



Clinical trial results:

201496: A Study to Evaluate the Efficacy and Safety of 15mg BID Losmapimod (GW856553) Compared to Placebo in Frequently Exacerbating Subjects with Chronic Obstructive Pulmonary Disease (COPD).

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-002992-27 |
| Trial protocol | SK DE BG ES |
| Global end of trial date | 30 June 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 08 March 2017 |
| First version publication date | 08 March 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 201496 |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |

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 | 01 September 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the yearly rate of moderate-severe COPD exacerbations in losmapimod compared to placebo treated subjects.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 09 December 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 59 |
| Country: Number of subjects enrolled | Bulgaria: 25 |
| Country: Number of subjects enrolled | Chile: 9 |
| Country: Number of subjects enrolled | Germany: 48 |
| Country: Number of subjects enrolled | Korea, Republic of: 19 |
| Country: Number of subjects enrolled | Slovakia: 22 |
| Country: Number of subjects enrolled | Spain: 8 |
| Worldwide total number of subjects | 190 |
| EEA total number of subjects | 103 |

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) | 90 |
| From 65 to 84 years | 100 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This was a randomized, double-blind (sponsor unblinded), parallel-group, multi-center study evaluating 15 milligrams (mg) twice daily (BID) of losmapimod versus placebo in addition to standard of care in male and female participants (par.) ≥ 40 years of age having chronic obstructive pulmonary disease (COPD).

Pre-assignment

Screening details:

This study consisted of a 28 day screening period followed by treatment period (TP) of minimum 26 weeks. Total duration of TP was variable from 26 weeks to 52 weeks, and safety follow-up after 1 week. Total 365 par. were screened (175 par. failed), of which 190 par. were enrolled in study. 184 par. were randomized in a TP.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Participants with COPD received placebo orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of inhaled corticosteroid (ICS). Salbutamol metered dose inhaler (MDI) was provided as a rescue medication.

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

Dosage and administration details:

Placebo tablet was administered orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period.

| | |
|------------------|------------------|
| Arm title | Losmapimod 15 mg |
|------------------|------------------|

Arm description:

Participants with COPD received losmapimod 15 mg tablets orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of ICS. Salbutamol MDI was provided as a rescue medication.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Losmapimod |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Losmapimod 15 mg tablet was administered orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period.

| Number of subjects in period 1^[1] | Placebo | Losmapimod 15 mg |
|---|---------|------------------|
| Started | 94 | 90 |
| Completed | 14 | 10 |
| Not completed | 80 | 80 |
| Physician decision | 1 | 1 |
| Consent withdrawn by subject | 1 | 4 |
| Other: Study closed/terminated | 66 | 55 |
| Adverse Event, non-fatal | 8 | 9 |
| Other: Met stopping criteria | 1 | - |
| Lost to follow-up | - | 2 |
| Adverse Event, serious fatal | 1 | 3 |
| Lack of efficacy | 1 | 3 |
| Protocol deviation | 1 | 3 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 190 enrolled participants, 184 were randomized in a TP.

Baseline characteristics

Reporting groups

| | |
|--|------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants with COPD received placebo orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of inhaled corticosteroid (ICS). Salbutamol metered dose inhaler (MDI) was provided as a rescue medication. | |
| Reporting group title | Losmapimod 15 mg |
| Reporting group description: | |
| Participants with COPD received losmapimod 15 mg tablets orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of ICS. Salbutamol MDI was provided as a rescue medication. | |

| Reporting group values | Placebo | Losmapimod 15 mg | Total |
|--|---------|------------------|-------|
| Number of subjects | 94 | 90 | 184 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Age continuous description | | | |
| Units: years | | | |
| arithmetic mean | 64.6 | 66.4 | |
| standard deviation | ± 8.27 | ± 6.66 | - |
| Gender categorical | | | |
| Gender categorical description | | | |
| Units: Subjects | | | |
| Female | 33 | 26 | 59 |
| Male | 61 | 64 | 125 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Japanese/East Asian /South East Asian Heritage | 10 | 9 | 19 |
| White | 84 | 81 | 165 |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants with COPD received placebo orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of inhaled corticosteroid (ICS). Salbutamol metered dose inhaler (MDI) was provided as a rescue medication. | |
| Reporting group title | Losmapimod 15 mg |
| Reporting group description: | |
| Participants with COPD received losmapimod 15 mg tablets orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of ICS. Salbutamol MDI was provided as a rescue medication. | |

Primary: Annual rate of moderate and severe exacerbations of COPD

| | |
|--|--|
| End point title | Annual rate of moderate and severe exacerbations of COPD |
| End point description: | |
| An exacerbation of COPD, is defined as the worsening of 2 or more major symptoms (dyspnea, sputum volume, sputum purulence) or the worsening of any 1 major symptom together with any 1 of the minor symptoms (sore throat, cold, fever without other cause, increased cough and wheeze), for at least 2 consecutive days. Moderate-severe exacerbations were defined as use of antibiotics and/or oral steroids and/or hospitalization. Summary only included exacerbations for which a date of resolution or death was provided. Analysis was performed by using Bayesian inference assuming non-informative priors. The mean exacerbation rate was adjusted for treatment group, smoking status, ICS use and region. The adjusted posterior median was summarized per treatment group. The number of exacerbation events per participant was assumed to follow a negative binomial distribution. Modified Intent-to-Treat (mITT) Population comprised of all randomized par. who received at least one dose of study treatment. | |
| End point type | Primary |
| End point timeframe: | |
| From the start of the study treatment up to 53 Weeks | |

| End point values | Placebo | Losmapimod 15 mg | | |
|---|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[1] | 90 ^[2] | | |
| Units: Exacerbations per participant per year | | | | |
| median (standard deviation) | 0.84 (± 0.19) | 0.88 (± 0.22) | | |

Notes:

[1] - mITT Population

[2] - mITT Population

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Losmapimod 15 mg v Placebo |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.44 ^[3] |
| Method | Bayesian inference |
| Parameter estimate | Adjusted median |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.73 |
| Variability estimate | Standard deviation |
| Dispersion value | 0.28 |

Notes:

[3] - Estimation of posterior probability that the true ratio losmapimod/placebo is <1 assuming non informative priors.

Secondary: Time to first occurrence of moderate or severe COPD exacerbation

| | |
|-----------------|--|
| End point title | Time to first occurrence of moderate or severe COPD exacerbation |
|-----------------|--|

End point description:

The time to first moderate-severe COPD exacerbation in par. treated with losmapimod compared to placebo treated par. was evaluated. The time to the first on-treatment moderate-severe exacerbation was calculated as exacerbation onset date of first on-treatment exacerbation minus exposure start date plus 1. Analysis was performed under the frequentist paradigm and the reported confidence intervals was calculated at the 5 percent significance level. mITT Population comprised of all randomized par. who received at least one dose of study treatment. Data were not analyzed because the study was stopped for futility.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the start of the study treatment up to 53 Weeks

| End point values | Placebo | Losmapimod 15 mg | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: Hours | | | | |
| median (standard deviation) | () | () | | |

Notes:

[4] - The study was stopped for futility

[5] - The study was stopped for futility

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants having any adverse events (AEs), Serious adverse events (SAEs)

| | |
|-----------------|---|
| End point title | Number of participants having any adverse events (AEs), Serious adverse events (SAEs) |
|-----------------|---|

End point description:

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly/birth defect, any other situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinaemia were categorized as SAE. AEs were considered as on-treatment If AE onset date is on or after treatment start date & on or before treatment stop date. par. having any AE or SAE were included in analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the start of the study treatment up to 53 Weeks

| End point values | Placebo | Losmapimod 15 mg | | |
|-----------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[6] | 90 ^[7] | | |
| Units: Participants | | | | |
| Non-serious AEs | 34 | 38 | | |
| SAEs | 8 | 19 | | |

Notes:

[6] - mITT Population

[7] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in spirometry parameters in pre and post forced expiratory volume in 1 second (FEV1); pre and post forced vital capacity (FVC); pre and post forced expiratory volume in 6 seconds (FEV6).

| | |
|-----------------|---|
| End point title | Change from Baseline in spirometry parameters in pre and post forced expiratory volume in 1 second (FEV1); pre and post forced vital capacity (FVC); pre and post forced expiratory volume in 6 seconds (FEV6). |
|-----------------|---|

End point description:

Pre and post FEV1, FVC and FEV6 were performed at Screening, Day 1 pre-dose and Weeks 2, 4, 8, 12, 18, 26, 39 and 52. Par. were asked to withheld all bronchodilator therapy included ipratropiumn bromide and salbutamol/albuterol for at least 4 hours prior to prebronchodilator spirometric test. Post-bronchodilator spirometric assessment was performed after inhalation of 400/360 micograms (µg) of salbutamol/albuterol in 10-15 minutes. Day 1 (pre-dose) values were considered as Baseline values. Change from Baseline was calculated as value at the indicated time point minus Baseline value. The maximum value of the 3 replicate assessments were used. Analysis performed using a mixed-effects repeated measures model. The adjusted mean values were summarized per treatment group. Par. were included in the analysis if they had at least one post-baseline measurement. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 52

| End point values | Placebo | Losmapimod 15 mg | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[8] | 90 ^[9] | | |
| Units: Liters | | | | |
| arithmetic mean (standard error) | | | | |
| FEV1 pre-dose, Week 2, n = 90, 83 | 0.002 (± 0.0241) | 0.028 (± 0.0258) | | |
| FEV1 Pre-dose, Week 4, n=88, 82 | -0.01 (± 0.0242) | 0.025 (± 0.0259) | | |
| FEV1 Pre-dose, Week 8, n=81, 79 | -0.031 (± 0.0247) | 0.028 (± 0.0261) | | |
| FEV1 Pre-dose, Week 12, n=78, 71 | -0.011 (± 0.025) | -0.014 (± 0.0267) | | |
| FEV1 Pre-dose, Week 18, n=67, 61 | -0.037 (± 0.026) | 0.013 (± 0.0277) | | |
| FEV1 Pre-dose, Week 26, n=53, 52 | -0.059 (± 0.0278) | 0.02 (± 0.0289) | | |
| FEV1 Pre-dose, Week 39, n=28, 28 | -0.085 (± 0.0342) | 0.001 (± 0.0353) | | |
| FEV1 Pre-dose, Week 52, n=14, 11 | -0.034 (± 0.0485) | 0.016 (± 0.0513) | | |
| FEV1 post-dose, Week 2, n=89, 82 | 0.012 (± 0.0188) | 0.026 (± 0.0203) | | |
| FEV1 post-dose, Week 4, n=87, 81 | -0.022 (± 0.0193) | 0.019 (± 0.0207) | | |
| FEV1 post-dose, Week 8, n=80, 78 | -0.01 (± 0.0232) | 0.023 (± 0.0242) | | |
| FEV1 post-dose, Week 12, n=76, 69 | -0.008 (± 0.0217) | -0.02 (± 0.0231) | | |
| FEV1 post-dose, Week 18, n=66, 60 | -0.035 (± 0.0256) | -0.012 (± 0.0271) | | |
| FEV1 post-dose, Week 26, n=52, 51 | -0.07 (± 0.0273) | 0.03 (± 0.0282) | | |
| FEV1 post-dose, Week 39, n=27, 27 | -0.086 (± 0.0346) | -0.031 (± 0.0356) | | |
| FEV1 post-dose, Week 52, n=13, 10 | -0.018 (± 0.0419) | 0.024 (± 0.0472) | | |
| FEV6 pre-dose, Week 2, n = 90,82 | -0.007 (± 0.0353) | 0.045 (± 0.0381) | | |
| FEV6 Pre-dose, Week 4, n=87, 81 | -0.034 (± 0.0353) | 0.012 (± 0.038) | | |
| FEV6 Pre-dose, Week 8, n=81, 78 | -0.043 (± 0.04) | 0.032 (± 0.0424) | | |
| FEV6 Pre-dose, Week 12, n=78, 71 | -0.036 (± 0.0366) | -0.034 (± 0.0392) | | |
| FEV6 Pre-dose, Week 18, n=67, 60 | -0.073 (± 0.0413) | -0.014 (± 0.0441) | | |
| FEV6 Pre-dose, Week 26, n=53, 52 | -0.076 (± 0.0405) | -0.003 (± 0.0425) | | |
| FEV6 Pre-dose, Week 39, n=28, 28 | -0.102 (± 0.0486) | 0.013 (± 0.0507) | | |
| FEV6 Pre-dose, Week 52, n=14, 11 | -0.101 (± 0.0731) | 0.071 (± 0.0745) | | |
| FEV6 post-dose, Week 2, n=89, 81 | -0.003 (± 0.0296) | 0.023 (± 0.0319) | | |
| FEV6 post-dose, Week 4, n=86, 80 | -0.027 (± 0.0273) | 0.01 (± 0.0295) | | |
| FEV6 post-dose, Week 8, n=80, 76 | -0.039 (± 0.0313) | 0.012 (± 0.0331) | | |

| | | | | |
|-----------------------------------|-------------------|-------------------|--|--|
| FEV6 post-dose, Week 12, n=76, 69 | -0.028 (± 0.0308) | -0.029 (± 0.033) | | |
| FEV6 post-dose, Week 18, n=66, 59 | -0.06 (± 0.0367) | -0.035 (± 0.0392) | | |
| FEV6 post-dose, Week 26, n=51, 51 | -0.081 (± 0.036) | 0.003 (± 0.0373) | | |
| FEV6 post-dose, Week 39, n=27, 27 | -0.095 (± 0.0428) | -0.067 (± 0.0443) | | |
| FEV6 post-dose, Week 52, n=13, 10 | -0.119 (± 0.0607) | -0.017 (± 0.0674) | | |
| FVC, Pre-dose, Week 2, n =90, 83 | -0.018 (± 0.0389) | 0.038 (± 0.0417) | | |
| FVC, Pre-dose, Week 4, n =88, 82 | -0.039 (± 0.0392) | 0.006 (± 0.0418) | | |
| FVC, Pre-dose Week 8, n = 81, 79 | -0.061 (± 0.0401) | 0.011 (± 0.0422) | | |
| FVC, Pre-dose, Week 12, n =78, 71 | -0.046 (± 0.0405) | -0.058 (± 0.043) | | |
| FVC, Pre-dose Week 18, n =67, 61 | -0.093 (± 0.0422) | -0.021 (± 0.0447) | | |
| FVC, Week 26, n=53, 52 | -0.095 (± 0.0451) | -0.028 (± 0.0468) | | |
| FVC, Pre-dose Week 39, n =28, 28 | -0.115 (± 0.0558) | -0.033 (± 0.0574) | | |
| FVC, Pre-dose Week 52, n =14, 11 | -0.052 (± 0.0806) | 0.031 (± 0.0837) | | |
| FVC, Post-dose Week 2, n =89, 82 | -0.007 (± 0.0359) | 0.037 (± 0.0385) | | |
| FVC, Post-dose Week 4, n =87, 81 | -0.021 (± 0.0316) | 0.033 (± 0.0341) | | |
| FVC, Post-dose Week 8, n =80, 78 | -0.052 (± 0.0366) | 0.019 (± 0.0385) | | |
| FVC,Post-dose Week 12, n =76, 69 | -0.02 (± 0.0361) | -0.008 (± 0.0385) | | |
| FVC, Post-dose Week 18, n =66, 60 | -0.075 (± 0.0422) | -0.016 (± 0.0449) | | |
| FVC, Post-dose Week 26, n=52, 51 | -0.135 (± 0.0495) | 0.003 (± 0.0513) | | |
| FVC, Post-dose Week 39, n =27, 27 | -0.092 (± 0.0499) | -0.043 (± 0.0518) | | |
| FVC, Post-dose Week 52, n =13, 10 | -0.081 (± 0.0612) | -0.039 (± 0.0671) | | |

Notes:

[8] - mITT Population

[9] - mITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------------|
| Statistical analysis description: | |
| FEV1 pre-dose, Week 2 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.371 ^[10] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.026 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.031 |
| upper limit | 0.084 |

Notes:

[10] - Analysis performed using a mixed-effects repeated measures (MERM) model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

FEV1 pre-dose, Week 4

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.244 ^[11] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.035 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.024 |
| upper limit | 0.093 |

Notes:

[11] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

FEV1 pre-dose, Week 8

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 ^[12] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.059 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.119 |

Notes:

[12] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

FEV1 pre-dose, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.942 ^[13] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.002 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.063 |
| upper limit | 0.058 |

Notes:

[13] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

FEV1 pre-dose, Week 18

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.127 ^[14] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.014 |
| upper limit | 0.114 |

Notes:

[14] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

FEV1 pre-dose, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.024 ^[15] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.079 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.011 |
| upper limit | 0.148 |

Notes:

[15] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

FEV1 pre-dose, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.057 ^[16] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.086 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.003 |
| upper limit | 0.174 |

Notes:

[16] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

FEV1 pre-dose, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.481 ^[17] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.05 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 0.191 |

Notes:

[17] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

FEV1 post-dose, Week 2

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.521 ^[18] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.014 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.059 |

Notes:

[18] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV1 post-dose, Week 4

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.084 ^[19] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.005 |
| upper limit | 0.086 |

Notes:

[19] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV1 post-dose, Week 8

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.266 ^[20] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.033 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.025 |
| upper limit | 0.09 |

Notes:

[20] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV1 post-dose, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.665 ^[21] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.012 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.066 |
| upper limit | 0.042 |

Notes:

[21] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV1 post-dose, Week 18

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.489 ^[22] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.023 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.043 |
| upper limit | 0.09 |

Notes:

[22] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 14 |
|-----------------------------------|-------------------------|

| | |
|--|--------------------------------|
| Statistical analysis description: FEV1 post-dose, Week 26 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.007 ^[23] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.099 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.028 |
| upper limit | 0.17 |

Notes:

[23] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis 15 |
| Statistical analysis description: FEV1 post-dose, Week 39 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.248 ^[24] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.055 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.039 |
| upper limit | 0.148 |

Notes:

[24] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis 16 |
| Statistical analysis description: FEV1 post-dose, Week 52 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.506 ^[25] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.043 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.087 |
| upper limit | 0.172 |

Notes:

[25] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 17 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 pre-dose, Week 2

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.223 ^[26] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.051 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.032 |
| upper limit | 0.134 |

Notes:

[26] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 18 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 pre-dose, Week 4

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.276 ^[27] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.046 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.037 |
| upper limit | 0.129 |

Notes:

[27] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 19 |
|-----------------------------------|-------------------------|

| | |
|---|--------------------------------|
| Statistical analysis description: | |
| FEV6 pre-dose, Week 8 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.131 ^[28] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.075 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.023 |
| upper limit | 0.173 |

Notes:

[28] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 20 |
| Statistical analysis description: | |
| FEV6 pre-dose, Week 12 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.949 ^[29] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.003 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.084 |
| upper limit | 0.09 |

Notes:

[29] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 21 |
| Statistical analysis description: | |
| FEV6 pre-dose, Week 18 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.259 ^[30] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.059 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.044 |
| upper limit | 0.163 |

Notes:

[30] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 22 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 pre-dose, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.152 ^[31] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.073 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.027 |
| upper limit | 0.172 |

Notes:

[31] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 23 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 pre-dose, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.076 ^[32] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.114 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.012 |
| upper limit | 0.241 |

Notes:

[32] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 24 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 pre-dose, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.107 ^[33] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.171 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.038 |
| upper limit | 0.381 |

Notes:

[33] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 25 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 post-dose, Week 2

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.484 ^[34] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.025 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.046 |
| upper limit | 0.097 |

Notes:

[34] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 26 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 post-dose, Week 4

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.256 ^[35] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.037 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.027 |
| upper limit | 0.1 |

Notes:

[35] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 27 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 post-dose, Week 8

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.184 ^[36] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.052 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.025 |
| upper limit | 0.128 |

Notes:

[36] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 28 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 post-dose, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.97 ^[37] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.001 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.077 |
| upper limit | 0.074 |

Notes:

[37] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 29 |
|-----------------------------------|-------------------------|

| | |
|--|--------------------------------|
| Statistical analysis description: FEV6 post-dose, Week 18 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.608 ^[38] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.025 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.07 |
| upper limit | 0.12 |

Notes:

[38] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis 30 |
| Statistical analysis description: FEV6 post-dose, Week 26 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.071 ^[39] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.084 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.007 |
| upper limit | 0.175 |

Notes:

[39] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis 31 |
| Statistical analysis description: FEV6 post-dose, Week 39 | |
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.622 ^[40] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.028 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.085 |
| upper limit | 0.141 |

Notes:

[40] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 32 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FEV6 post-dose, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.277 ^[41] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.102 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.086 |
| upper limit | 0.291 |

Notes:

[41] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 33 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Pre-dose, Week 2

| | |
|---|--------------------------------|
| Comparison groups | Losmapimod 15 mg v Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.241 ^[42] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.056 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.038 |
| upper limit | 0.15 |

Notes:

[42] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 34 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Pre-dose, Week 4

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.348 ^[43] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.045 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.049 |
| upper limit | 0.14 |

Notes:

[43] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 35 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Pre-dose, Week 8

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.138 ^[44] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.073 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.024 |
| upper limit | 0.169 |

Notes:

[44] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 36 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Pre-dose, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.813 ^[45] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.012 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.111 |
| upper limit | 0.087 |

Notes:

[45] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 37 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Pre-dose, Week 18

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.172 ^[46] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.073 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.032 |
| upper limit | 0.177 |

Notes:

[46] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 38 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Pre-dose, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.242 ^[47] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.067 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.045 |
| upper limit | 0.18 |

Notes:

[47] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 39 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Pre-dose, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.267 ^[48] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.082 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.063 |
| upper limit | 0.228 |

Notes:

[48] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 40 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Pre-dose, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.471 ^[49] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.083 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.143 |
| upper limit | 0.309 |

Notes:

[49] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 41 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Post-dose, Week 2

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.315 ^[50] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.045 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.043 |
| upper limit | 0.132 |

Notes:

[50] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 42 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Post-dose, Week 4

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.143 ^[51] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.054 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.018 |
| upper limit | 0.126 |

Notes:

[51] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 43 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Post-dose, Week 8

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.111 ^[52] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.072 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.017 |
| upper limit | 0.16 |

Notes:

[52] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 44 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Post-dose, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.783 ^[53] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.012 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.075 |
| upper limit | 0.1 |

Notes:

[53] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 45 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Post-dose, Week 18

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.283 ^[54] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.059 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.049 |
| upper limit | 0.167 |

Notes:

[54] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 46 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Post-dose, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.038 ^[55] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.138 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.008 |
| upper limit | 0.267 |

Notes:

[55] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 47 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Post-dose, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.467 ^[56] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.048 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.083 |
| upper limit | 0.18 |

Notes:

[56] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 48 |
|-----------------------------------|-------------------------|

Statistical analysis description:

FVC Post-dose, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.64 ^[57] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.042 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.138 |
| upper limit | 0.222 |

Notes:

[57] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Secondary: Change from Baseline in spirometry parameters in pre and post FEV1/FVC, Percent Predicted (PP) FEV1, PP FEV6 and PP FVC

| | |
|--|---|
| End point title | Change from Baseline in spirometry parameters in pre and post FEV1/FVC, Percent Predicted (PP) FEV1, PP FEV6 and PP FVC |
| End point description: | |
| Pre and post FEV1/FVC, PP FEV1, PP FEV6 and PP FVC were assessed at Screening, Day 1 pre-dose and Weeks 2, 4, 8, 12, 18, 26, 39 and 52. Par. were asked to withheld all bronchodilator therapy included ipratropiumn bromide and salbutamol/albuterol for at least 4 hours prior to the prebronchodilator spirometric test. Post-bronchodilator spirometric assessment was performed after inhalation of 400/360 µg of salbutamol/albuterol in 10-15 minutes. Day 1 (pre-dose) values were considered as Baseline values. Change from Baseline was calculated as value at indicated time point minus Baseline value. The maximum value of the 3 replicate assessments were used. Analysis performed using a mixed-effects repeated measures model. The adjusted mean values were summarized per treatment group. Par. were included in the analysis if they had at least one post-baseline measurement. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and up to Week 52 | |

| End point values | Placebo | Losmapimod 15 mg | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[58] | 90 ^[59] | | |
| Units: Percentage | | | | |
| arithmetic mean (standard error) | | | | |
| PP FVC, Week 2, n =90, 82 | 0.72 (± 1.156) | 1.31 (± 1.228) | | |
| PP FVC, Week 4, n =88, 81 | -0.73 (± 1.16) | 1.72 (± 1.228) | | |
| PP FVC, Week 8, n =81, 78 | -2.05 (± 1.556) | 0.47 (± 1.604) | | |
| PP FVC, Week 12 , n =78, 70 | -0.64 (± 1.324) | -0.78 (± 1.399) | | |
| PP FVC, Week 18, n =67, 60 | -1.58 (± 1.286) | 1.12 (± 1.356) | | |
| PP FVC, Week 26, n =53, 51 | -2.81 (± 1.518) | 1.88 (± 1.575) | | |
| PP FVC, Week 39, n =28, 27 | -2.06 (± 1.548) | 1.24 (± 1.604) | | |
| PP FVC, Week 52, n =14, 11 | -1.24 (± 2.017) | 0.92 (± 2.137) | | |
| PP FEV1, Week 2, n =90, 82 | 0.28 (± 0.858) | 2.03 (± 0.932) | | |
| PP FEV1, Week 4, n =88, 81 | -0.24 (± 0.877) | 1.52 (± 0.95) | | |
| PP FEV1, Week 8, n =81, 78 | -1.14 (± 0.979) | 1.04 (± 1.037) | | |
| PP FEV1, Week 12 , n =78, 70 | -0.1 (± 0.94) | 0.12 (± 1.013) | | |
| PP FEV1, Week 18, n =67, 60 | -0.79 (± 1.094) | 0.58 (± 1.172) | | |
| PP FEV1, Week 26, n =53, 51 | -2.07 (± 1.075) | 1.26 (± 1.134) | | |
| PP FEV1, Week 39, n =28, 27 | -2.33 (± 1.307) | 0.79 (± 1.37) | | |
| PP FEV1, Week 52, n =14, 11 | -0.32 (± 1.714) | 2.03 (± 1.901) | | |
| PP FEV6, Week 2, n =87, 75 | 0.63 (± 1.163) | 3.45 (± 1.252) | | |
| PP FEV6, Week 4, n =84, 75 | -0.72 (± 1.135) | 2.15 (± 1.212) | | |
| PP FEV6, Week 8, n =79, 74 | -1.71 (± 1.332) | 2.04 (± 1.395) | | |

| | | | | |
|--|-----------------|-----------------|--|--|
| PP FEV6, Week 12 , n =76, 67 | -0.42 (± 1.214) | -0.02 (± 1.284) | | |
| PP FEV6, Week 18, n =65, 56 | -1.47 (± 1.347) | 1.87 (± 1.438) | | |
| PP FEV6, Week 26, n =51, 48 | -1.69 (± 1.359) | 1.84 (± 1.436) | | |
| PP FEV6, Week 39, n =26, 24 | -2.1 (± 1.543) | 2.09 (± 1.652) | | |
| PP FEV6, Week 52, n =13, 11 | 0.99 (± 2.936) | 3.66 (± 3.209) | | |
| FEV1/FVC, Pre-dose, Week 2, n =90, 83 | 0.22 (± 0.571) | 0.43 (± 0.611) | | |
| FEV1/FVC, Pre-dose, Week 4, n =88, 82 | 0.3 (± 0.674) | 0.43 (± 0.716) | | |
| FEV1/FVC, Pre-dose Week 8, n = 81, 79 | 0.1 (± 0.632) | 0.46 (± 0.663) | | |
| FVC, Pre-dose, Week 12, n =78, 71 | 0.31 (± 0.649) | 0.02 (± 0.688) | | |
| FEV1/FVC, Pre-dose Week 18, n =67, 61 | 0.11 (± 0.735) | 0.34 (± 0.78) | | |
| FEV1/FVC, Week 26, n=53, 52 | -0.48 (± 0.767) | 0.84 (± 0.803) | | |
| FEV1/FVC, Pre-dose Week 39, n =28, 28 | -1.36 (± 0.932) | 0.7 (± 0.963) | | |
| FEV1/FVC, Pre-dose Week 52, n =14, 11 | -0.18 (± 1.177) | 1.26 (± 1.27) | | |
| FEV1/FVC, Post-dose Week 2, n =89, 82 | 0.09 (± 0.682) | 0.51 (± 0.726) | | |
| FEV1/FVC, Post-dose Week 4, n =87, 81 | -0.9 (± 0.619) | -0.23 (± 0.662) | | |
| FEV1/FVC, Post-dose Week 8, n =80, 78 | 0.12 (± 0.646) | 0.28 (± 0.679) | | |
| FEV1/FVC, Post-dose Week 12, n =76, 69 | -0.51 (± 0.693) | -0.97 (± 0.736) | | |
| FEV1/FVC, Post-dose Week 18, n =66, 60 | -0.65 (± 0.643) | -0.23 (± 0.682) | | |
| FEV1/FEV1/FVC, Post-dose Week 26, n=52, 51 | -0.6 (± 2.272) | 3.23 (± 2.292) | | |
| FEV1/FVC, Post-dose Week 39, n =27, 27 | -1.27 (± 0.939) | 0.18 (± 0.961) | | |
| FEV1/FVC, Post-dose Week 52, n =13, 10 | 0.34 (± 1.28) | 1.51 (± 1.397) | | |

Notes:

[58] - mITT Population

[59] - mITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------------|
| Statistical analysis description: | |
| PP FVC, Week 2 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.661 ^[60] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.08 |
| upper limit | 3.27 |

Notes:

[60] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: PP FVC, Week 6 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.074 ^[61] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | 5.12 |

Notes:

[61] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Statistical analysis description: PP FVC, Week 8 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.21 ^[62] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.43 |
| upper limit | 6.46 |

Notes:

[62] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|--|----------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Statistical analysis description: PP FVC, Week 12 | |
| Comparison groups | Placebo v Losmapimod 15 mg |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.933 ^[63] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 3.12 |

Notes:

[63] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis 5 |
| Statistical analysis description: PP FVC, Week 18 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.091 ^[64] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.43 |
| upper limit | 5.82 |

Notes:

[64] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis 6 |
| Statistical analysis description: PP FVC, Week 26 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.018 ^[65] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.69 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 8.56 |

Notes:

[65] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

PP FVC, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.103 ^[66] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.3 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.69 |
| upper limit | 7.29 |

Notes:

[66] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

PP FVC, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.448 ^[67] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.16 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | 7.82 |

Notes:

[67] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

PP FEV1, Week 2

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.089 ^[68] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | 3.77 |

Notes:

[68] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV1, Week 4

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.095 ^[69] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | 3.84 |

Notes:

[69] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV1, Week 8

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.073 ^[70] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.19 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 4.58 |

Notes:

[70] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV1, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.853 ^[71] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.22 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.08 |
| upper limit | 2.51 |

Notes:

[71] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV1, Week 18

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.334 ^[72] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.37 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.43 |
| upper limit | 4.17 |

Notes:

[72] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 14 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV1, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.017 ^[73] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 6.05 |

Notes:

[73] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV1, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.077 ^[74] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | 6.59 |

Notes:

[74] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV1, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.355 ^[75] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.34 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7 |
| upper limit | 7.38 |

Notes:

[75] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 17 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV6, Week 2

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.044 ^[76] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.82 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.08 |
| upper limit | 5.55 |

Notes:

[76] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 18 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV6, Week 4

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.032 ^[77] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.87 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.25 |
| upper limit | 5.49 |

Notes:

[77] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 19 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV6, Week 8

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.025 ^[78] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 7.01 |

Notes:

[78] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 20 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV6, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.785 ^[79] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 3.29 |

Notes:

[79] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 21 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV6, Week 18

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.052 ^[80] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.34 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 6.7 |

Notes:

[80] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 22 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV6, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.041 ^[81] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.53 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.14 |
| upper limit | 6.92 |

Notes:

[81] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 23 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV6, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.043 ^[82] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.19 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.13 |
| upper limit | 8.25 |

Notes:

[82] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 24 |
|-----------------------------------|-------------------------|

Statistical analysis description:

PP FEV6, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.562 ^[83] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.58 |
| upper limit | 11.92 |

Notes:

[83] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 25 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Pre-dose FEV1/FVC, Week 2

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.746 ^[84] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.09 |
| upper limit | 1.52 |

Notes:

[84] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 26 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Pre-dose FEV1/FVC, Week 4

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.878 ^[85] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.13 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.53 |
| upper limit | 1.79 |

Notes:

[85] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 27 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Pre-dose FEV1/FVC, Week 8

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.644 ^[86] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.35 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.15 |
| upper limit | 1.85 |

Notes:

[86] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 28 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Pre-dose FEV1/FVC, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.715 ^[87] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.29 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.86 |
| upper limit | 1.28 |

Notes:

[87] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 29 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Pre-dose FEV1/FVC, Week 18

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.803 ^[88] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.62 |
| upper limit | 2.1 |

Notes:

[88] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 30 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Pre-dose FEV1/FVC, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.184 ^[89] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.63 |
| upper limit | 3.27 |

Notes:

[89] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 31 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Pre-dose FEV1/FVC, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.102 ^[90] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.05 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.42 |
| upper limit | 4.52 |

Notes:

[90] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 32 |
| Statistical analysis description: Pre-dose FEV1/FVC, Week 52 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.383 ^[91] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.85 |
| upper limit | 4.73 |

Notes:

[91] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 33 |
| Statistical analysis description: Post-dose FEV1/FVC, Week 2 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.607 ^[92] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 2.06 |

Notes:

[92] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 34 |
|-----------------------------------|-------------------------|

| | |
|---|--------------------------------|
| Statistical analysis description: | |
| Post-dose FEV1/FVC, Week 4 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.348 ^[93] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.74 |
| upper limit | 2.08 |

Notes:

[93] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 35 |
| Statistical analysis description: | |
| Post-dose FEV1/FVC, Week 8 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.826 ^[94] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.32 |
| upper limit | 1.65 |

Notes:

[94] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 36 |
| Statistical analysis description: | |
| Post-dose FEV1/FVC, Week 12 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.588 ^[95] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.46 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.13 |
| upper limit | 1.21 |

Notes:

[95] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 37 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Post-dose FEV1/FVC, Week 18

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.585 ^[96] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.41 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.08 |
| upper limit | 1.91 |

Notes:

[96] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 38 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Post-dose FEV1/FVC, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.231 ^[97] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.82 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.48 |
| upper limit | 10.12 |

Notes:

[97] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 39 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Post-dose FEV1/FVC, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.24 ^[98] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.99 |
| upper limit | 3.89 |

Notes:

[98] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 40 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Post-dose FEV1/FVC, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.517 ^[99] |
| Method | MERM Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.49 |
| upper limit | 4.84 |

Notes:

[99] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Secondary: Number of participants with electrocardiogram (ECG) findings

| | |
|-----------------|--|
| End point title | Number of participants with electrocardiogram (ECG) findings |
|-----------------|--|

End point description:

12-lead ECGs were obtained in triplicate at Screening then singly at Baseline (day 1, pre-dose) and post dose at Weeks 2, 4, 8, 12, 26, 39, 52 and at follow up using an ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT, and QT duration corrected for heart rate by Fridericia's formula (QTcF) or QT duration corrected for heart rate by Bazett's formula (QTcB) intervals. Change in ECG findings were categorized as normal and abnormal. Abnormal ECG values could be clinically significant (CS) or not clinically significant (NCS), as determined by the investigator. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 53 Weeks

| End point values | Placebo | Losmapimod 15 mg | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[100] | 90 ^[101] | | |
| Units: Participants | | | | |
| Normal-SCREENING, (n=94,90) | 49 | 51 | | |
| Abnormal-NCS-SCREENING, (n=94,90) | 39 | 36 | | |
| Abnormal-CS-SCREENING, (n=94,90) | 9 | 5 | | |
| Normal-Baseline, (n=94,90) | 44 | 54 | | |
| Abnormal-NCS-Baseline, (n=94,90) | 46 | 31 | | |
| Abnormal-CS-Baseline, (n=90,90) | 4 | 5 | | |
| Normal-Week 2, (n=90,84) | 40 | 52 | | |
| Abnormal-NCS-Week 2, (n=90,84) | 45 | 29 | | |
| Abnormal-CS-Week 2, (n=90,84) | 5 | 3 | | |
| Normal-Week 4, (n=89,82) | 45 | 53 | | |
| Abnormal-NCS-Week 4, (n=89,82) | 40 | 27 | | |
| Abnormal-CS-Week 4, (n=89,82) | 4 | 2 | | |
| Normal-Week 8, (n=80,80) | 42 | 50 | | |
| Abnormal-NCS-Week 8, (n=80,80) | 35 | 28 | | |
| Abnormal-CS-Week 8, (n=80,80) | 3 | 2 | | |
| Normal-Week 12, (n=78,72) | 45 | 42 | | |
| Abnormal-NCS-Week 12, (n=78,72) | 29 | 29 | | |
| Abnormal-CS-Week 12, (n=78,72) | 4 | 1 | | |
| Normal-Week 26, (n=53,52) | 31 | 35 | | |
| Abnormal-NCS-Week 26, (n=53,52) | 21 | 16 | | |
| Abnormal-CS-Week 26, (n=53,52) | 1 | 1 | | |
| Normal-Week 39, (n=28,29) | 18 | 20 | | |
| Abnormal-NCS-Week 39, (n=28,29) | 9 | 8 | | |
| Abnormal-CS-Week 39, (n=28,29) | 1 | 1 | | |
| Normal-Week 52, (n=14,11) | 11 | 7 | | |
| Abnormal-NCS-Week 52, (n=14,11) | 2 | 4 | | |
| Abnormal-CS-Week 52, (n=14,11) | 1 | 0 | | |
| Normal-Follow up, (n=83,68) | 37 | 42 | | |
| Abnormal-NCS-Follow up, (n=83,68) | 40 | 25 | | |
| Abnormal-CS-Follow up, (n=83,68) | 6 | 1 | | |

Notes:

[100] - mITT Population

[101] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the indicated time points

| | |
|-----------------|---|
| End point title | Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the indicated time points |
|-----------------|---|

End point description:

SBP and DBP were taken at Screening, Baseline (day 1, pre-dose) and post dose at Weeks 2, 4, 8, 12,

26, 39, 52 and at follow up. Measurements were taken in a semi-recumbent position after 5 minutes rest. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The Baseline value of an assessment is defined as the value at day 1, pre-dose. Par. were included in the analysis if they had at least one post-baseline measurement. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and up to Week 53 | |

| End point values | Placebo | Losmapimod 15 mg | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[102] | 90 ^[103] | | |
| Units: Millimeter of mercury (mmHg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| SBP, Week 2, (n=90,84) | 0.2 (± 12) | -2.9 (± 11.85) | | |
| SBP, Week 4, (n=89,82) | -0.8 (± 11.49) | -0.4 (± 12.49) | | |
| SBP, Week 8, (n=81,80) | -1.9 (± 14.53) | -0.3 (± 11.48) | | |
| SBP, Week 12, (n=78,72) | 0.5 (± 12.97) | -1.6 (± 13.84) | | |
| SBP, Week 26, (n=53,53) | -1.5 (± 15.39) | -1.3 (± 13.25) | | |
| SBP, Week 39, (n=28,29) | 0.3 (± 16.3) | -3.4 (± 10.99) | | |
| SBP, Week 52, (n=14,11) | 6.1 (± 17.81) | -7.6 (± 12.89) | | |
| SBP, Follow up, (n=83,68) | 1.8 (± 14.46) | 0.2 (± 13.41) | | |
| DBP, Week 2, (n=90,84) | 0 (± 7.18) | -3.8 (± 9.81) | | |
| DBP, Week 4, (n=89,82) | -0.3 (± 8.57) | -2.2 (± 9.32) | | |
| DBP, Week 8, (n=81,80) | -1.4 (± 8.75) | -1.5 (± 7.92) | | |
| DBP, Week 12, (n=78,72) | 1.5 (± 9.79) | -1.5 (± 9.59) | | |
| DBP, Week 26, (n=53,53) | 0.9 (± 8.33) | -1.2 (± 7.87) | | |
| DBP, Week 39, (n=28,29) | -0.5 (± 10.4) | -1.9 (± 9.58) | | |
| DBP, Week 52, (n=14,11) | 3.4 (± 8.08) | -0.2 (± 8.46) | | |
| DBP, Follow up, (n=83,68) | 1.5 (± 10.57) | -1.7 (± 9.94) | | |

Notes:

[102] - mITT Population

[103] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate (HR) values at the indicated time points

| | |
|-----------------|---|
| End point title | Change from Baseline in heart rate (HR) values at the indicated time points |
|-----------------|---|

End point description:

HR was assessed at Screening, Baseline (day 1, pre-dose) and post dose at Weeks 2, 4, 8, 12, 26, 39, 52 and at follow up. Measurements were taken in a semi-recumbent position after 5 minutes rest. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The Baseline value of an assessment is defined as the value at day 1, pre-dose. Par. were included in the analysis if they had at least one post-baseline measurement. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[104] | 90 ^[105] | | |
| Units: Beats per minute (bpm) | | | | |
| arithmetic mean (standard deviation) | | | | |
| HR, Week 2, (n=90,84) | 1.2 (± 7.99) | 1.5 (± 9.92) | | |
| HR, Week 4, (n=89,82) | 1.4 (± 7.18) | 0.6 (± 8.72) | | |
| HR, Week 8, (n=81,80) | 1 (± 8.39) | 1.6 (± 9.5) | | |
| HR, Week 12, (n=78,72) | 3.3 (± 8.8) | 2.2 (± 8.89) | | |
| HR, Week 26, (n=53,53) | 4.1 (± 10.99) | 1.8 (± 8.32) | | |
| HR, Week 39, (n=28,29) | 3.3 (± 9.48) | 4.4 (± 12.64) | | |
| HR, Week 52, (n=14,11) | 4.3 (± 9.55) | 1.3 (± 8.72) | | |
| HR, Follow up, (n=83,68) | 3.6 (± 6.72) | 4.2 (± 10.99) | | |

Notes:

[104] - mITT Population

[105] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Losmapimod area under the plasma concentration time curve (AUC) from time zero to the end of dosing interval (AUC[0-tau])

| | |
|-----------------|---|
| End point title | Plasma Losmapimod area under the plasma concentration time curve (AUC) from time zero to the end of dosing interval (AUC[0-tau]) ^[106] |
|-----------------|---|

End point description:

Pharmacokinetics (PK) of losmapimod was evaluated in participants with COPD using PK samples collected at pre-dose at Week 2 and Week 12. At Week 26, a sample was collected at pre-dose and a second sample was collected at 2 hours post-dose. Par. of mITT population that provided at least one observed concentration data in this study were considered for PK analysis. Drug plasma concentration-time data were modelled by nonlinear mixed effects modelling. AUC[0-tau] (tau=12 hours) was estimated from the model.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 2, 12 and 26

Notes:

[106] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

| | | | | |
|---|-------------------------|--|--|--|
| End point values | Losmapimod 15 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 85 ^[107] | | | |
| Units: hour (h)*nanogram (ng)/milliliter (mL) | | | | |
| geometric mean (confidence interval 95%) | 668.5 (361.7 to 1235.6) | | | |

Notes:

[107] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma losmapimod maximum concentration (Cmax) and lowest concentration (Ctrough) at steady state

| | |
|-----------------|--|
| End point title | Plasma losmapimod maximum concentration (Cmax) and lowest concentration (Ctrough) at steady state ^[108] |
|-----------------|--|

End point description:

Pharmacokinetics of losmapimod was evaluated in participants with COPD using PK samples collected at pre-dose at Week 2 and Week 12. At Week 26, a sample was collected at pre-dose and a second sample was collected at 2 hours post-dose. Par. of mITT population that provided at least one observed concentration data in this study were considered for PK analysis (represented by n=X, X in the category titles). Drug plasma concentration-time data were modelled by nonlinear mixed effects modelling to develop a Population PK model. Cmax and Ctrough were estimated from the PK model.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 2, 12 and 26

Notes:

[108] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

| | | | | |
|--|----------------------|--|--|--|
| End point values | Losmapimod 15 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 85 ^[109] | | | |
| Units: ng/ mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Cmax | 49.7 (17.6 to 140.5) | | | |
| Ctrough | 23.7 (12.9 to 43.3) | | | |

Notes:

[109] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in frequency of short acting beta-agonist or anti-cholinergic use

| | |
|--|--|
| End point title | Change from Baseline in frequency of short acting beta-agonist or anti-cholinergic use |
| End point description: Use of short acting bronchodilators (short-acting beta2-agonists or short-acting anti-cholinergic) was allowed and was recorded in daily patient diary. It included inhaled short-acting beta2-agonists (e.g. Ipratropium bromide, salbutamol, Ipratropium/salbutamol (albuterol) combination product) and short-acting anti-cholinergics (e.g., ipratropium bromide3). Use of these medications was allowed through out the study except 4 hours prior to and during each clinic visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles). Data were not summarized because the study was stopped for futility. | |
| End point type | Secondary |
| End point timeframe: Baseline and up to Week 26 | |

| End point values | Placebo | Losmapimod 15 mg | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[110] | 0 ^[111] | | |
| Units: Hours | | | | |
| number (not applicable) | | | | |

Notes:

[110] - The study was stopped for futility

[111] - The study was stopped for futility

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in St Georges Respiratory Questionnaire (SGRQ) total, SGRQ symptoms score, SGRQ activity score and SGRQ impact score over time

| | |
|---|---|
| End point title | Change from Baseline in St Georges Respiratory Questionnaire (SGRQ) total, SGRQ symptoms score, SGRQ activity score and SGRQ impact score over time |
| End point description: The total and component SGRQ-C Scores (Activity, Symptoms, Impacts) were calculated at Weeks 0, 12, 26, 39 and 52. SGRQ-C is a health related quality of life questionnaire consisting of 14 questions. SGRQ-C total score was calculated as 100 multiplied by summed weights from all positive items divided by sum of weights for all items in questionnaire. Components were calculated as 100 multiplied by summed weights from all positive items in that component divided by sum of weights for all items in that component. SGRQ-C was transformed to SGRQ for reporting. Score at Day 1, pre-dose (Week 0) was considered as Baseline. Change from Baseline was calculated as score at indicated time point minus Baseline value. Analysis performed using a mixed-effects repeated measures model. Par. were included in the analysis if they had at least one post-baseline measurement. Only those par. with analyzable data at the given time points (represented by n=X, X in category titles) were included in analysis. | |
| End point type | Secondary |
| End point timeframe: Baseline and up to Week 52 | |

| End point values | Placebo | Losmapimod 15 mg | | |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[112] | 90 ^[113] | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | | | | |
| SGRQ Total, Week 12, (n=74, 71) | -0.75 (± 1.541) | -1.42 (± 1.638) | | |
| SGRQ Total, Week 26, (n=50, 49) | -2.2 (± 1.833) | -1.31 (± 1.904) | | |
| SGRQ Total, Week 39, (n=28, 28) | -0.37 (± 2.451) | -3.19 (± 2.502) | | |
| SGRQ Total, Week 52, (n=14, 11) | -2.95 (± 2.769) | -3.43 (± 3.098) | | |
| SGRQ Symptoms, Week 12, (n=78, 72) | -2.41 (± 1.999) | -4.08 (± 2.115) | | |
| SGRQ Symptoms, Week 26, (n=52, 52) | -5.04 (± 2.264) | -4.3 (± 2.335) | | |
| SGRQ Symptoms, Week 39, (n=28, 29) | -4.61 (± 3.411) | -8.21 (± 3.37) | | |
| SGRQ Symptoms, Week 52, (n=14, 11) | -3.69 (± 3.99) | -11.67 (± 4.296) | | |
| SGRQ Activity, Week 12, (n=77, 71) | -0.08 (± 1.968) | 1.15 (± 2.097) | | |
| SGRQ Activity, Week 26, (n=50, 49) | -0.33 (± 2.217) | 0.7 (± 2.303) | | |
| SGRQ Activity, Week 39, (n=28, 28) | 1.41 (± 3.027) | -1 (± 3.095) | | |
| SGRQ Activity, Week 52, (n=14, 11) | -1.8 (± 3.308) | 2.59 (± 3.65) | | |
| SGRQ Impact, Week 12, (n=75, 71) | -0.53 (± 1.78) | -2.22 (± 1.893) | | |
| SGRQ Impact, Week 26, (n=52, 50) | -1.84 (± 2.169) | -2.19 (± 2.255) | | |
| SGRQ Impact, Week 39, (n=28, 28) | -0.59 (± 2.868) | -2.8 (± 2.931) | | |
| SGRQ Impact, Week 52, (n=14, 11) | -2.01 (± 3.693) | -3.31 (± 4.099) | | |

Notes:

[112] - mITT Population

[113] - mITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--------------------------------|
| Statistical analysis description: | |
| SGRQ Total, Week 12 | |
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.706 ^[114] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.67 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.2 |
| upper limit | 2.85 |

Notes:

[114] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

SGRQ Total, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.694 ^[115] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.89 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.58 |
| upper limit | 5.36 |

Notes:

[115] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

SGRQ Total, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.382 ^[116] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.83 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.23 |
| upper limit | 3.58 |

Notes:

[116] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

SGRQ Total, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.903 ^[117] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.54 |
| upper limit | 7.57 |

Notes:

[117] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

SGRQ Symptoms, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.481 ^[118] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.33 |
| upper limit | 2.99 |

Notes:

[118] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

SGRQ Symptoms, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.793 ^[119] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.73 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.79 |
| upper limit | 6.25 |

Notes:

[119] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

SGRQ Symptoms, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.421 ^[120] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -3.6 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.45 |
| upper limit | 5.26 |

Notes:

[120] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

SGRQ Symptoms, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.162 ^[121] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -7.98 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.35 |
| upper limit | 3.4 |

Notes:

[121] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

SGRQ Activity, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.592 ^[122] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.31 |
| upper limit | 5.78 |

Notes:

[122] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

SGRQ Activity, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.704 ^[123] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.31 |
| upper limit | 6.36 |

Notes:

[123] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

SGRQ Activity, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.546 ^[124] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.41 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.32 |
| upper limit | 5.5 |

Notes:

[124] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

SGRQ Activity, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.35 ^[125] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.39 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.06 |
| upper limit | 13.84 |

Notes:

[125] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

SGRQ Impact, Week 12

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.411 ^[126] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.69 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.75 |
| upper limit | 2.37 |

Notes:

[126] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 14 |
|-----------------------------------|-------------------------|

Statistical analysis description:

SGRQ Impact, Week 26

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.896 ^[127] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.67 |
| upper limit | 4.97 |

Notes:

[127] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

SGRQ Impact, Week 39

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.559 ^[128] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.73 |
| upper limit | 5.3 |

Notes:

[128] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

SGRQ Impact, Week 52

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Losmapimod 15 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.809 ^[129] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.29 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.19 |
| upper limit | 9.6 |

Notes:

[129] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Secondary: Number of participants with abnormal liver events during the treatment period

| | |
|-----------------|---|
| End point title | Number of participants with abnormal liver events during the treatment period |
|-----------------|---|

End point description:

Various liver chemistry parameters were monitored periodically to ensure the safety and tolerability of Losmapimod as compared to placebo. Study treatments were discontinued for par. if alanine aminotransferase (ALT) absolute $\geq 5 \times$ upper limit of normal (ULN) or; ALT $\geq 3 \times$ ULN persists for ≥ 4 Weeks or; ALT $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN or; ALT $\geq 3 \times$ ULN and International normalized ratio (INR) ≥ 1.5 or; ALT $\geq 3 \times$ ULN and cannot be monitored weekly for 4 Weeks or; ALT $\geq 3 \times$ ULN symptomatic.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[130] | 90 ^[131] | | |
| Units: Participants | 0 | 0 | | |

Notes:

[130] - mITT Population

[131] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hemoglobin, total protein, albumin and mean corpuscle hemoglobin concentration (MCHC) at the indicated time points

| | |
|-----------------|--|
| End point title | Change from Baseline in hemoglobin, total protein, albumin and mean corpuscle hemoglobin concentration (MCHC) at the indicated time points |
|-----------------|--|

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate hemoglobin, total protein, albumin and MCHC. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[132] | 90 ^[133] | | |
| Units: Gram (G)/Liter (L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Hemoglobin, Week 2 (n=85,82) | -0.3 (± 7.12) | 0 (± 4.86) | | |
| Hemoglobin, Week 4 (n=87,80) | -0.6 (± 7.01) | -1 (± 6.34) | | |
| Hemoglobin, Week 8 (n=80,77) | -0.9 (± 8.38) | -2.5 (± 6.93) | | |
| Hemoglobin, Week 12 (n=76,70) | -0.5 (± 7.61) | -1.4 (± 9.9) | | |
| Hemoglobin, Week 18 (n=66,61) | 0.1 (± 9.24) | -2.3 (± 9.66) | | |
| Hemoglobin, Week 26 (n=52,50) | -0.7 (± 9.27) | -2.9 (± 8.86) | | |
| Hemoglobin, Week 39 (n=28,29) | 0 (± 11.71) | -0.1 (± 10.09) | | |
| Hemoglobin, Week 52 (n=14,11) | 2.9 (± 8.43) | -1.8 (± 7.9) | | |
| Hemoglobin, Follow up (n=80,67) | -0.2 (± 9.3) | -4.5 (± 9.42) | | |
| Albumin, Week 2 (n=90,84) | -0.3 (± 2.23) | -0.6 (± 2.55) | | |
| Albumin, Week 4 (n=88,81) | -0.5 (± 2.35) | -0.3 (± 2.28) | | |
| Albumin, Week 8 (n=81,79) | -1.1 (± 2.43) | -1.2 (± 2.38) | | |
| Albumin, Week 12 (n=78,72) | -0.4 (± 2.62) | -0.8 (± 2.64) | | |
| Albumin, Week 18 (n=67,60) | -1.1 (± 2.53) | -1.1 (± 2.32) | | |
| Albumin, Week 26 (n=53,50) | -0.9 (± 2.89) | -1.1 (± 2.25) | | |
| Albumin, Week 39 (n=28,29) | -0.8 (± 2.76) | -1.2 (± 2.35) | | |
| Albumin, Week 52 (n=14,11) | -0.4 (± 2.95) | -1.5 (± 2.07) | | |
| Albumin, Follow up (n=80,68) | -0.8 (± 2.49) | -1.6 (± 2.71) | | |
| Total protein, Week 2 (n=90,84) | -0.4 (± 3.68) | -1.6 (± 2.96) | | |
| Total protein, Week 4 (n=88,81) | -0.8 (± 3.93) | -1.2 (± 3.18) | | |
| Total protein, Week 8 (n=81,79) | -1.8 (± 3.67) | -2 (± 3.01) | | |
| Total protein, Week 12 (n=78,72) | -0.6 (± 4.14) | -0.8 (± 3.45) | | |
| Total protein, Week 18 (n=67,60) | -0.8 (± 4) | -1.5 (± 2.66) | | |
| Total protein, Week 26 (n=53,50) | -0.5 (± 4.59) | -1.5 (± 3.7) | | |
| Total protein, Week 39 (n=28,29) | -0.6 (± 4.5) | -2.2 (± 3.51) | | |
| Total protein, Week 52 (n=14,11) | -0.8 (± 4.66) | -3 (± 3.66) | | |
| Total protein, Follow up (n=80,68) | -1.6 (± 4.05) | -2 (± 3.87) | | |
| MCHC, Week 2 (n=85,82) | 0.1 (± 6.94) | 1.7 (± 6.4) | | |
| MCHC, Week 4 (n=87,80) | 0.3 (± 6.31) | -0.6 (± 6.8) | | |
| MCHC, Week 8 (n=80,77) | -1 (± 7.63) | -0.9 (± 6.88) | | |
| MCHC, Week 12 (n=76,70) | -3.1 (± 8.45) | -3.3 (± 10.7) | | |
| MCHC, Week 18 (n=66,61) | -5 (± 10.38) | -4.8 (± 8.75) | | |
| MCHC, Week 26 (n=52,50) | -4.4 (± 7.06) | -5.3 (± 8.48) | | |
| MCHC, Week 39 (n=28,29) | -2.8 (± 5.19) | -1.5 (± 5.35) | | |
| MCHC, Week 52 (n=14,11) | -3.9 (± 5.55) | -3.3 (± 6.15) | | |
| MCHC, Follow up (n=80,67) | 1.5 (± 9.77) | 0.6 (± 8.73) | | |

Notes:

[132] - mITT Population

[133] - mITT Population

Statistical analyses

Secondary: Change from Baseline in hematocrit at the indicated time points

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|--|---|
| End point title | Change from Baseline in hematocrit at the indicated time points |
| End point description: | |
| Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate hematocrit. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles). | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and up to Week 53 | |

| End point values | Placebo | Losmapimod 15 mg | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[134] | 90 ^[135] | | |
| Units: Liter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Hematocrit, Week 2 (n=85,82) | -0.001 (± 0.0238) | -0.002 (± 0.0169) | | |
| Hematocrit, Week 4 (n=87,80) | -0.002 (± 0.0236) | -0.002 (± 0.0218) | | |
| Hematocrit, Week 8 (n=80,77) | -0.001 (± 0.0274) | -0.006 (± 0.0229) | | |
| Hematocrit, Week 12 (n=76,70) | 0.002 (± 0.0251) | 0 (± 0.0361) | | |
| Hematocrit, Week 18 (n=66,61) | 0.007 (± 0.0296) | 0 (± 0.0337) | | |
| Hematocrit, Week 26 (n=52,50) | 0.003 (± 0.0302) | 0 (± 0.0318) | | |
| Hematocrit, Week 39 (n=28,29) | 0.003 (± 0.0373) | 0.001 (± 0.0329) | | |
| Hematocrit, Week 52 (n=14,11) | 0.014 (± 0.0231) | -0.001 (± 0.0255) | | |
| Hematocrit, Follow up (n=80,67) | -0.003 (± 0.0305) | -0.015 (± 0.0302) | | |

Notes:

[134] - mITT Population

[135] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in absolute white blood cell (WBC) count, total neutrophil, total lymphocyte, basophil, eosinophil, monocyte and platelet count at the indicated time point

| | |
|-----------------|--|
| End point title | Change from Baseline in absolute white blood cell (WBC) count, total neutrophil, total lymphocyte, basophil, eosinophil, monocyte and platelet count at the indicated time point |
|-----------------|--|

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate absolute WBC count, total neutrophil, total lymphocyte, basophil, absolute eosinophil, percentage eosinophil, monocyte and platelet count. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|---|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[136] | 90 ^[137] | | |
| Units: Giga per liter (GI/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Absolute WBC count, Week 2 (n=85,82) | -0.04 (± 1.586) | 0.21 (± 1.71) | | |
| Absolute WBC count, Week 4 (n=86,80) | 0.03 (± 1.742) | 0.12 (± 2.116) | | |
| Absolute WBC count, Week 8 (n=80,77) | 0.04 (± 1.474) | 0.32 (± 1.939) | | |
| Absolute WBC count, Week 12 (n=76,70) | -0.07 (± 1.628) | 0.51 (± 1.905) | | |
| Absolute WBC count, Week 18 (n=66,60) | 0.29 (± 1.921) | 0.17 (± 1.842) | | |
| Absolute WBC count, Week 26 (n=52,50) | -0.07 (± 1.625) | 0.09 (± 1.876) | | |
| Absolute WBC count, Week 39 (n=28,29) | 0.29 (± 1.777) | 1.08 (± 2.857) | | |
| Absolute WBC count, Week 52 (n=14,11) | 0.86 (± 1.687) | 0.75 (± 1.637) | | |
| Absolute WBC count, Follow up (n=79,67) | 0.73 (± 1.691) | 0.5 (± 2.195) | | |
| Total neutrophils, Week 2 (n=85,82) | -0.038 (± 1.598) | -0.08 (± 1.7982) | | |
| Total neutrophils, Week 4 (n=86,80) | -0.014 (± 1.7572) | -0.012 (± 2.0753) | | |
| Total neutrophils, Week 8 (n=80,77) | -0.052 (± 1.606) | 0.06 (± 2.0525) | | |
| Total neutrophils, Week 12 (n=76,70) | 0.023 (± 1.7039) | 0.316 (± 2.0173) | | |
| Total neutrophils, Week 18 (n=66,60) | 0.189 (± 1.9556) | -0.161 (± 1.7378) | | |
| Total neutrophils, Week 26 (n=52,50) | -0.067 (± 1.4529) | -0.19 (± 1.8779) | | |
| Total neutrophils, Week 39 (n=28,29) | 0.24 (± 1.7846) | 0.689 (± 2.9389) | | |
| Total neutrophils, Week 52 (n=14,11) | 1.001 (± 1.8753) | 0.248 (± 1.4497) | | |
| Total neutrophils, Follow up (n=79,67) | 0.555 (± 1.7317) | 0.309 (± 2.3168) | | |
| Total lymphocyte, Week 2 (n=85,82) | 0.022 (± 0.4739) | 0.282 (± 0.7058) | | |
| Total lymphocyte, Week 4 (n=86,80) | 0.043 (± 0.6599) | 0.161 (± 0.5497) | | |

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|---------------------------------------|-------------------|-------------------|--|--|
| Total lymphocyte, Week 8 (n=80,77) | 0.089 (± 0.5532) | 0.263 (± 0.7366) | | |
| Total lymphocyte, Week 12 (n=76,70) | -0.083 (± 0.5983) | 0.21 (± 0.6986) | | |
| Total lymphocyte, Week 18 (n=66,60) | 0.076 (± 0.4751) | 0.321 (± 0.6855) | | |
| Total lymphocyte, Week 26 (n=52,50) | -0.042 (± 0.6673) | 0.296 (± 0.7236) | | |
| Total lymphocyte, Week 39 (n=28,29) | 0.019 (± 0.4731) | 0.387 (± 0.6355) | | |
| Total lymphocyte, Week 52 (n=14,11) | -0.107 (± 0.4707) | 0.449 (± 0.5762) | | |
| Total lymphocyte, Follow up (n=79,67) | 0.1 (± 0.5969) | 0.09 (± 0.6346) | | |
| Basophils, Week 2 (n=85,82) | 0 (± 0.0194) | 0.002 (± 0.029) | | |
| Basophils, Week 4 (n=86,80) | -0.001 (± 0.0332) | -0.002 (± 0.0231) | | |
| Basophils, Week 8 (n=80,77) | -0.003 (± 0.0288) | 0.003 (± 0.0254) | | |
| Basophils, Week 12 (n=76,70) | 0.001 (± 0.0328) | 0 (± 0.0212) | | |
| Basophils, Week 18 (n=66,60) | -0.002 (± 0.0249) | -0.002 (± 0.0191) | | |
| Basophils, Week 26 (n=52,50) | 0.001 (± 0.0241) | -0.006 (± 0.0173) | | |
| Basophils, Week 39 (n=28,29) | -0.001 (± 0.018) | -0.005 (± 0.019) | | |
| Basophils, Week 52 (n=14,11) | -0.006 (± 0.0109) | 0 (± 0.0184) | | |
| Basophils, Follow up (n=79,67) | -0.004 (± 0.0305) | 0 (± 0.0234) | | |
| Eosinophil, Week 2 (n=85,82) | 0 (± 0.066) | 0.025 (± 0.0941) | | |
| Eosinophil, Week 4 (n=86,80) | -0.002 (± 0.1092) | 0.013 (± 0.0713) | | |
| Eosinophil, Week 8 (n=80,77) | 0.008 (± 0.0948) | 0.014 (± 0.0918) | | |
| Eosinophil, Week 12 (n=76,70) | -0.001 (± 0.0817) | 0.013 (± 0.1173) | | |
| Eosinophil, Week 18 (n=66,60) | 0.03 (± 0.1287) | 0.046 (± 0.1926) | | |
| Eosinophil, Week 26 (n=52,50) | 0.037 (± 0.1554) | 0.051 (± 0.1646) | | |
| Eosinophil, Week 39 (n=28,29) | 0.037 (± 0.0628) | 0.028 (± 0.1035) | | |
| Eosinophil, Week 52 (n=14,11) | -0.001 (± 0.0539) | 0.006 (± 0.1688) | | |
| Eosinophil, Follow up (n=79,67) | 0.011 (± 0.0935) | 0.025 (± 0.0903) | | |
| Monocytes, Week 2 (n=85,82) | -0.029 (± 0.1598) | -0.024 (± 0.1898) | | |
| Monocytes, Week 4 (n=86,80) | 0.002 (± 0.1404) | -0.029 (± 0.1975) | | |
| Monocytes, Week 8 (n=80,77) | 0.001 (± 0.1785) | -0.014 (± 0.1653) | | |
| Monocytes, Week 12 (n=76,70) | -0.007 (± 0.1709) | -0.026 (± 0.2145) | | |
| Monocytes, Week 18 (n=66,60) | -0.01 (± 0.2023) | -0.025 (± 0.2235) | | |
| Monocytes, Week 26 (n=52,50) | 0.001 (± 0.2093) | -0.057 (± 0.179) | | |

| | | | | |
|-------------------------------------|-------------------|------------------|--|--|
| Monocytes, Week 39 (n=28,29) | -0.005 (± 0.121) | -0.02 (± 0.2376) | | |
| Monocytes, Week 52 (n=14,11) | -0.034 (± 0.1075) | 0.02 (± 0.1511) | | |
| Monocytes, Follow up (n=79,67) | 0.071 (± 0.2319) | 0.083 (± 0.219) | | |
| Platelet count, Week 2 (n=85,82) | -3.3 (± 45.84) | -2.3 (± 47.94) | | |
| Platelet count, Week 4 (n=87,80) | -6.4 (± 41.43) | -0.4 (± 35.5) | | |
| Platelet count, Week 8 (n=79,77) | -2.2 (± 40.51) | 6.3 (± 53.31) | | |
| Platelet count, Week 12 (n=75,70) | -10 (± 44.01) | 5.1 (± 55.82) | | |
| Platelet count, Week 18 (n=66,59) | 5.3 (± 53.14) | 3.2 (± 50.43) | | |
| Platelet count, Week 26 (n=52,50) | -2.7 (± 48.66) | -0.4 (± 42.21) | | |
| Platelet count, Week 39 (n=28,29) | -3.4 (± 35.47) | 0 (± 45.29) | | |
| Platelet count, Week 52 (n=14,11) | -13.6 (± 34.98) | -0.5 (± 30.06) | | |
| Platelet count, Follow up (n=80,67) | 9.7 (± 58.86) | 10.5 (± 50.76) | | |

Notes:

[136] - mITT Population

[137] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in eosinophil percentage at the indicated time points

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|-----------------|--|
| End point title | Change from Baseline in eosinophil percentage at the indicated time points |
|-----------------|--|

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate eosinophil percentage. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[138] | 90 ^[139] | | |
| Units: Percent change of eosinophil percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Eosinophil percentage, Week 2 (n=85,82) | 0.09 (± 0.969) | 0.3 (± 0.995) | | |
| Eosinophil percentage, Week 4 (n=86,80) | 0.03 (± 1.583) | 0.16 (± 0.93) | | |
| Eosinophil percentage, Week 8 (n=80,77) | 0.14 (± 1.419) | 0.11 (± 1.248) | | |

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|--|-----------------|----------------|--|--|
| Eosinophil percentage, Week 12 (n=76,70) | 0.08 (± 1.087) | 0.08 (± 1.517) | | |
| Eosinophil percentage, Week 18 (n=66,60) | 0.3 (± 1.513) | 0.6 (± 2.387) | | |
| Eosinophil percentage, Week 26 (n=52,50) | 0.58 (± 2.39) | 0.58 (± 2.082) | | |
| Eosinophil percentage, Week 39 (n=28,29) | 0.39 (± 0.865) | 0.21 (± 1.434) | | |
| Eosinophil percentage, Week 52 (n=14,11) | -0.11 (± 0.805) | 0.05 (± 2.819) | | |
| Eosinophil percentage, Follow up (n=79,67) | -0.01 (± 1.245) | 0.29 (± 1.215) | | |

Notes:

[138] - mITT Population

[139] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in total bilirubin, direct bilirubin, uric acid and creatinine at the indicated time point

| | |
|-----------------|---|
| End point title | Change from Baseline in total bilirubin, direct bilirubin, uric acid and creatinine at the indicated time point |
|-----------------|---|

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate total bilirubin, direct bilirubin, uric acid and creatinine. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[140] | 90 ^[141] | | |
| Units: Micromole (UMOL)/ L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Total bilirubin, Week 2 (n=90,84) | -0.5 (± 3.12) | 0.2 (± 3.62) | | |
| Total bilirubin, Week 4 (n=88,81) | 0.2 (± 3.07) | -0.1 (± 2.97) | | |
| Total bilirubin, Week 8 (n=81,79) | -0.4 (± 3.03) | -0.7 (± 3.28) | | |
| Total bilirubin, Week 12 (n=78,72) | -0.2 (± 3.33) | -0.1 (± 3.56) | | |
| Total bilirubin, Week 18 (n=67,60) | 0 (± 3.84) | 0.2 (± 2.66) | | |
| Total bilirubin, Week 26 (n=53,50) | 0 (± 3.03) | -0.5 (± 3.05) | | |
| Total bilirubin, Week 39 (n=28,29) | 0 (± 2.06) | 0.2 (± 3.55) | | |
| Total bilirubin, Week 52 (n=14,11) | 1.1 (± 3.38) | 0.9 (± 2.91) | | |
| Total bilirubin, Follow up (n=80,68) | 0.2 (± 3.62) | -0.4 (± 2.67) | | |
| Direct bilirubin, Week 2 (n=90,84) | -0.1 (± 1.09) | 0.2 (± 1.04) | | |
| Direct bilirubin, Week 4 (n=88,81) | 0.1 (± 0.89) | 0 (± 0.94) | | |
| Direct bilirubin, Week 8 (n=81,79) | 0 (± 0.92) | -0.1 (± 0.98) | | |

| | | | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Direct bilirubin, Week 12 (n=78,72) | 0.1 (± 0.92) | 0.3 (± 1.17) | | |
| Direct bilirubin, Week 18 (n=67,60) | 0.1 (± 1) | 0.2 (± 0.98) | | |
| Direct bilirubin, Week 26 (n=53,50) | -0.1 (± 0.79) | 0 (± 1.14) | | |
| Direct bilirubin, Week 39 (n=28,29) | -0.1 (± 0.72) | 0.1 (± 0.88) | | |
| Direct bilirubin, Week 52 (n=14,11) | -0.1 (± 1.14) | 0.1 (± 0.7) | | |
| Direct bilirubin, Follow up (n=80,68) | 0.1 (± 1.09) | 0 (± 0.96) | | |
| Uric acid, Week 2 (n=90,83) | 1.7 (± 44.47) | -7 (± 45.87) | | |
| Uric acid, Week 4 (n=88,80) | -3.8 (± 53.43) | -14 (± 44.47) | | |
| Uric acid, Week 8 (n=81,78) | 2.1 (± 47.41) | -12.1 (± 52.91) | | |
| Uric acid, Week 12 (n=78,71) | 7.5 (± 54.68) | -10.2 (± 62.09) | | |
| Uric acid, Week 18 (n=67,60) | 6.7 (± 49.87) | -5.9 (± 54.33) | | |
| Uric acid, Week 26 (n=53,50) | 0.6 (± 54.09) | -3.7 (± 61.19) | | |
| Uric acid, Week 39 (n=28,29) | 13.7 (± 50.99) | 16.6 (± 87.59) | | |
| Uric acid, Week 52 (n=14,11) | 7.9 (± 48.23) | 8.3 (± 57.49) | | |
| Uric acid, Follow up (n=80,67) | -2.6 (± 62.22) | 1.7 (± 63.56) | | |
| Creatinine, Week 2 (n=90,84) | 0.2 (± 7.974) | 3.22 (± 9.14) | | |
| Creatinine, Week 4 (n=88,81) | 0.04 (± 7.224) | 1.78 (± 9.899) | | |
| Creatinine, Week 8 (n=81,79) | 0.53 (± 11.111) | 2.23 (± 10.424) | | |
| Creatinine, Week 12 (n=78,72) | -0.11 (± 9.917) | 3.46 (± 17.547) | | |
| Creatinine, Week 18 (n=67,60) | 0.41 (± 11.973) | 5.32 (± 18.863) | | |
| Creatinine, Week 26 (n=53,50) | 1.61 (± 8.018) | 1.3 (± 8.927) | | |
| Creatinine, Week 39 (n=28,29) | 2.16 (± 6.164) | 5.64 (± 12.546) | | |
| Creatinine, Week 52 (n=14,11) | 2.94 (± 6.757) | 0.33 (± 5.15) | | |
| Creatinine, Follow up (n=80,68) | 0.62 (± 12.075) | 0.23 (± 9.463) | | |

Notes:

[140] - mITT Population

[141] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyl transferase at the indicated time points

| | |
|-----------------|--|
| End point title | Change from Baseline in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyl transferase at the indicated time points |
|-----------------|--|

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyl transferase at the indicated time point. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[142] | 90 ^[143] | | |
| Units: International units (IU)/ L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Alanine aminotransferase, Week 2 (n=90,84) | -0.3 (± 3.78) | 1.2 (± 5.52) | | |
| Alanine aminotransferase, Week 4 (n=88,81) | 1.8 (± 8.22) | 0.3 (± 6.56) | | |
| Alanine aminotransferase, Week 8 (n=81,79) | -0.3 (± 6) | -0.1 (± 6.53) | | |
| Alanine aminotransferase, Week 12 (n=78,72) | 1.3 (± 9.61) | 1.7 (± 7.48) | | |
| Alanine aminotransferase, Week 18 (n=67,60) | 0.3 (± 8.03) | 2.4 (± 7.67) | | |
| Alanine aminotransferase, Week 26 (n=53,50) | -0.2 (± 7.88) | 3 (± 10.79) | | |
| Alanine aminotransferase, Week 39 (n=28,29) | 3 (± 14.98) | 1.9 (± 9.74) | | |
| Alanine aminotransferase, Week 52 (n=14,11) | -1.1 (± 5.79) | 1.9 (± 3.24) | | |
| Alanine aminotransferase, Follow up (n=80,68) | 0.7 (± 12.02) | 0.7 (± 6.86) | | |
| Aspartate aminotransferase, Week 2 (n=90,84) | -0.5 (± 3.68) | 1.4 (± 4.25) | | |
| Aspartate aminotransferase, Week 4 (n=88,80) | 2 (± 7.65) | 0.5 (± 5.16) | | |
| Aspartate aminotransferase, Week 8 (n=81,79) | -0.4 (± 6.54) | 0.5 (± 5.13) | | |
| Aspartate aminotransferase, Week 12 (n=78,72) | 2.2 (± 11.91) | 2 (± 7.73) | | |
| Aspartate aminotransferase, Week 18 (n=67,60) | 0.9 (± 5.72) | 2.9 (± 6.25) | | |
| Aspartate aminotransferase, Week 26 (n=53,49) | 0.3 (± 5.75) | 4.7 (± 9.94) | | |
| Aspartate aminotransferase, Week 39 (n=28,29) | 1.3 (± 6.5) | 2.4 (± 9.79) | | |
| Aspartate aminotransferase, Week 52 (n=14,11) | -1.1 (± 9.22) | 1.7 (± 3.23) | | |
| Aspartate aminotransferase, Follow up (n=80,67) | 0.3 (± 6.55) | 0.1 (± 4.56) | | |
| Alkaline phosphatase, Week 2 (n=90,84) | 0.3 (± 9.14) | -2 (± 11.62) | | |
| Alkaline phosphatase, Week 4 (n=88,81) | 0 (± 10.43) | -2.8 (± 10.32) | | |
| Alkaline phosphatase, Week 8 (n=81,79) | -2.5 (± 10.46) | -5.3 (± 12.71) | | |
| Alkaline phosphatase, Week 12 (n=78,72) | -2.9 (± 12.67) | -4.7 (± 12.64) | | |
| Alkaline phosphatase, Week 18 (n=67,60) | 1 (± 9.87) | -4.9 (± 13.57) | | |
| Alkaline phosphatase, Week 26 (n=53,50) | 0.2 (± 13.06) | -4.4 (± 16.89) | | |
| Alkaline phosphatase, Week 39 (n=28,29) | 0.9 (± 9.77) | -4.1 (± 22.29) | | |

| | | | | |
|---|----------------|----------------|--|--|
| Alkaline phosphatase, Week 52 (n=14,11) | 0.1 (± 6.39) | -9.5 (± 9.37) | | |
| Alkaline phosphatase, Follow up (n=80,68) | -4.2 (± 15.26) | -4.4 (± 13.57) | | |
| Gamma glutamyl transferase, Week 2 (n=90,84) | -0.3 (± 11.45) | -1.5 (± 16.55) | | |
| Gamma glutamyl transferase, Week 4 (n=88,81) | 1.4 (± 19.82) | -3.7 (± 19.85) | | |
| Gamma glutamyl transferase, Week 8 (n=81,79) | -1.8 (± 17.32) | -5.3 (± 20.2) | | |
| Gamma glutamyl transferase, Week 12 (n=78,72) | -0.1 (± 17.11) | -1.1 (± 24.97) | | |
| Gamma glutamyl transferase, Week 18 (n=67,60) | 0.6 (± 15.42) | -1.7 (± 21.15) | | |
| Gamma glutamyl transferase, Week 26 (n=53,50) | -1.8 (± 13.53) | 2.5 (± 19.87) | | |
| Gamma glutamyl transferase, Week 39 (n=28,29) | -1.7 (± 10.4) | 1.4 (± 25.46) | | |
| Gamma glutamyl transferase, Week 52 (n=14,11) | -0.5 (± 13.39) | 0.1 (± 9.06) | | |
| Gamma glutamyl transferase, Follow up (n=80,68) | -2.5 (± 17.16) | 0.1 (± 14.92) | | |

Notes:

[142] - mITT Population

[143] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in chloride, calcium, glucose, potassium, sodium and blood urea nitrogen at the indicated time points

| | |
|-----------------|--|
| End point title | Change from Baseline in chloride, calcium, glucose, potassium, sodium and blood urea nitrogen at the indicated time points |
|-----------------|--|

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate calcium, chloride, glucose, potassium, sodium and blood urea nitrogen at the indicated time point. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[144] | 90 ^[145] | | |
| Units: Millimole (MMOL)/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Chloride, Week 2 (n=90,84) | 0.3 (± 2.59) | 0.5 (± 2.4) | | |
| Chloride, Week 4 (n=88,81) | -0.2 (± 2.42) | 1.1 (± 2.51) | | |

| | | | | |
|--------------------------------|-------------------|-------------------|--|--|
| Chloride, Week 8 (n=81,79) | 0.3 (± 2.88) | 0.7 (± 2.85) | | |
| Chloride, Week 12 (n=77,72) | 0 (± 2.48) | 0.2 (± 2.93) | | |
| Chloride, Week 18 (n=67,60) | 0.2 (± 2.73) | 0.3 (± 2.66) | | |
| Chloride, Week 26 (n=53,50) | -0.3 (± 3.35) | 0.5 (± 2.57) | | |
| Chloride, Week 39 (n=28,29) | -0.8 (± 2.45) | 0.1 (± 2.15) | | |
| Chloride, Week 52 (n=14,11) | -1.8 (± 2.12) | -1.4 (± 2.66) | | |
| Chloride, Follow up (n=80,68) | -0.2 (± 2.87) | -0.5 (± 2.24) | | |
| Calcium, Week 2 (n=90,84) | -0.002 (± 0.1031) | -0.042 (± 0.0774) | | |
| Calcium, Week 4 (n=88,80) | -0.024 (± 0.1007) | -0.31 (± 0.0908) | | |
| Calcium, Week 8 (n=81,79) | -0.017 (± 0.0934) | -0.039 (± 0.0843) | | |
| Calcium, Week 12 (n=78,72) | -0.008 (± 0.1106) | -0.029 (± 0.0982) | | |
| Calcium, Week 18 (n=67,60) | -0.017 (± 0.0891) | -0.033 (± 0.0928) | | |
| Calcium, Week 26 (n=53,49) | -0.024 (± 0.0855) | -0.023 (± 0.1014) | | |
| Calcium, Week 39 (n=28,29) | -0.017 (± 0.0922) | -0.032 (± 0.0927) | | |
| Calcium, Week 52 (n=14,11) | 0.002 (± 0.1004) | -0.061 (± 0.0791) | | |
| Calcium, Follow up (n=80,67) | -0.018 (± 0.1042) | -0.01 (± 0.0959) | | |
| Glucose, Week 2 (n=90,84) | -0.13 (± 1.456) | 0.22 (± 1.619) | | |
| Glucose, Week 4 (n=88,81) | -0.01 (± 1.5) | 0.04 (± 1.204) | | |
| Glucose, Week 8 (n=81,79) | 0.01 (± 1.33) | 0.28 (± 1.272) | | |
| Glucose, Week 12 (n=78,72) | -0.08 (± 1.661) | 0.24 (± 1.439) | | |
| Glucose, Week 18 (n=67,60) | 0.22 (± 1.607) | 0.5 (± 1.974) | | |
| Glucose, Week 26 (n=53,50) | -0.08 (± 1.518) | 0 (± 1.117) | | |
| Glucose, Week 39 (n=28,29) | -0.11 (± 1.553) | -0.16 (± 1.202) | | |
| Glucose, Week 52 (n=14,11) | 0.31 (± 1.075) | -0.09 (± 0.896) | | |
| Glucose, Follow up (n=80,68) | 0.2 (± 1.645) | 0.34 (± 2.104) | | |
| Potassium, Week 2 (n=90,84) | 0.02 (± 0.349) | -0.01 (± 0.391) | | |
| Potassium, Week 4 (n=88,80) | 0.01 (± 0.498) | 0.06 (± 0.393) | | |
| Potassium, Week 8 (n=81,79) | 0.05 (± 0.406) | -0.03 (± 0.306) | | |
| Potassium, Week 12 (n=77,72) | 0.02 (± 0.352) | -0.06 (± 0.354) | | |
| Potassium, Week 18 (n=67,60) | 0.02 (± 0.39) | 0.14 (± 0.525) | | |
| Potassium, Week 26 (n=53,49) | 0.02 (± 0.309) | -0.02 (± 0.381) | | |
| Potassium, Week 39 (n=28,29) | 0.13 (± 0.395) | -0.03 (± 0.415) | | |
| Potassium, Week 52 (n=14,11) | 0.1 (± 0.39) | -0.13 (± 0.422) | | |
| Potassium, Follow up (n=80,67) | 0.01 (± 0.385) | -0.02 (± 0.395) | | |
| Sodium, Week 2 (n=90,84) | 0.1 (± 2.16) | -0.2 (± 2.06) | | |
| Sodium, Week 4 (n=88,81) | -0.1 (± 2.18) | 0.3 (± 2.37) | | |
| Sodium, Week 8 (n=81,79) | 0 (± 2.33) | -0.1 (± 2.5) | | |
| Sodium, Week 12 (n=77,72) | -0.1 (± 1.96) | -0.4 (± 2.39) | | |

| | | | | |
|--|-----------------|----------------|--|--|
| Sodium, Week 18 (n=67,60) | 0.1 (± 2.8) | -0.7 (± 2.49) | | |
| Sodium, Week 26 (n=53,50) | 0.1 (± 2.92) | -0.2 (± 1.83) | | |
| Sodium, Week 39 (n=28,29) | -0.4 (± 2.33) | -0.3 (± 2.18) | | |
| Sodium, Week 52 (n=14,11) | -0.6 (± 1.28) | -0.9 (± 1.45) | | |
| Sodium, Follow up (n=80,68) | -0.2 (± 2.4) | -0.1 (± 2.14) | | |
| Blood urea nitrogen, Week 2 (n=90,84) | -0.04 (± 1.368) | 0.46 (± 1.474) | | |
| Blood urea nitrogen, Week 4 (n=88,81) | -0.21 (± 1.399) | 0.14 (± 1.392) | | |
| Blood urea nitrogen, Week 8 (n=81,79) | -0.11 (± 1.635) | 0.15 (± 1.464) | | |
| Blood urea nitrogen, Week 12 (n=78,72) | -0.12 (± 1.511) | 0.62 (± 1.993) | | |
| Blood urea nitrogen, Week 18 (n=67,60) | -0.41 (± 1.332) | 0.72 (± 2.31) | | |
| Blood urea nitrogen, Week 26 (n=53,50) | -0.34 (± 1.267) | 0.24 (± 1.636) | | |
| Blood urea nitrogen, Week 39 (n=28,29) | -0.26 (± 1.385) | 0.62 (± 1.68) | | |
| Blood urea nitrogen, Week 52 (n=14,11) | 0.01 (± 0.975) | 1.07 (± 1.209) | | |
| Blood urea nitrogen, Follow up (n=80,68) | 0.07 (± 1.577) | 0.11 (± 1.545) | | |

Notes:

[144] - mITT Population

[145] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Red blood cell count at the indicated time points

| | |
|-----------------|---|
| End point title | Change from Baseline in Red blood cell count at the indicated time points |
|-----------------|---|

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate Red blood cell count. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[146] | 90 ^[147] | | |
| Units: Trillion (TI)/ L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Red blood cell count, Week 2 (n=85,82) | -0.01 (± 0.248) | 0 (± 0.183) | | |

| | | | | |
|---|-----------------|-----------------|--|--|
| Red blood cell count, Week 4 (n=87,80) | -0.03 (± 0.242) | -0.02 (± 0.219) | | |
| Red blood cell count, Week 8 (n=80,77) | -0.03 (± 0.281) | -0.05 (± 0.205) | | |
| Red blood cell count, Week 12 (n=76,70) | 0.02 (± 0.278) | 0.02 (± 0.328) | | |
| Red blood cell count, Week 18 (n=66,61) | 0.04 (± 0.341) | 0 (± 0.287) | | |
| Red blood cell count, Week 26 (n=52,50) | 0.01 (± 0.318) | -0.02 (± 0.268) | | |
| Red blood cell count, Week 39 (n=28,29) | 0.08 (± 0.352) | 0.09 (± 0.265) | | |
| Red blood cell count, Week 52 (n=14,11) | 0.23 (± 0.32) | 0.01 (± 0.23) | | |
| Red blood cell count, Follow up (n=80,67) | 0.06 (± 0.354) | -0.04 (± 0.28) | | |

Notes:

[146] - mITT Population

[147] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in mean corpuscle hemoglobin at the indicated time points

| | |
|-----------------|--|
| End point title | Change from Baseline in mean corpuscle hemoglobin at the indicated time points |
|-----------------|--|

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate mean corpuscle hemoglobin. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[148] | 90 ^[149] | | |
| Units: Picograms | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean corpuscle hemoglobin, Week 2 (n=85,82) | 0.02 (± 0.551) | 0.03 (± 0.701) | | |
| Mean corpuscle hemoglobin, Week 4 (n=87,80) | 0.09 (± 0.516) | -0.04 (± 0.48) | | |
| Mean corpuscle hemoglobin, Week 8 (n=80,77) | 0.02 (± 0.801) | -0.2 (± 0.7) | | |
| Mean corpuscle hemoglobin, Week 12 (n=76,70) | -0.22 (± 0.773) | -0.46 (± 0.964) | | |
| Mean corpuscle hemoglobin, Week 18 (n=66,61) | -0.27 (± 1.167) | -0.52 (± 0.944) | | |

| | | | | |
|--|-----------------|-----------------|--|--|
| Mean corpuscle hemoglobin, Week 26 (n=52,50) | -0.25 (± 0.692) | -0.48 (± 0.983) | | |
| Mean corpuscle hemoglobin, Week 39 (n=28,29) | -0.55 (± 1.121) | -0.6 (± 1.1) | | |
| Mean corpuscle hemoglobin, Week 52 (n=14,11) | -0.72 (± 1.022) | -0.32 (± 0.676) | | |
| Mean corpuscle hemoglobin, Follow up (n=80,67) | -0.46 (± 1.13) | -0.73 (± 1.279) | | |

Notes:

[148] - mITT Population

[149] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in mean corpuscle volume at the indicated time points

| | |
|-----------------|--|
| End point title | Change from Baseline in mean corpuscle volume at the indicated time points |
|-----------------|--|

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate mean corpuscle volume. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and up to Week 53

| End point values | Placebo | Losmapimod 15 mg | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[150] | 90 ^[151] | | |
| Units: Picograms | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean corpuscle volume, Week 2 (n=85,82) | 0 (± 1.72) | -0.4 (± 1.97) | | |
| Mean corpuscle volume, Week 4 (n=87,80) | 0.1 (± 1.66) | 0.1 (± 1.88) | | |
| Mean corpuscle volume, Week 8 (n=80,77) | 0.2 (± 2.49) | -0.4 (± 2.11) | | |
| Mean corpuscle volume, Week 12 (n=76,70) | 0.3 (± 2.29) | -0.4 (± 2.45) | | |
| Mean corpuscle volume, Week 18 (n=66,61) | 0.6 (± 2.85) | -0.1 (± 3.12) | | |
| Mean corpuscle volume, Week 26 (n=52,50) | 0.5 (± 2.34) | 0.2 (± 3.07) | | |
| Mean corpuscle volume, Week 39 (n=28,29) | -1 (± 3.5) | -1.4 (± 3.82) | | |
| Mean corpuscle volume, Week 52 (n=14,11) | -1.4 (± 3.15) | 0 (± 2.05) | | |
| Mean corpuscle volume, Follow up (n=80,67) | -1.9 (± 2.73) | -2.4 (± 3.36) | | |

Notes:

[150] - mITT Population

[151] - mITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment SAEs and non-serious AEs were collected from start of Investigational Medicinal Product (Week 0) until Week 53 including 1 Week of follow up.

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs are reported for mITT Population, comprised of all par. who were randomized to treatment and who received at least one dose of study medication.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants with COPD received placebo orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of inhaled corticosteroid (ICS). Salbutamol metered dose inhaler (MDI) was provided as a rescue medication.

| | |
|-----------------------|-----------------|
| Reporting group title | Losmapimod 15mg |
|-----------------------|-----------------|

Reporting group description:

Participants with COPD received losmapimod 15 mg tablets orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of ICS. Salbutamol MDI was provided as a rescue medication.

| Serious adverse events | Placebo | Losmapimod 15mg | |
|---|----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 94 (8.51%) | 19 / 90 (21.11%) | |
| number of deaths (all causes) | 1 | 3 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bile duct cancer | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastric cancer | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm rupture | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac disorders | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 2 / 90 (2.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness unilateral | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Ileal ulcer | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 2 / 94 (2.13%) | 7 / 90 (7.78%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 94 (1.06%) | 4 / 90 (4.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 94 (0.00%) | 1 / 90 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Losmapimod 15mg | |
|---|----------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | 13 / 90 (14.44%) | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 94 (9.57%) | 13 / 90 (14.44%) | |
| occurrences (all) | 13 | 20 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported