Clinical trial results:
Title: A multicenter, randomized, double-blind, placebo-controlled Phase 3 trial to evaluate efficacy and safety of lenabasum in diffuse cutaneous systemic sclerosis

Design: This was a Phase 3, 2-part, randomised, double-blind, placebo-controlled, multicentre, interventional, parallel-dose study (Part A), followed by an open-label extension study (Part B), to assess the efficacy and safety of lenabasum in subjects with diffuse cutaneous systemic sclerosis (dcSSc). In Part A, subjects were randomised to receive blinded study product (lenabasum 5 mg twice daily [BID] or 20 mg BID, or placebo) for 52 weeks. Subjects treated with study product who completed Part A and a 31-day off treatment withdrawal period were rolled over to Part B. In Part B (open-label), subjects received powder-in-capsules of lenabasum 20 mg BID for up to 2 years.

Summary

EudraCT number	2017-000372-29
Trial protocol	GB DE NL ES PL IT
Global end of trial date	14 December 2020
Results information	
Result version number	v1 (current)
This version publication date	22 May 2022
First version publication date	22 May 2022

Trial information

Trial identification	
Sponsor protocol code	JBT101-SSc-002
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02465437
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Corbus Pharmaceuticals, Inc.
Sponsor organisation address	500 River Ridge Drive, Norwood, United States, MA 02062
Public contact	Corbus General Information, Corbus Pharmaceuticals, Inc., +1 617-963-0100, info@corbuspharma.com
Scientific contact	Corbus General Information, Corbus Pharmaceuticals, Inc., +1 617-963-0100, info@corbuspharma.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	17 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2020
Global end of trial reached?	Yes
Global end of trial date	14 December 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Part A:
In all countries except Japan, the primary efficacy objective was to evaluate the efficacy of lenabasum compared to placebo in the treatment of SSc by assessing the American College of Rheumatology (ACR) Provisional Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score at Visit 11 (Week 52), comparing lenabasum 20 mg twice per day (BID) and placebo cohorts. In Japan, the primary efficacy objective was the change in mRSS at Visit 11 (Week 52), comparing lenabasum 20 mg BID and placebo cohorts.

Part B: To evaluate the efficacy and safety of lenabasum in the treatment of dcSSc by evaluating changes in the CRISS at the end of the open-label follow-up period (Part B) compared with Part A baseline. In Part B, all subjects were treated with Lenabasum 20 mg twice daily (BID).

Protection of trial subjects:

The final region-specific protocols, amendments or addendums, and informed consent documentation were reviewed and approved by the Ethics Committee at the investigational centre(s) participating in the study.

This study was conducted in accordance with the international ethical principles originating in or derived from the Declaration of Helsinki and in compliance with the principles of the International Council for Harmonisation Good Clinical Practice. In addition, the guidelines from relevant regulatory authorities, applicable government regulations, and institutional research policies and procedures were followed.

Background therapy:

Concomitant therapies taken for chronic treatment of pre-existing conditions could be continued during the study provided they were in accordance with the eligibility criteria. It was preferred that these medications be stabilised before entry and continued wherever practical without variation of dose or regimen during the study.

Doses of non-corticosteoiod immunosuppressant medications had to be stable for ≥8 weeks at Screening. The intent was to allow all immunosuppressive medications that the subject had been receiving as standard-of-care by the treating physician, with the exception that doses of oral prednisone greater than 10 mg per day (or equivalent) were not permitted for at least 28 days prior to Visit 1. Intravenous prednisone was not permitted within 28 days before Visit 1. However, it was acknowledged that signs and symptoms of SSc may worsen or improve during this long-term study and adjustments in medications could have been required to provide the subject with best medical care.

Evidence for comparator:

Part A: the randomised comparator was placebo. Subjects continued on immunosuppressive medications as needed, as detailed above.

Part B: No comparator; this was an open-label treatment period with all patients treated with lenabasum 20 mg BID.

Actual start date of recruitment	29 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Japan: 35
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Israel: 35
Country: Number of subjects enrolled	United States: 135
Worldwide total number of subjects	365
EEA total number of subjects	82

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)	313
From 65 to 84 years	51
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The first subject was randomised on 29 Jan 2018 and the last visit in Part B was 14 December 2020. In total, 365 subjects were randomised and treated worldwide, including 82 in the EEA and 135 in the USA. Baseline data is presented for randomised, treated patients.

Pre-assignment

Screening details:

Screening occurred up to 28 days prior to Visit 1 of Part A of the study, to ensure patients met entry criteria. Patients were on stable background treatments for SSc, including background immunosuppressive therapy (IST), except cyclophosphamide. They were not to have started or increased their dose of IST therapy within 8 weeks of screening.

Period 1

Period 1 title	Randomised controlled trial (Part A)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

In Part A of the study, treatment with lenabasum (5 mg BID or 20 mg BID) or placebo was randomly assigned and blinded. Lenabasum and placebo capsules had similar physical appearance and were packaged, labelled, and handled so that patients and site staff were not able to distinguish treatments.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenabasum 5 mg BID Part A

Arm description:

Patients in Part A randomised to treatment with lenabasum 5 mg BID. Data presented represents the modified intent-to-treat (mITT) population.

Arm type	All treated patients
Investigational medicinal product name	Lenabasum 5 mg BID
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5 mg Lenabasum, taken orally twice daily (total dose: 10 mg lenabasum per day)

Arm title	Lenabasum 20 mg BID Part A

Arm description:

Patients in Part A randomised to treatment with lenabasum 20 mg BID. Data presented represents the modified intent-to-treat (mITT) population.

Arm type	Experimental
Investigational medicinal product name	Lenabasum 20 mg BID
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg Lenabasum, taken orally twice daily (total dose: 40 mg lenabasum per day)

Arm title	Placebo in Part A

Arm description:

Patients in Part A randomised to treatment with placebo. Data presented represents the modified intent-to-treat (mITT) population.

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

Dosage and administration details:

Placebo, taken orally twice daily.

Number of subjects in period 1	Lenabasum 5 mg BID Part A	Lenabasum 20 mg BID Part A	Placebo in Part A
Started	122	120	123
Completed	113	100	115
Not completed	9	20	8
Adverse event, serious fatal	-	2	1
Consent withdrawn by subject	3	10	1
Physician decision	-	2	-
Non-compliance with study	2	-	-
Adverse event, non-fatal	1	5	6
Lack of efficacy - physician decision	1	-	-
Lack of efficacy - withdrawal by subject	1	-	-
Lost to follow-up	1	1	-

Period 2

Period 2 title	Open label extension (Part B)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Part B was an open-label treatment period following on from Part A. All patients were treated with lenabasum 20 mg (no blinding required). Reporting groups present patients according to randomised treatment in Part A (lenabasum or placebo) as well as a group with the total patients in Part B (i.e., all patients appear twice in the reporting groups - once in one of the randomised groups AND once in the total group for Part B).

Arms

Are arms mutually exclusive?	No

Arm title	Part B (Lenabasum in Part A)

Arm description:

All patients treated with 20 mg lenabasum twice daily in Part B (patients who had been treated with either 5 mg or 20 lenabasum in Part A). This represents the safety population.

Arm type	Experimental
Investigational medicinal product name	Lenabasum 20 mg BID
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg Lenabasum, taken orally twice daily (total dose: 40 mg lenabasum per day)

Arm title	Part B (placebo in Part A)

Arm description:

All patients treated with 20 mg lenabasum twice daily in Part B (patients who had been treated with placebo in Part A). This represents the safety population.

Arm type	Experimental
Investigational medicinal product name	Lenabasum 20 mg BID
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg Lenabasum, taken orally twice daily (total dose: 40 mg lenabasum per day)

Arm title	Part B (all patients)

Arm description:

All patients treated with 20 mg lenabasum twice daily in Part B (patients who had been treated with either 5 mg or 20 lenabasum or placebo in Part A). This represents the safety population.

Arm type	Experimental
Investigational medicinal product name	Lenabasum 20 mg BID
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg Lenabasum, taken orally twice daily (total dose: 40 mg lenabasum per day)

Number of subjects in period 2	Part B (Lenabasum in Part A)	Part B (placebo in Part A)	Part B (all patients)
Started	205	111	316
Completed	0	0	0
Not completed	205	111	316
Consent withdrawn by subject	6	2	8
Physician decision	-	1	1
Study terminated by Sponsor	195	107	302
Adverse event, non-fatal	2	-	2
Lost to follow-up	1	-	1

Lack of efficacy	1	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Lenabasum 5 mg BID Part A
Reporting group description:	
Patients in Part A randomised to treatment with lenabasum 5 mg BID. Data presented represents the modified intent-to-treat (mITT) population.	
Reporting group title	Lenabasum 20 mg BID Part A
Reporting group description:	
Patients in Part A randomised to treatment with lenabasum 20 mg BID. Data presented represents the modified intent-to-treat (mITT) population.	
Reporting group title	Placebo in Part A
Reporting group description:	
Patients in Part A randomised to treatment with placebo. Data presented represents the modified intent-to-treat (mITT) population.	

Reporting group values	Lenabasum 5 mg BID Part A	Lenabasum 20 mg BID Part A	Placebo in Part A
Number of subjects	122	120	123
Age categorical Units: Subjects			
Adults (18-64 years)	102	107	104
From 65-84 years	20	12	19
85 years and over	0	1	0
Gender categorical Units: Subjects			
Female	89	96	91
Male	33	24	32
Part A baseline mRSS total score			
modified Rodnan Skin Score Note, summary statistics were calculated for patients included in the analysis of mRSS score (i.e., the mITT population); consequently, 2 patients in the baseline reporting group (safety population) for Lenabasum 5 mg are not included in this table (N=120 for Lenabasum 5 mg).			
Units: mRSS score			
arithmetic mean	22.0	22.1	23.3
standard deviation	± 7.35	± 8.55	± 8.68
Part A baseline HAQ-DI score			
Health Assessment Questionnaire Disability Index			
Units: HAQ-DI score			
arithmetic mean	1.0719	1.1219	1.575
standard deviation	± 0.76468	± 0.78179	± 0.76769
Part A baseline FVC% predicted			
The FEV1/FVC Ratio (FVC%) parameter is calculated by dividing the measured FEV1 value by the measured FVC value. The predicted value shows the ratio expressed as a percentage.			
Units: percent			
arithmetic mean	79.481	81.279	78.925
standard deviation	± 16.1321	± 18.8347	± 15.2292

Reporting group values	Total		
Number of subjects	365		

Age categorical Units: Subjects			
Adults (18-64 years)	313		
From 65-84 years	51		
85 years and over	1		
Gender categorical Units: Subjects			
Female	276		
Male	89		
Part A baseline mRSS total score			
modified Rodnan Skin Score Note, summary statistics were calculated for patients included in the analysis of mRSS score (i.e., the mITT population); consequently, 2 patients in the baseline reporting group (safety population) for Lenabasum 5 mg are not included in this table (N=120 for Lenabasum 5 mg).			
Units: mRSS score arithmetic mean standard deviation	 -		
Part A baseline HAQ-DI score			
Health Assessment Questionnaire Disability Index			
Units: HAQ-DI score arithmetic mean standard deviation	 -		
Part A baseline FVC% predicted			
The FEV1/FVC Ratio (FVC%) parameter is calculated by dividing the measured FEV1 value by the measured FVC value. The predicted value shows the ratio expressed as a percentage.			
Units: percent arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Lenabasum 5 mg BID Part A
Reporting group description:	
Patients in Part A randomised to treatment with lenabasum 5 mg BID. Data presented represents the modified intent-to-treat (mITT) population.	
Reporting group title	Lenabasum 20 mg BID Part A
Reporting group description:	
Patients in Part A randomised to treatment with lenabasum 20 mg BID. Data presented represents the modified intent-to-treat (mITT) population.	
Reporting group title	Placebo in Part A
Reporting group description:	
Patients in Part A randomised to treatment with placebo. Data presented represents the modified intent-to-treat (mITT) population.	
Reporting group title	Part B (Lenabasum in Part A)
Reporting group description:	
All patients treated with 20 mg lenabasum twice daily in Part B (patients who had been treated with either 5 mg or 20 lenabasum in Part A). This represents the safety population.	
Reporting group title	Part B (placebo in Part A)
Reporting group description:	
All patients treated with 20 mg lenabasum twice daily in Part B (patients who had been treated with placebo in Part A). This represents the safety population.	
Reporting group title	Part B (all patients)
Reporting group description:	
All patients treated with 20 mg lenabasum twice daily in Part B (patients who had been treated with either 5 mg or 20 lenabasum or placebo in Part A). This represents the safety population.	

Primary: ACR CRISS Score (Improvement Probability) - Part A

End point title	ACR CRISS Score (Improvement Probability) - Part A
End point description:	
End point type	Primary
End point timeframe:	
The ACR CRISS Score (Improvement Probability) at Visit 11 (Week 52).	

End point values	Lenabasum 5 mg BID Part A	Lenabasum 20 mg BID Part A	Placebo in Part A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	100	115	
Units: ACR CRISS score				
median (inter-quartile range (Q1-Q3))	0.8270 (0.0700 to 0.9880)	0.8880 (0.0610 to 0.9970)	0.8870 (0.0710 to 0.9990)	

Statistical analyses

Statistical analysis title	Lenabasum 20 mg vs Placebo

Statistical analysis description:

A comparison of median ACR CRISS scores between the 20 mg lenabasum group and the placebo group.

Comparison groups	Lenabasum 20 mg BID Part A v Placebo in Part A
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.4972
Method	Mixed models analysis

Notes:

[1] - Combined inference statistics. Each imputation dataset is analysed using mixed models for repeated measures (MMRM) on the ranked ACR CRISS score with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline mRSS as a covariate.

Statistical analysis title	Lenabasum 5 mg vs Placebo

Statistical analysis description:

A comparison of median ACR CRISS scores between the 5 mg lenabasum group and the placebo group.

Comparison groups	Lenabasum 5 mg BID Part A v Placebo in Part A
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.3486
Method	Mixed models analysis

Notes:

[2] - Combined inference statistics. Each imputation dataset is analysed using mixed models for repeated measures (MMRM) on the ranked ACR CRISS score with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline mRSS as a covariate.

Secondary: Change in mRSS Score - Part A

End point title	Change in mRSS Score - Part A

End point description:

Change in mRSS score from baseline in subjects treated with lenabasum 5 mg or 20 mg BID and placebo BID in Part A of the study. This was a secondary endpoint for the study, but the primary endpoint for patients in Japan.

End point type	Secondary

End point timeframe:

Change from baseline to Visit 11 (Week 52).

End point values	Lenabasum 5 mg BID Part A	Lenabasum 20 mg BID Part A	Placebo in Part A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	100	115	
Units: mRSS Score				
arithmetic mean (standard deviation)	-7.1 (± 6.24)	-6.7 (± 6.59)	-8.1 (± 7.72)	

Statistical analyses

Statistical analysis title	Lenabasum 20 mg vs Placebo

Statistical analysis description:

A comparison of mean mRSS scores between the 20 mg lenabasum group and the placebo group.

Comparison groups	Lenabasum 20 mg BID Part A v Placebo in Part A
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.1183
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	3.3

Notes:

[3] - Based on an MMRM with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline mRSS as a covariate.

Statistical analysis title	Lenabasum 5 mg vs Placebo

Statistical analysis description:

A comparison of mean mRSS scores between the 5 mg lenabasum group and the placebo group.

Comparison groups	Placebo in Part A v Lenabasum 5 mg BID Part A
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.5036
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	2.4

Notes:

[4] - Based on an MMRM with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline mRSS as a covariate.

Secondary: Change in HAQ-DI Score - Part A

End point title	Change in HAQ-DI Score - Part A

End point description:

Change in HAQ-DI score from baseline in subjects treated with lenabasum 5 mg or 20 mg BID and placebo BID in Part A of the study.

End point type	Secondary

End point timeframe:

Change from baseline to Visit 11 (Week 52).

End point values	Lenabasum 5 mg BID Part A	Lenabasum 20 mg BID Part A	Placebo in Part A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	99	114	
Units: HAQ-DI Score				
arithmetic mean (standard deviation)	-0.0603 (± 0.39170)	-0.1326 (± 0.43625)	-0.1272 (± 0.46770)	

Statistical analyses

Statistical analysis title	Lenabasum 20 mg vs Placebo

Statistical analysis description:

A comparison of HAQ-DI scores between the 20 mg lenabasum group and the placebo group.

Comparison groups	Lenabasum 20 mg BID Part A v Placebo in Part A
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.7449
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.095
upper limit	0.1328

Notes:

[5] - Based on an MMRM with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline HAQ-DI score as a covariate.

Statistical analysis title	Lenabasum 5 mg vs Placebo

Statistical analysis description:

A comparison of HAQ-DI scores between the 5 mg lenabasum group and the placebo group.

Comparison groups	Placebo in Part A v Lenabasum 5 mg BID Part A
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.3216
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0557
upper limit	0.1691

Notes:

[6] - Based on an MMRM with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline HAQ-DI score as a covariate.

Secondary: Change in FVC% predicted value - Part A

End point title	Change in FVC% predicted value - Part A

End point description:

Change in FVC% predicted values from baseline in subjects treated with lenabasum 5 mg or 20 mg BID and placebo BID in Part A of the study.

End point type	Secondary

End point timeframe:

Change from baseline to Visit 11 (Week 52).

End point values	Lenabasum 5 mg BID Part A	Lenabasum 20 mg BID Part A	Placebo in Part A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	99	112	
Units: change in percentage score				
arithmetic mean (standard deviation)	-2.248 (± 6.2099)	-1.602 (± 6.9106)	-0.993 (± 8.6840)	

Statistical analyses

Statistical analysis title	Lenabasum 20 mg vs Placebo

Statistical analysis description:

A comparison of FVC% predicted scores between the 20 mg lenabasum group and the placebo group.

Comparison groups	Lenabasum 20 mg BID Part A v Placebo in Part A
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.5393
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.509
upper limit	1.315

Notes:

[7] - Based on an MMRM with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline FVC % predicted as a covariate.

Statistical analysis title	Lenabasum 5 mg vs Placebo

Statistical analysis description:

A comparison of FVC% predicted scores between the 5 mg lenabasum group and the placebo group.

Comparison groups	Placebo in Part A v Lenabasum 5 mg BID Part A
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.5158
Method	Mixed models analysis
Parameter estimate	LS Mean Difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.497
upper limit	1.256

Notes:

[8] - Based on an MMRM with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline FVC % predicted as a covariate.

Secondary: Change in FVC absolute value - Part A

End point title	Change in FVC absolute value - Part A

End point description:

Change in FVC absolute values from baseline in subjects treated with lenabasum 5 mg or 20 mg BID and placebo BID in Part A of the study.

End point type	Secondary

End point timeframe:

Change from baseline to Visit 11 (Week 52).

End point values	Lenabasum 5 mg BID Part A	Lenabasum 20 mg BID Part A	Placebo in Part A	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	99	112	
Units: litre(s)				
arithmetic mean (standard deviation)	-0.105 (± 0.2516)	-0.075 (± 0.2655)	-0.043 (± 0.3124)	

Statistical analyses

Statistical analysis title	Lenabasum 20 mg vs Placebo

Statistical analysis description:

A comparison of FVC absolute scores between the 20 mg lenabasum group and the placebo group.

Comparison groups	Lenabasum 20 mg BID Part A v Placebo in Part A
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.3219
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.036

Notes:

[9] - Based on an MMRM with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline FVC as a covariate.

Statistical analysis title	Lenabasum 5 mg vs Placebo

Statistical analysis description:

A comparison of FVC absolute scores between the 5 mg lenabasum group and the placebo group.

Comparison groups	Placebo in Part A v Lenabasum 5 mg BID Part A
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.3175
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.108
upper limit	0.035

Notes:

[10] - Based on an MMRM with region, disease duration (≤ 24 months vs > 24 months), Baseline mycophenolate use (Yes vs No), visit, treatment, and treatment-by-visit interaction as fixed effects and Baseline FVC as a covariate.

Secondary: ACR CRISS Score (Improvement Probability) - Part B

End point title	ACR CRISS Score (Improvement Probability) - Part B

End point description:

All patients treated with 20 mg lenabasum twice daily in Part B (patients who had been treated with either 5 mg or 20 lenabasum or placebo in Part A).

End point type	Secondary

End point timeframe:

The ACR CRISS Score (Improvement Probability) at Visit 10B (Week 68) related to baseline in Part A.

End point values	Part B (Lenabasum in Part A)	Part B (placebo in Part A)	Part B (all patients)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	17	
Units: ACR CRISS Score				
median (full range (min-max))	0.9835 (0.052 to 1.000)	0.9990 (0.640 to 1.000)	0.9920 (0.052 to 1.000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in mRSS Score - Part B

End point title	Change in mRSS Score - Part B

End point description:

Change in mRSS score from Part A baseline in subjects treated with lenabasum 20 mg BID in Part B of the study.

End point type	Secondary

End point timeframe:

Change from Part A baseline to Visit 10B (Week 68).

End point values	Part B (Lenabasum in Part A)	Part B (placebo in Part A)	Part B (all patients)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	6	18	
Units: mRSS Score				
arithmetic mean (standard deviation)	-10.3 (± 5.24)	-14.7 (± 6.95)	-11.7 (± 6.05)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HAQ-DI Score - Part B

End point title	Change in HAQ-DI Score - Part B

End point description:

Change in HAQ-DI score from Part A baseline in subjects treated with lenabasum 20 mg BID in Part B of the study.

End point type	Secondary

End point timeframe:

Change from Part A baseline to Visit 10B (Week 68).

End point values	Part B (Lenabasum in Part A)	Part B (placebo in Part A)	Part B (all patients)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	5	14	
Units: HAQ-DI Score				
arithmetic mean (standard deviation)	-0.4861 (± 0.39747)	-0.3250 (± 0.54199)	-0.4286 (± 0.44048)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in FVC% predicted value - Part B

End point title	Change in FVC% predicted value - Part B

End point description:

Change in FVC% predicted value from Part A baseline in subjects treated with lenabasum 20 mg BID in Part B of the study.

End point type	Secondary

End point timeframe:

Change from Part A baseline to Visit 10B (Week 68).

End point values	Part B (Lenabasum in Part A)	Part B (placebo in Part A)	Part B (all patients)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	17	
Units: change in percentage score				
arithmetic mean (standard deviation)	-0.185 (± 6.8241)	-0.494 (± 3.2118)	-0.276 (± 5.8835)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in FVC absolute value - Part B

End point title	Change in FVC absolute value - Part B

End point description:

Change in FVC absolute value from Part A baseline in subjects treated with lenabasum 20 mg BID in Part B of the study.

End point type	Secondary

End point timeframe:

Change from Part A baseline to Visit 10B (Week 68).

End point values	Part B (Lenabasum in Part A)	Part B (placebo in Part A)	Part B (all patients)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	5	17	
Units: litre(s)				
arithmetic mean (standard deviation)	-0.028 (± 0.2253)	-0.088 (± 0.1432)	-0.046 (± 0.2020)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to the end of the study. Part A comprised a 52-week double-bind treatment period. Part B was an open-label period with all patients treated with lenabasum (20 mg twice daily) for up to 2 years.

Adverse event reporting additional description:

Part A: Mean durations of exposure were 331.9 days and 349.8 days for lenabasum 20 mg and 5 mg BID, respectively, and 348.2 days for placebo.
Part B of the study was terminated early (primary efficacy endpoint in Part A was not met). The mean duration of exposure in Part B was 266.1 days (min, max: 1, 560).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Lenabasum 5 mg BID Part A

Reporting group description:

Patients in Part A randomised to treatment with lenabasum 5 mg BID.

Reporting group title	Lenabasum 20 mg BID Part A

Reporting group description:

Patients in Part A randomised to treatment with lenabasum 20 mg BID.

Reporting group title	Placebo Part A

Reporting group description:

Patients in Part A randomised to treatment with placebo.

Reporting group title	Part B lenabasum 20 mg BID (Lenabasum in Part A)

Reporting group description:

All patients in Part B were treated with 20 mg lenabasum BID (open label).

Reporting group title	Part B 20 mg lenabasum BID (placebo in Part A)

Reporting group description:

All patients in Part B were treated with 20 mg lenabasum BID (open label).

Reporting group title	Part B 20 mg lenabasum BID (all patients)

Reporting group description:

All patients in Part B were treated with 20 mg lenabasum BID (open label), regardless of double-blind treatment assignment in Part A.

Serious adverse events	Lenabasum 5 mg BID Part A	Lenabasum 20 mg BID Part A	Placebo Part A
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 122 (8.20%)	11 / 120 (9.17%)	18 / 123 (14.63%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Breast cancer			
subjects affected / exposed	0 / 122 (0.00%)	2 / 120 (1.67%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Epstein-Barr virus associated lymphoma			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Lung neoplasm			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer metastatic			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Thyroid cancer			

subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Leriche syndrome			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Pain			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Peripheral swelling			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (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

Pyrexia			
subjects affected / exposed	2 / 122 (1.64%)	0 / 120 (0.00%)	0 / 123 (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
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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			
Dyspnoea			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (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
Hypoxia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (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
Organising pneumonia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			

subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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			
Concussion			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (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
Femur fracture			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Procedural haemorrhage			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Radius fracture			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (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	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure congestive			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Myocarditis			
subjects affected / exposed	1 / 122 (0.82%)	1 / 120 (0.83%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spondylitic myelopathy			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	2 / 123 (1.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Iron deficiency anaemia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
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			
Enteritis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Faecaloma			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Gastritis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Gastrointestinal inflammation			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Haematemesis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Intestinal ischaemia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal food impaction			

subjects affected / exposed	0 / 122 (0.00%)	1 / 120 (0.83%)	0 / 123 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Skin and subcutaneous tissue disorders			
Scleroderma associated digital ulcer			
subjects affected / exposed	5 / 122 (4.10%)	1 / 120 (0.83%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Scleroderma renal crisis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	2 / 123 (1.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Joint contracture			

subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Osteochondritis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (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
Systemic scleroderma			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenosynovitis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Cellulitis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Diverticulitis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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 clostridial			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Infected skin ulcer			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (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
Localised infection			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	3 / 123 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Sepsis			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Skin infection			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	0 / 123 (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
Tonsillitis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 123 (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
Urinary tract infection			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B lenabasum 20 mg BID (Lenabasum in Part A)	Part B 20 mg lenabasum BID (placebo in Part A)	Part B 20 mg lenabasum BID (all patients)
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 205 (7.80%)	9 / 111 (8.11%)	25 / 316 (7.91%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus associated lymphoma			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Lung neoplasm			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Ovarian cancer metastatic			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 205 (0.49%)	1 / 111 (0.90%)	2 / 316 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thyroid cancer			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Leriche syndrome			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Chest pain			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Peripheral swelling			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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

Pyrexia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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			
Uterine polyp			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Interstitial lung disease			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Organising pneumonia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			

subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Femur fracture			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural haemorrhage			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure congestive			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Pericardial effusion			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Spondylitic myelopathy			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Transient global amnesia			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Iron deficiency anaemia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Gastrointestinal inflammation			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Haematemesis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Ileus paralytic			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Intestinal ischaemia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Oesophageal food impaction			

subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Volvulus			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 205 (0.49%)	1 / 111 (0.90%)	2 / 316 (0.63%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Scleroderma associated digital ulcer			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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			
Scleroderma renal crisis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint contracture			

subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondritis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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 scleroderma			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Tenosynovitis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Device related infection			

subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Diarrhoea infectious			
subjects affected / exposed	0 / 205 (0.00%)	1 / 111 (0.90%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Osteomyelitis			

subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Salmonellosis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 205 (0.49%)	0 / 111 (0.00%)	1 / 316 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (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
Urinary tract infection			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Lenabasum 5 mg BID Part A	Lenabasum 20 mg BID Part A	Placebo Part A
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 122 (90.16%)	110 / 120 (91.67%)	106 / 123 (86.18%)
Investigations			
Weight decreased			
subjects affected / exposed	3 / 122 (2.46%)	7 / 120 (5.83%)	6 / 123 (4.88%)
occurrences (all)	4	7	6
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 122 (2.46%)	7 / 120 (5.83%)	5 / 123 (4.07%)
occurrences (all)	4	7	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 122 (9.02%)	22 / 120 (18.33%)	6 / 123 (4.88%)
occurrences (all)	12	29	6
Headache			
subjects affected / exposed	14 / 122 (11.48%)	17 / 120 (14.17%)	9 / 123 (7.32%)
occurrences (all)	15	20	12
Paraesthesia			
subjects affected / exposed	8 / 122 (6.56%)	3 / 120 (2.50%)	2 / 123 (1.63%)
occurrences (all)	8	4	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 122 (8.20%)	10 / 120 (8.33%)	7 / 123 (5.69%)
occurrences (all)	10	12	8
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 122 (6.56%)	2 / 120 (1.67%)	5 / 123 (4.07%)
occurrences (all)	8	2	6
Diarrhoea			
subjects affected / exposed	16 / 122 (13.11%)	21 / 120 (17.50%)	18 / 123 (14.63%)
occurrences (all)	18	26	20
Dry mouth			
subjects affected / exposed	7 / 122 (5.74%)	6 / 120 (5.00%)	2 / 123 (1.63%)
occurrences (all)	7	6	2
Dysphagia			

subjects affected / exposed	9 / 122 (7.38%)	2 / 120 (1.67%)	0 / 123 (0.00%)
occurrences (all)	9	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 122 (4.10%)	7 / 120 (5.83%)	8 / 123 (6.50%)
occurrences (all)	5	8	8
Mouth ulceration			
subjects affected / exposed	2 / 122 (1.64%)	6 / 120 (5.00%)	0 / 123 (0.00%)
occurrences (all)	2	6	0
Nausea			
subjects affected / exposed	5 / 122 (4.10%)	17 / 120 (14.17%)	13 / 123 (10.57%)
occurrences (all)	5	21	13
Vomiting			
subjects affected / exposed	7 / 122 (5.74%)	15 / 120 (12.50%)	7 / 123 (5.69%)
occurrences (all)	7	22	11
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 122 (5.74%)	9 / 120 (7.50%)	9 / 123 (7.32%)
occurrences (all)	7	9	10
Dyspnoea			
subjects affected / exposed	7 / 122 (5.74%)	3 / 120 (2.50%)	3 / 123 (2.44%)
occurrences (all)	7	3	3
Oropharyngeal pain			
subjects affected / exposed	8 / 122 (6.56%)	2 / 120 (1.67%)	3 / 123 (2.44%)
occurrences (all)	8	2	4
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	10 / 122 (8.20%)	12 / 120 (10.00%)	9 / 123 (7.32%)
occurrences (all)	11	15	10
Scleroderma associated digital ulcer			
subjects affected / exposed	21 / 122 (17.21%)	15 / 120 (12.50%)	18 / 123 (14.63%)
occurrences (all)	62	45	36
Skin ulcer			
subjects affected / exposed	7 / 122 (5.74%)	5 / 120 (4.17%)	3 / 123 (2.44%)
occurrences (all)	10	5	7
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	4 / 122 (3.28%)	6 / 120 (5.00%)	0 / 123 (0.00%)
occurrences (all)	5	8	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 122 (12.30%)	12 / 120 (10.00%)	20 / 123 (16.26%)
occurrences (all)	17	15	26
Back pain			
subjects affected / exposed	8 / 122 (6.56%)	5 / 120 (4.17%)	5 / 123 (4.07%)
occurrences (all)	9	5	7
Pain in extremity			
subjects affected / exposed	8 / 122 (6.56%)	9 / 120 (7.50%)	6 / 123 (4.88%)
occurrences (all)	8	10	6
Infections and infestations			
Infected skin ulcer			
subjects affected / exposed	5 / 122 (4.10%)	4 / 120 (3.33%)	7 / 123 (5.69%)
occurrences (all)	7	4	9
Nasopharyngitis			
subjects affected / exposed	25 / 122 (20.49%)	18 / 120 (15.00%)	10 / 123 (8.13%)
occurrences (all)	42	21	16
Sinusitis			
subjects affected / exposed	5 / 122 (4.10%)	6 / 120 (5.00%)	4 / 123 (3.25%)
occurrences (all)	7	6	4
Upper respiratory tract infection			
subjects affected / exposed	18 / 122 (14.75%)	17 / 120 (14.17%)	20 / 123 (16.26%)
occurrences (all)	20	23	25
Urinary tract infection			
subjects affected / exposed	10 / 122 (8.20%)	13 / 120 (10.83%)	5 / 123 (4.07%)
occurrences (all)	13	18	6
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 122 (2.46%)	6 / 120 (5.00%)	1 / 123 (0.81%)
occurrences (all)	3	6	1

Non-serious adverse events	Part B lenabasum 20 mg BID (Lenabasum in Part A)	Part B 20 mg lenabasum BID (placebo in Part A)	Part B 20 mg lenabasum BID (all patients)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	152 / 205 (74.15%)	69 / 111 (62.16%)	221 / 316 (69.94%)

Investigations			
Weight decreased			
subjects affected / exposed	4 / 205 (1.95%)	3 / 111 (2.70%)	7 / 316 (2.22%)
occurrences (all)	4	3	7
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 205 (1.46%)	1 / 111 (0.90%)	4 / 316 (1.27%)
occurrences (all)	3	1	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 205 (7.80%)	9 / 111 (8.11%)	25 / 316 (7.91%)
occurrences (all)	17	11	28
Headache			
subjects affected / exposed	5 / 205 (2.44%)	5 / 111 (4.50%)	10 / 316 (3.16%)
occurrences (all)	5	5	10
Paraesthesia			
subjects affected / exposed	2 / 205 (0.98%)	1 / 111 (0.90%)	3 / 316 (0.95%)
occurrences (all)	2	2	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 205 (4.39%)	4 / 111 (3.60%)	13 / 316 (4.11%)
occurrences (all)	9	4	13
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 205 (3.90%)	2 / 111 (1.80%)	10 / 316 (3.16%)
occurrences (all)	8	2	10
Diarrhoea			
subjects affected / exposed	13 / 205 (6.34%)	10 / 111 (9.01%)	23 / 316 (7.28%)
occurrences (all)	15	12	27
Dry mouth			
subjects affected / exposed	7 / 205 (3.41%)	2 / 111 (1.80%)	9 / 316 (2.85%)
occurrences (all)	7	2	9
Dysphagia			
subjects affected / exposed	5 / 205 (2.44%)	1 / 111 (0.90%)	6 / 316 (1.90%)
occurrences (all)	5	1	6
Gastrooesophageal reflux disease			

subjects affected / exposed	4 / 205 (1.95%)	5 / 111 (4.50%)	9 / 316 (2.85%)
occurrences (all)	4	6	10
Mouth ulceration			
subjects affected / exposed	2 / 205 (0.98%)	1 / 111 (0.90%)	3 / 316 (0.95%)
occurrences (all)	2	1	3
Nausea			
subjects affected / exposed	10 / 205 (4.88%)	7 / 111 (6.31%)	17 / 316 (5.38%)
occurrences (all)	11	8	19
Vomiting			
subjects affected / exposed	8 / 205 (3.90%)	4 / 111 (3.60%)	12 / 316 (3.80%)
occurrences (all)	9	5	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 205 (1.95%)	0 / 111 (0.00%)	4 / 316 (1.27%)
occurrences (all)	5	0	5
Dyspnoea			
subjects affected / exposed	6 / 205 (2.93%)	0 / 111 (0.00%)	6 / 316 (1.90%)
occurrences (all)	6	0	6
Oropharyngeal pain			
subjects affected / exposed	6 / 205 (2.93%)	1 / 111 (0.90%)	7 / 316 (2.22%)
occurrences (all)	6	1	7
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	11 / 205 (5.37%)	2 / 111 (1.80%)	13 / 316 (4.11%)
occurrences (all)	11	3	14
Scleroderma associated digital ulcer			
subjects affected / exposed	25 / 205 (12.20%)	14 / 111 (12.61%)	39 / 316 (12.34%)
occurrences (all)	44	23	67
Skin ulcer			
subjects affected / exposed	6 / 205 (2.93%)	2 / 111 (1.80%)	8 / 316 (2.53%)
occurrences (all)	9	2	11
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 205 (0.00%)	0 / 111 (0.00%)	0 / 316 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	9 / 205 (4.39%)	11 / 111 (9.91%)	20 / 316 (6.33%)
occurrences (all)	10	14	24
Back pain			
subjects affected / exposed	6 / 205 (2.93%)	2 / 111 (1.80%)	8 / 316 (2.53%)
occurrences (all)	6	2	8
Pain in extremity			
subjects affected / exposed	3 / 205 (1.46%)	4 / 111 (3.60%)	7 / 316 (2.22%)
occurrences (all)	3	5	8
Infections and infestations			
Infected skin ulcer			
subjects affected / exposed	4 / 205 (1.95%)	3 / 111 (2.70%)	7 / 316 (2.22%)
occurrences (all)	5	3	8
Nasopharyngitis			
subjects affected / exposed	15 / 205 (7.32%)	4 / 111 (3.60%)	19 / 316 (6.01%)
occurrences (all)	16	4	20
Sinusitis			
subjects affected / exposed	1 / 205 (0.49%)	1 / 111 (0.90%)	2 / 316 (0.63%)
occurrences (all)	1	1	2
Upper respiratory tract infection			
subjects affected / exposed	15 / 205 (7.32%)	8 / 111 (7.21%)	23 / 316 (7.28%)
occurrences (all)	17	11	28
Urinary tract infection			
subjects affected / exposed	11 / 205 (5.37%)	3 / 111 (2.70%)	14 / 316 (4.43%)
occurrences (all)	14	3	17
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 205 (0.49%)	1 / 111 (0.90%)	2 / 316 (0.63%)
occurrences (all)	1	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2018	This amendment was the same for all countries, and region/country-specific protocols took effect after implementation of version 2.0 of the protocol. The following changes were included: • Added minimal important difference as a tertiary efficacy objective • Added Patient Improvement Questionnaire for Subjects and Patient Improvement Questionnaire for Physicians • Added long-term signals of efficacy as a tertiary efficacy objective • Added evaluation of long-term safety of lenabasum as a secondary safety objective • Revised study design • Revised treatment duration to 2 years • Revised secondary safety endpoints for laboratory safety tests, physical examinations, and 12 lead ECGs • Added language regarding study product supply for subjects in Part B • Added evaluation of potential late-emerging AEs after discontinuation of lenabasum treatment as a secondary safety objective and endpoint • Late emerging AEs added as a secondary safety endpoint • Added that subjects who discontinued from Part A (but did not withdraw consent) or choose not to participate in the OLE would be asked to participate in a 2-year Safety Follow up • Revised the removal of subjects from therapy or assessments from "any life-threatening AE" to "any life-threatening AE probably or definitely related to lenabasum" • Revised follow-up procedures for subjects who discontinued from Part B of the study • Revised the risk/benefit assessment • Added the following text: If any of the tests are not obtained or cannot be processed at a given visit, they should be obtained when feasible before the subsequent scheduled study visit. With permission from the medical monitor, such tests may be obtained at a local licensed laboratory. • Added criteria for Investigators to determine subject eligibility for an ACR CRISS score of 0 at Visits 2 to 11 in Part A
18 September 2019	The following changes were introduced with this amendment in the US: • Changed ACR CRISS score at Week 52 from the 2nd secondary efficacy objective to the primary efficacy objective • Changed ACR CRISS score, Week 52, lenabasum 20 mg BID vs placebo to the primary efficacy outcome • Changed the change in mRSS at Week 52 from the primary efficacy objective to the 1st secondary efficacy objective • Changed the change in mRSS, Week 52, lenabasum 20 mg BID vs placebo to the 1st secondary efficacy outcome. The change in mRSS at Week 52, lenabasum 5 mg BID vs placebo, remains a secondary efficacy outcome • Added assessments "Patient End of Treatment Survey" and "Patient End of Treatment Interview" to the end of Part A. Revised the "Investigator Prospective Questionnaire for CRISS Eligibility" to "CRISS Step 1 Criteria for Lack of Improvement in SSc". • Added assessment of subjects "who are taking concomitant mycophenolate or mycophenolic acid" • Added 7 study visits (Visit 9 to Visit 15) to Part B of the study • Changed the 2-sided alpha for primary and secondary efficacy analyses from a significance level of 0.01 to a significance level of 0.05 • Revised current inclusion/exclusion criteria to state Part A and added new inclusion/exclusion criteria for Part B of the study

02 October 2019	The following changes were introduced with this amendment in the rest of the world (except US [see above] and Japan [see below]) and in Korea: • Changed ACR CRISS score at Week 52 from the 2nd secondary efficacy objective to the primary efficacy objective • Changed ACR CRISS score, Week 52, lenabasum 20 mg BID vs placebo to the primary efficacy outcome • Changed the change in mRSS at Week 52 from the primary efficacy objective to the 1st secondary efficacy objective • Changed the change in mRSS, Week 52, lenabasum 20 mg BID vs placebo to the 1st secondary efficacy outcome. The change in mRSS at Week 52, lenabasum 5 mg BID vs placebo, remains a secondary efficacy outcome • Added assessments "Patient End of Treatment Survey" and "Patient End of Treatment Interview" to the end of Part A. Revised the "Investigator Prospective Questionnaire for CRISS Eligibility" to "CRISS Step 1 Criteria for Lack of Improvement in SSc". • Added assessment of subjects "who are taking concomitant mycophenolate or mycophenolic acid" • Added 7 study visits (Visit 9 to Visit 15) to Part B of the study • Changed the 2-sided alpha for primary and secondary efficacy analyses from a significance level of 0.01 to a significance level of 0.05 • Revised current inclusion/exclusion criteria to state Part A and added new inclusion/exclusion criteria for Part B of the study
16 January 2020	The following changes were introduced with this amendment in Japan: • Adjusted order of secondary efficacy objectives: moved ACR CRISS score at Week 52 to the 1st secondary objective and HAQ-DI to the 2nd secondary objective • Added assessments "Patient End of Treatment Survey" and "Patient End of Treatment Interview" to the end of Part A. • Revised the "Investigator Prospective Questionnaire for CRISS Eligibility" to "CRISS Step 1 Criteria for Lack of Improvement in SSc". • Added assessment of subjects "who are taking concomitant mycophenolate or mycophenolic acid" • Added 7 study visits (Visit 9 to Visit 15) to Part B of the study • Revised current inclusion/exclusion criteria to state Part A and added new inclusion/exclusion criteria for Part B of the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported