

**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-corticosteroid 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 (\pm 0.39170) | -0.1326 (\pm 0.43625) | -0.1272 (\pm 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 (\leq 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 (\leq 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 (\pm 6.2099) | -1.602 (\pm 6.9106) | -0.993 (\pm 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 (\leq 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 (\pm 0.2516) | -0.075 (\pm 0.2655) | -0.043 (\pm 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-blind 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 occurrences (all) | 3 / 122 (2.46%) 4 | 7 / 120 (5.83%) 7 | 6 / 123 (4.88%) 6 |
| Cardiac disorders Palpitations subjects affected / exposed occurrences (all) | 3 / 122 (2.46%) 4 | 7 / 120 (5.83%) 7 | 5 / 123 (4.07%) 6 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) | 11 / 122 (9.02%) 12 14 / 122 (11.48%) 15 8 / 122 (6.56%) 8 | 22 / 120 (18.33%) 29 17 / 120 (14.17%) 20 3 / 120 (2.50%) 4 | 6 / 123 (4.88%) 6 9 / 123 (7.32%) 12 2 / 123 (1.63%) 2 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 10 / 122 (8.20%) 10 | 10 / 120 (8.33%) 12 | 7 / 123 (5.69%) 8 |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dysphagia | 8 / 122 (6.56%) 8 16 / 122 (13.11%) 18 7 / 122 (5.74%) 7 | 2 / 120 (1.67%) 2 21 / 120 (17.50%) 26 6 / 120 (5.00%) 6 | 5 / 123 (4.07%) 6 18 / 123 (14.63%) 20 2 / 123 (1.63%) 2 |

| | | | |
|---|-------------------|-------------------|-------------------|
| 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 occurrences (all) | 4 / 122 (3.28%) 5 | 6 / 120 (5.00%) 8 | 0 / 123 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 15 / 122 (12.30%) 17 | 12 / 120 (10.00%) 15 | 20 / 123 (16.26%) 26 |
| Back pain subjects affected / exposed occurrences (all) | 8 / 122 (6.56%) 9 | 5 / 120 (4.17%) 5 | 5 / 123 (4.07%) 7 |
| Pain in extremity subjects affected / exposed occurrences (all) | 8 / 122 (6.56%) 8 | 9 / 120 (7.50%) 10 | 6 / 123 (4.88%) 6 |
| Infections and infestations | | | |
| Infected skin ulcer subjects affected / exposed occurrences (all) | 5 / 122 (4.10%) 7 | 4 / 120 (3.33%) 4 | 7 / 123 (5.69%) 9 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 25 / 122 (20.49%) 42 | 18 / 120 (15.00%) 21 | 10 / 123 (8.13%) 16 |
| Sinusitis subjects affected / exposed occurrences (all) | 5 / 122 (4.10%) 7 | 6 / 120 (5.00%) 6 | 4 / 123 (3.25%) 4 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 18 / 122 (14.75%) 20 | 17 / 120 (14.17%) 23 | 20 / 123 (16.26%) 25 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 10 / 122 (8.20%) 13 | 13 / 120 (10.83%) 18 | 5 / 123 (4.07%) 6 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 122 (2.46%) 3 | 6 / 120 (5.00%) 6 | 1 / 123 (0.81%) 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 occurrences (all) | 4 / 205 (1.95%) 4 | 3 / 111 (2.70%) 3 | 7 / 316 (2.22%) 7 |
| Cardiac disorders Palpitations subjects affected / exposed occurrences (all) | 3 / 205 (1.46%) 3 | 1 / 111 (0.90%) 1 | 4 / 316 (1.27%) 4 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) | 16 / 205 (7.80%) 17 5 / 205 (2.44%) 5 2 / 205 (0.98%) 2 | 9 / 111 (8.11%) 11 5 / 111 (4.50%) 5 1 / 111 (0.90%) 2 | 25 / 316 (7.91%) 28 10 / 316 (3.16%) 10 3 / 316 (0.95%) 4 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 9 / 205 (4.39%) 9 | 4 / 111 (3.60%) 4 | 13 / 316 (4.11%) 13 |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease | 8 / 205 (3.90%) 8 13 / 205 (6.34%) 15 7 / 205 (3.41%) 7 5 / 205 (2.44%) 5 | 2 / 111 (1.80%) 2 10 / 111 (9.01%) 12 2 / 111 (1.80%) 2 1 / 111 (0.90%) 1 | 10 / 316 (3.16%) 10 23 / 316 (7.28%) 27 9 / 316 (2.85%) 9 6 / 316 (1.90%) 6 |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 4 / 205 (1.95%) 4 | 5 / 111 (4.50%) 6 | 9 / 316 (2.85%) 10 |
| Mouth ulceration subjects affected / exposed occurrences (all) | 2 / 205 (0.98%) 2 | 1 / 111 (0.90%) 1 | 3 / 316 (0.95%) 3 |
| Nausea subjects affected / exposed occurrences (all) | 10 / 205 (4.88%) 11 | 7 / 111 (6.31%) 8 | 17 / 316 (5.38%) 19 |
| Vomiting subjects affected / exposed occurrences (all) | 8 / 205 (3.90%) 9 | 4 / 111 (3.60%) 5 | 12 / 316 (3.80%) 14 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 4 / 205 (1.95%) 5 | 0 / 111 (0.00%) 0 | 4 / 316 (1.27%) 5 |
| Dyspnoea subjects affected / exposed occurrences (all) | 6 / 205 (2.93%) 6 | 0 / 111 (0.00%) 0 | 6 / 316 (1.90%) 6 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 6 / 205 (2.93%) 6 | 1 / 111 (0.90%) 1 | 7 / 316 (2.22%) 7 |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 11 / 205 (5.37%) 11 | 2 / 111 (1.80%) 3 | 13 / 316 (4.11%) 14 |
| Scleroderma associated digital ulcer subjects affected / exposed occurrences (all) | 25 / 205 (12.20%) 44 | 14 / 111 (12.61%) 23 | 39 / 316 (12.34%) 67 |
| Skin ulcer subjects affected / exposed occurrences (all) | 6 / 205 (2.93%) 9 | 2 / 111 (1.80%) 2 | 8 / 316 (2.53%) 11 |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 0 / 205 (0.00%) 0 | 0 / 111 (0.00%) 0 | 0 / 316 (0.00%) 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 | <p>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:</p> <ul style="list-style-type: none"> • 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 | <p>The following changes were introduced with this amendment in the US:</p> <ul style="list-style-type: none"> • 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 | <p>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:</p> <ul style="list-style-type: none"> • 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 | <p>The following changes were introduced with this amendment in Japan:</p> <ul style="list-style-type: none"> • 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