reporting group description:	
Participants with primary Sjögren's syndrome (pSS) receive branebrutinib 9mg once daily (QD) during a 24-week double-blind placebo-controlled treatment period.	
Reporting group title	RA- Placebo
Reporting group description:	
Participants with rheumatoid arthritis (RA) receive placebo once daily (QD) during a 12-week double-blind placebo-controlled treatment period, followed by an additional 12 weeks of treatment with open-label abatacept.	
Reporting group title	RA- Branebrutinib
Reporting group description:	
Participants with rheumatoid arthritis (RA) receive branebrutinib 9mg once daily (QD) during a 12-week double-blind placebo-controlled treatment period, followed by an additional 12 weeks of treatment with open-label abatacept.	

Primary: The Percent of Participants with mCLASI Response at Week 24 and Corticosteroid (CS) < 10 mg/day at Week 20 and Week 24 - SLE

End point title	The Percent of Participants with mCLASI Response at Week 24 and Corticosteroid (CS) < 10 mg/day at Week 20 and Week 24 - SLE[1]
End point description:	
mCLASI response is defined as a decrease of ≥ 50% from baseline mCLASI activity score, in participants with a baseline mCLASI activity score ≥ 10, at Week 24. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment. To be considered as meeting the second criterion, the CS (prednisone or equivalent) dose had to remain stable and ≤ 10 mg from Week 16 until Week 24. The modified CLASI (mCLASI) is defined as the activity portions of CLASI that describe skin erythema and scale/hypertrophy and inflammation of the scalp. The percentage of patients who entered the study with a positive mCLASI activity score (≥ 10) and who achieved a ≥ 50% decrease from baseline at Week 24 is considered to likely represent a clinically meaningful improvement. The scores are calculated by simple addition based on the extent of the symptoms. mCLASI: Modified Cutaneous Lupus Erythematosus Disease Area and Severity Index	
End point type	Primary
End point timeframe:	
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: Endpoint is Specific only to the SLE Cohort

End point values	SLE- Placebo	SLE- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	15		
Units: Percentage of participants				
number (confidence interval 95%)	60.0 (17.1 to 100)	33.3 (9.5 to 57.2)		

Statistical analyses

Statistical analysis title	ODDS RATIO (95% CI) VS PLACEBO
Comparison groups	SLE- Placebo v SLE- Branebrutinib
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3117
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	2.73

Statistical analysis title	RESPONSE DIFFERENCE (95% CI) VS PLACEBO
Comparison groups	SLE- Placebo v SLE- Branebrutinib
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Response Difference
Point estimate	-27.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77.5
upper limit	21.9

Primary: The Percent of Participants with Composite Response at Week 24 - pSS

End point title	The Percent of Participants with Composite Response at Week

	24 - pSS[2]

End point description:

Composite response is defined as the percent of participants with at least 3 of the following at Week 24:
• Decrease of ≥ 1 point or 15% from baseline in the ESSPRI Total Score
• Decrease of ≥ 3 points from baseline in ESSDAI score
• Decrease of ≥ 25% from baseline in ocular staining score, or if normal score at baseline no change to abnormal
• Increase of ≥ 25% from baseline in stimulated salivary flow
• Improvement in one or more serological markers (rheumatoid factor (RF), immunoglobulin G protein (IgG), complement C3 or C4, cryoglobulin).

End point type	Primary

End point timeframe:

Week 24

Notes:

[2] - 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: Endpoint is Specific only to the pSS Cohort

End point values	pSS- Placebo	pSS- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	10		
Units: Percent of Participants				
number (confidence interval 95%)	25 (0.0 to 67.4)	10.0 (0.0 to 28.6)		

Statistical analyses

Statistical analysis title	ODDS RATIO VS PLACEBO
Comparison groups	pSS- Placebo v pSS- Branebrutinib
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.1639
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.39

Statistical analysis title	RESPONSE DIFFERENCE (95% CI) VS PLACEBO
Comparison groups	pSS- Placebo v pSS- Branebrutinib

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response Difference
Point estimate	-11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.1
upper limit	33.3

Primary: Percent of Participants with ACR50 Response at Week 12 Compared to Baseline - RA

End point title	Percent of Participants with ACR50 Response at Week 12 Compared to Baseline - RA[3]

End point description:

ACR50 response is defined as both improvement of 50% in the number of tender and swollen joints and a 50% improvement in 3 of the following 5 criteria:

- Subject global assessment (SGA)
- Physician global assessment (PGA)
- Functional ability measure
- Pain visual analog scale (VAS)
- Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

Baseline values are defined as the last nonmissing value prior to the first dose of study treatment.

End point type	Primary

End point timeframe:

Week 12

Notes:

[3] - 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: Endpoint is Specific only to the RA Cohort

End point values	RA- Placebo	RA- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	64		
Units: Percent of Participants				
number (confidence interval 95%)	33.3 (13.2 to 53.5)	18.8 (9.2 to 28.3)		

Statistical analyses

Statistical analysis title	ODDS RATIO VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1639
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.39

Statistical analysis title	RESPONSE DIFFERENCE VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response Difference
Point estimate	-14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.9
upper limit	7.7

Secondary: Change from Baseline in SLEDAI-2K Score at Week 24 - SLE

End point title	Change from Baseline in SLEDAI-2K Score at Week 24 - SLE[4]

End point description:

The SLEDAI-2K is a global index providing a total score of overall disease activity ranging from 0 to 105, with higher scores representing more active disease. The SLEDAI index includes 24 items divided into 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and hematological. Each item is scored based on the severity of the symptom or finding, with higher scores indicating more severe disease activity. The weighted scores for each item range from 0 to 8. To calculate the SLEDAI-2K score, the scores for each of the 24 items are added together.

Baseline values are defined as the last nonmissing value prior to the first dose of study treatment.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[4] - 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: Endpoint is Specific only to the SLE Cohort

End point values	SLE- Placebo	SLE- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Change in "score on a scale"				
arithmetic mean (standard deviation)	-7.0 (± 5.29)	-7.0 (± 6.54)		

Statistical analyses

Statistical analysis title	ADJUSTED MEAN DIFFERENCE VS PLACEBO
Comparison groups	SLE- Placebo v SLE- Branebrutinib
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	4.9

Secondary: Percent of Participants with BICLA Response at Week 24 - SLE

End point title	Percent of Participants with BICLA Response at Week 24 -

End point description:

BILAG-based composite lupus assessment (BICLA) response is defined as:
1. At least one gradation of improvement in baseline BILAG scores in all body systems with moderate or severe disease activity at entry
2. No new BILAG A or more than one new BILAG B scores
3. No worsening of total SLEDAI score from baseline
4. No significant deterioration (< 10%) in PGA and
5. No treatment failure (initiation of nonprotocol treatment).

BILAG scores: A (severe disease), B (moderate), C (mild), or D (no activity).
Baseline values are defined as the last nonmissing value prior to the first dose of study treatment.

End point type	Secondary

End point timeframe:

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: Endpoint is Specific only to the SLE Cohort

End point values	SLE- Placebo	SLE- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	15		
Units: Percent of participants				
number (confidence interval 95%)	20.0 (0.5 to 71.6)	33.3 (11.8 to 61.6)		

Statistical analyses

Statistical analysis title	ODDS RATIO VS PLACEBO
Comparison groups	SLE- Placebo v SLE- Branebrutinib
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	18.04

Statistical analysis title	RESPONSE DIFFERENCE VS PLACEBO
Comparison groups	SLE- Placebo v SLE- Branebrutinib
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response Difference
Point estimate	16.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.8
upper limit	65.2

Secondary: Change from Baseline in DAS28-CRP at Week 12 - RA	
End point title	Change from Baseline in DAS28-CRP at Week 12 - RA[6]

End point description:

The Disease Activity Score-28-C-Reactive Protein (DAS28CRP) is a composite outcome assessment that measures: 1) How many joints in the hands, wrists, elbows, shoulders, and knees are swollen and/or tender over a total of 28, 2) CRP in the blood to measure the degree of inflammation, and 3) SGA of disease activity.

DAS28-CRP scores range from 1.0 to 9.4, where lower scores indicate less disease activity. The results are combined to produce the DAS28-CRP score, which correlates with the extent of disease activity:
< 2.6: Disease remission
2.6 – 3.2: Low disease activity
3.2 – 5.1: Moderate disease activity
> 5.1: High disease activity

A negative change from baseline in DAS28-CRP indicates an improvement. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[6] - 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: Endpoint is Specific only to the RA Cohort

End point values	RA- Placebo	RA- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	58		
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.615 (± 1.19545)	-1.542 (± 1.0790)		

Statistical analyses

Statistical analysis title	ADJUSTED MEAN DIFFERENCE VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.534
upper limit	0.62

Secondary: Change from baseline in SDAI at Week 12- RA

End point title	Change from baseline in SDAI at Week 12- RA[7]

End point description:

The Simplified Disease Activity Index (SDAI) is the sum of the tender joint score (range 0 to 28), the swollen joint score (range 0 to 28), the subject global assessment (SGA) of disease activity (range 0 to 10 in increments of 0.5), the PGA of disease activity (range 0 to 10 in increments of 0.5), and C-reactive protein (CRP) test result. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[7] - 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: Endpoint is Specific only to the RA Cohort

End point values	RA- Placebo	RA- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	58		
Units: Score on a scale				
arithmetic mean (standard deviation)	-19.430 (± 12.5890)	-18.303 (± 11.5793)		

Statistical analyses

Statistical analysis title	ADJUSTED MEAN DIFFERENCE VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.728
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.463
upper limit	6.919

Secondary: Change from baseline in DAS28-ESR at Week 12 - RA

End point title	Change from baseline in DAS28-ESR at Week 12 - RA[8]

End point description:

The Disease Activity Score Erythrocyte Sedimentation Rate - DAS28ESR is a composite outcome assessment that measures:

1) How many joints in the hands, wrists, elbows, shoulders, and knees are swollen and/or tender over a total of 28
2) ESR in the blood to measure the degree of inflammation
3) SGA of disease activity

DAS28-ESR scores range from 1.0 to 9.4, where lower scores indicate less disease activity. The results are combined to produce the DAS28-ESR score, which correlates with the extent of disease activity:
< 2.6: Disease remission
2.6 – 3.2: Low disease activity
3.2 – 5.1: Moderate disease activity
> 5.1: High disease activity

A negative change from baseline in DAS28-ESR indicates an improvement. Baseline values are defined as the last nonmissing value prior to the first dose of study treatment.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[8] - 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: Endpoint is Specific only to the RA Cohort

End point values	RA- Placebo	RA- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	58		
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.758 (± 1.1932)	-1.670 (± 1.1487)		

Statistical analyses

Statistical analysis title	ADJUSTED MEAN DIFFERENCE VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.553
upper limit	0.639

Secondary: Percent of Participants with ACR20 Response Compared to Baseline at Week 12 - RA

End point title	Percent of Participants with ACR20 Response Compared to Baseline at Week 12 - RA[9]

End point description:

ACR20 defined as both improvement of 20% in the number of tender and swollen joints and a 20% improvement in 3 of the following 5 criteria:

- Subject global assessment (SGA)
- Physician global assessment (PGA)
- Functional ability measure
- Pain visual analog scale (VAS)
- Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

Baseline values are defined as the last nonmissing value prior to the first dose of study treatment.

End point type	Secondary

End point timeframe:

Week 12

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: Endpoint is Specific only to the RA Cohort

End point values	RA- Placebo	RA- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	64		
Units: Percent of Participants				
number (confidence interval 95%)	61.9 (41.1 to 82.7)	57.8 (45.7 to 69.9)		

Statistical analyses

Statistical analysis title	ODDS RATIO VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	2.32

Statistical analysis title	RESPONSE DIFFERENCE VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response Difference
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.1
upper limit	19.9

Secondary: Change from baseline in CDAI at Week 12 - RA

End point title	Change from baseline in CDAI at Week 12 - RA[10]

End point description:

The Clinical Disease Activity Index (CDAI) is the sum of the tender joint score (range 0 to 28), the swollen joint score (range 0 to 28), the SGA of disease activity (range 0 to 10 in increments of 0.5), and the PGA of disease activity (range 0 to 10 in increments of 0.5). Baseline values are defined as the last nonmissing value prior to the first dose of study treatment.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[10] - 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: Endpoint is Specific only to the RA Cohort

End point values	RA- Placebo	RA- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	58		
Units: Score on a scale				
arithmetic mean (standard deviation)	-19.4 (± 12.07)	-18.0 (± 11.01)		

Statistical analyses

Statistical analysis title	ADJUSTED MEAN DIFFERENCE VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	6.6

Secondary: Percent of Participants with ACR70 Response Compared to Baseline at Week 12 - RA

End point title	Percent of Participants with ACR70 Response Compared to Baseline at Week 12 - RA[11]

End point description:

ACR70 is defined as both improvement of 70% in the number of tender and swollen joints and a 70% improvement in 3 of the following 5 criteria:

- Subject global assessment (SGA)
- Physician global assessment (PGA)
- Functional ability measure
- Pain visual analog scale (VAS)
- Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

Baseline values are defined as the last nonmissing value prior to the first dose of study treatment.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[11] - 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: Endpoint is Specific only to the RA Cohort

End point values	RA- Placebo	RA- Branebrutinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	64		
Units: Percent of Participants				
number (confidence interval 95%)	14.3 (0.0 to 29.3)	7.8 (1.2 to 14.4)		

Statistical analyses

Statistical analysis title	RESPONSE DIFFERENCE VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response Difference
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.8
upper limit	9.9

Statistical analysis title	ODDS RATIO VS PLACEBO
Comparison groups	RA- Placebo v RA- Branebrutinib
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	2.34

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from participants first dose to their study completion (up to approximately 32 weeks) SAEs and Other AEs were assessed from first dose to 30 days following last dose (up to approximately 30 weeks)

Adverse event reporting additional description:

TEAEs are defined as AEs that occur after the participant received first dose of study treatment or if a preexisting condition worsens in severity or becomes serious after receiving the first dose of study treatment up to 30 days after the last dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	SLE- Placebo

Reporting group description:

Participants with systemic lupus erythematosus (SLE) receive placebo once daily (QD) during a 24-week double-blind placebo-controlled treatment period.

Reporting group title	SLE- Branebrutinib

Reporting group description:

Participants with systemic lupus erythematosus (SLE) receive branebrutinib 9mg once daily (QD) during a 24-week double-blind placebo-controlled treatment period.

Reporting group title	pSS- Placebo

Reporting group description:

Participants with primary Sjögren's syndrome (pSS) receive placebo once daily (QD) during a 24-week double-blind placebo-controlled treatment period.

Reporting group title	RA- Abatacept

Reporting group description:

Participants with rheumatoid arthritis (RA) receive 12 weeks of treatment with open-label abatacept.

Reporting group title	RA- Placebo

Reporting group description:

Participants with rheumatoid arthritis (RA) receive placebo once daily (QD) during a 12-week double-blind placebo-controlled treatment period, followed by an additional 12 weeks of treatment with open-label abatacept.

Reporting group title	RA- Branebrutinib

Reporting group description:

Participants with rheumatoid arthritis (RA) receive branebrutinib 9mg once daily (QD) during a 12-week double-blind placebo-controlled treatment period.

Reporting group title	pSS- Branebrutinib

Reporting group description:

Participants with primary Sjögren's syndrome (pSS) receive branebrutinib 9mg once daily (QD) during a 24-week double-blind placebo-controlled treatment period.

Serious adverse events	SLE- Placebo	SLE- Branebrutinib	pSS- Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from			

adverse events

Serious adverse events	RA- Abatacept	RA- Placebo	RA- Branebrutinib
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	pSS- Branebrutinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	SLE- Placebo	SLE- Branebrutinib	pSS- Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	14 / 15 (93.33%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injection site swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Asthenia			

subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Stress			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastric pH decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Animal scratch			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Scratch			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vaccination complication			

subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Enterocolitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Drug eruption			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rotator cuff syndrome			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Pharyngotonsillitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	3 / 4 (75.00%)
occurrences (all)	0	3	3
Hordeolum			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	3 / 15 (20.00%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dyslipidaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	RA- Abatacept	RA- Placebo	RA- Branebrutinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 81 (6.17%)	6 / 21 (28.57%)	13 / 64 (20.31%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Discomfort			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Stress			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Gastric pH decreased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 81 (0.00%)	1 / 21 (4.76%)	1 / 64 (1.56%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Animal scratch			

subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Scratch			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Vaccination complication			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 81 (0.00%)	2 / 21 (9.52%)	1 / 64 (1.56%)
occurrences (all)	0	2	1
Headache			
subjects affected / exposed	1 / 81 (1.23%)	1 / 21 (4.76%)	1 / 64 (1.56%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Dry eye			

subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 81 (1.23%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Enterocolitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Drug eruption			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 21 (4.76%)	0 / 64 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Rotator cuff syndrome			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	0 / 81 (0.00%)	2 / 21 (9.52%)	5 / 64 (7.81%)
occurrences (all)	0	2	5
Upper respiratory tract infection			
subjects affected / exposed	0 / 81 (0.00%)	1 / 21 (4.76%)	2 / 64 (3.13%)
occurrences (all)	0	1	2
Pharyngotonsillitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Otitis media acute			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 21 (4.76%)	1 / 64 (1.56%)
occurrences (all)	1	1	1
Hordeolum			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Dyslipidaemia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 21 (0.00%)	0 / 64 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	pSS- Branebrutinib		
Total subjects affected by non-serious			

adverse events subjects affected / exposed	8 / 10 (80.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma subjects affected / exposed occurrences (all)	 0 / 10 (0.00%) 0		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Injection site swelling subjects affected / exposed occurrences (all) Discomfort subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all)	 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 0 / 10 (0.00%) 0		
Psychiatric disorders Stress subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all) Gastric pH decreased subjects affected / exposed occurrences (all) Gamma-glutamyltransferase increased	 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0		

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Animal scratch			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Scratch			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Vaccination complication			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Sunburn			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Ventricular extrasystoles			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Eye disorders Ocular hyperaemia subjects affected / exposed occurrences (all) Dry eye subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Enterocolitis subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all)	 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all) Drug eruption subjects affected / exposed occurrences (all)	 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0		
Musculoskeletal and connective tissue disorders Myalgia			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Bursitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
COVID-19			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pharyngotonsillitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Otitis media acute			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Hordeolum			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Metabolism and nutrition disorders Hypertriglyceridaemia subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2019	Updated RA sub-protocol to exclude combination therapy of branebrutinib and abatacept, revised timing period for collection of nonserious AEs in all sub-protocols, updated and aligned branebrutinib PK sampling schedule in all sub-protocols to accommodate change in RA protocol design
18 December 2019	Updated RA sub-protocol to include omitted joint assessor instructions, Updated all sub-protocols to current BMS standards for reproductive status inclusion criteria
30 March 2021	Added section for study termination for unexpectedly unfavorable risk/benefit balance; added information/guidance related to SARS-CoV-2 infection/COVID-19 pandemic, changed the maximum age of the study population; clarified CS requirements (SLE sub-protocol only); excluded subjects with diagnosis of antiphospholipid syndrome from SLE sub-protocol, etc
01 December 2021	Changed timing for primary endpoint and other efficacy, safety, PK, and PD analysis for the RA sub-protocol; included patient-reported outcome assessments as Additional endpoints in all 3 sub-protocols; updated unintentionally omitted changes in inclusion criteria in RA sub-protocol schema; clarified PK and biomarker blood samples to be collected for abatacept and branebrutinib, respectively, at Week 24 in the RA sub-protocol; added unintentionally omitted biomarker blood sample collections for BTK occupancy from Week 0 to Week 12 in the RA sub-protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported