



Clinical trial results:

A Randomised, Phase 2, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Filgotinib, GS-9876 and GS-4059 in Adult Subjects with Active Sjogren's Syndrome

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2016-003558-34 |
| Trial protocol | GB ES PL |
| Global end of trial date | 02 October 2019 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 04 January 2020 |
| First version publication date | 04 January 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-445-4189 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03100942 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|-----------------------------------------------------------------------------------------------|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com |
| Scientific contact | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|-----------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 10 January 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 10 January 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy of filgotinib, lanraplenib, and tirabrutinib in adults with active Sjogren's Syndrome (SjS).

Protection of trial subjects:

The protocol and consent forms were submitted for each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent forms (if applicable) after initial IEC/IRB approval were submitted on behalf of the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment | 01 May 2017 |
| 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 | United States: 106 |
| Country: Number of subjects enrolled | Poland: 22 |
| Country: Number of subjects enrolled | Spain: 15 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Worldwide total number of subjects | 152 |
| EEA total number of subjects | 46 |

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 | 0 |

| | |
|---------------------------|-----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 130 |
| From 65 to 84 years | 22 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States and Europe. The first participant was screened on 01 May 2017. The last study visit occurred on 02 Oct 2019.

Pre-assignment

Screening details:

347 participants were screened. Data submitted represent interim analysis performed on data collected by the participants through Week 24. Complete data will be submitted in October 2020.

Period 1

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

Arms

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

Arm description:

Filgotinib (1 x 200 mg) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Filgotinib |
| Investigational medicinal product code | |
| Other name | GS-6034 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x 200 mg tablet administered orally once daily for 48 weeks

| | |
|----------------------------------------|---------------------|
| Investigational medicinal product name | Lanraplenib placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

| | |
|----------------------------------------|----------------------|
| Investigational medicinal product name | Tirabrutinib placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

| | |
|------------------|-------------|
| Arm title | Lanraplenib |
|------------------|-------------|

Arm description:

Lanraplenib (1 x 30 mg) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|----------------------------------------|-------------|
| Investigational medicinal product name | Lanraplenib |
| Investigational medicinal product code | |
| Other name | GS-9876 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x 30 mg tablet administered orally once daily for 48 weeks

| | |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Filgotinib placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

| | |
|----------------------------------------|----------------------|
| Investigational medicinal product name | Tirabrutinib placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

| | |
|------------------|--------------|
| Arm title | Tirabrutinib |
|------------------|--------------|

Arm description:

Tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet) orally once daily for 48 weeks

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tirabrutinib |
| Investigational medicinal product code | |
| Other name | GS-4059 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x 40 mg tablet administered orally once daily for 48 weeks

| | |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Filgotinib placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1x tablet administered orally once daily for 48 weeks

| | |
|----------------------------------------|---------------------|
| Investigational medicinal product name | Lanraplenib placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Participants received filgotinib placebo + lanraplenib placebo + tirabrutinib placebo tablets orally once daily for 24 weeks. At Week 24 Visit, participants were rerandomised 1:1:1, in a blinded fashion and received either of the three experimental study drugs orally once daily through Week 48:

- filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
- lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
- tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)

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

Dosage and administration details:

1 x tablet administered orally once daily for 24 weeks. At Week 24 visit, 1 x tablet administered orally once daily through Week 48 in either of the following experimental arms:

- lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
- tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)

| | |
|----------------------------------------|---------------------|
| Investigational medicinal product name | Lanraplenib placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x tablet administered orally once daily for 24 weeks. At Week 24 visit, 1 x tablet administered orally once daily through Week 48 in either of the following experimental arms:

- filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
- tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)

| | |
|----------------------------------------|----------------------|
| Investigational medicinal product name | Tirabrutinib placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x tablet administered orally once daily for 24 weeks. At Week 24 visit, 1 x tablet administered orally once daily through Week 48 in either of the following experimental arms:

- filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
- lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)

| | |
|----------------------------------------|------------|
| Investigational medicinal product name | Filgotinib |
| Investigational medicinal product code | |
| Other name | GS-6034 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x 200 mg tablet administered once daily from Week 24 through Week 48

| | |
|----------------------------------------|-------------|
| Investigational medicinal product name | Lanraplenib |
| Investigational medicinal product code | |
| Other name | GS-9876 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1x 30 mg tablet administered orally once daily from Week 24 through Week 48

| | |
|----------------------------------------|--------------|
| Investigational medicinal product name | Tirabrutinib |
| Investigational medicinal product code | |
| Other name | GS-4059 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 x 40 mg tablet administered orally once daily from Week 24 through Week 48

| Number of subjects in period 1^[1] | Filgotinib | Lanraplenib | Tirabrutinib |
|-----------------------------------------------------|------------|-------------|--------------|
| Started | 38 | 37 | 39 |
| Completed up to Week 24 | 35 | 30 | 37 |
| Completed | 9 | 11 | 13 |
| Not completed | 29 | 26 | 26 |
| Withdrew Consent | 4 | 4 | 2 |
| Adverse Event | 1 | 6 | 1 |
| Investigator's Discretion | 1 | 1 | - |
| Still on the Study | 22 | 15 | 23 |
| Protocol Violation | 1 | - | - |

| Number of subjects in period 1^[1] | Placebo |
|-----------------------------------------------------|---------|
| Started | 36 |
| Completed up to Week 24 | 32 |
| Completed | 14 |
| Not completed | 22 |
| Withdrew Consent | 4 |
| Adverse Event | - |
| Investigator's Discretion | - |
| Still on the Study | 17 |
| Protocol Violation | 1 |

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: 2 participants (Lanraplenib arm: N = 1; Placebo arm: N= 1) were randomised but did not receive a single dose of study drug and therefore are not included in the subject disposition or any further analysis.

Comment regarding the number in the placebo arm for 'Completed up to week 24': 32 participants in the placebo group were rerandomized at Week 24.

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Filgotinib |
|-----------------------|------------|

Reporting group description:

Filgotinib (1 x 200 mg) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks

| | |
|-----------------------|-------------|
| Reporting group title | Lanraplenib |
|-----------------------|-------------|

Reporting group description:

Lanraplenib (1 x 30 mg) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks

| | |
|-----------------------|--------------|
| Reporting group title | Tirabrutinib |
|-----------------------|--------------|

Reporting group description:

Tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet) orally once daily for 48 weeks

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

Reporting group description:

Participants received filgotinib placebo + lanraplenib placebo + tirabrutinib placebo tablets orally once daily for 24 weeks. At Week 24 Visit, participants were rerandomised 1:1:1, in a blinded fashion and received either of the three experimental study drugs orally once daily through Week 48:

- filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
- lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
- tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)

| Reporting group values | Filgotinib | Lanraplenib | Tirabrutinib |
|------------------------------------|------------|-------------|--------------|
| Number of subjects | 38 | 37 | 39 |
| Age categorical Units: Subjects | | | |

| | | | |
|---------------------------------------|---------|--------|---------|
| Age continuous Units: years | | | |
| arithmetic mean | 52.2 | 56.2 | 55.8 |
| standard deviation | ± 10.54 | ± 9.72 | ± 10.06 |
| Gender categorical Units: Subjects | | | |
| Female | 38 | 36 | 37 |
| Male | 0 | 1 | 2 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 1 | 0 | 1 |
| Black | 5 | 5 | 4 |
| White | 32 | 31 | 34 |
| Other | 0 | 1 | 0 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 4 | 6 | 1 |
| Not Hispanic or Latino | 34 | 31 | 38 |
| Not Permitted | 0 | 0 | 0 |

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|--------|
| European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) | | | |
| Overall score (ranged from 0 (best) to 123 (worst activity)) was calculated as sum of all individual weighted domain scores . For additional details on this index, please see Endpoints section. | | | |
| Units: Score on a scale | | | |
| arithmetic mean | 10.2 | 10.5 | 10.4 |
| standard deviation | ± 6.23 | ± 4.89 | ± 5.36 |
| EULAR Sjogren's syndrome patient reported index (ESSPRI) | | | |
| The ESSPRI is a patient-reported questionnaire to assess subjective patient symptoms and includes 3 domains (dryness, pain, and fatigue). Each domain scored on scale of 0-10 (0 =no symptom at all and 10 = worst symptom imaginable), and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Minimum score can be 0 and maximum score can be 10. | | | |
| Units: Score on a scale | | | |
| arithmetic mean | 6.3 | 6.6 | 5.9 |
| standard deviation | ± 2.31 | ± 1.90 | ± 2.39 |

| Reporting group values | Placebo | Total | |
|-------------------------------|---------|-------|--|
| Number of subjects | 36 | 150 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-----|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 53.2 | | |
| standard deviation | ± 10.28 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 35 | 146 | |
| Male | 1 | 4 | |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | |
| Asian | 0 | 2 | |
| Black | 5 | 19 | |
| White | 30 | 127 | |
| Other | 0 | 1 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 6 | 17 | |
| Not Hispanic or Latino | 29 | 132 | |
| Not Permitted | 1 | 1 | |
| European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) | | | |
| Overall score (ranged from 0 (best) to 123 (worst activity)) was calculated as sum of all individual weighted domain scores . For additional details on this index, please see Endpoints section. | | | |
| Units: Score on a scale | | | |
| arithmetic mean | 9.3 | | |
| standard deviation | ± 3.96 | - | |
| EULAR Sjogren's syndrome patient reported index (ESSPRI) | | | |
| The ESSPRI is a patient-reported questionnaire to assess subjective patient symptoms and includes 3 | | | |

domains (dryness, pain, and fatigue). Each domain scored on scale of 0-10 (0 =no symptom at all and 10 = worst symptom imaginable), and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Minimum score can be 0 and maximum score can be 10.

| | | | |
|-------------------------|--------|---|--|
| Units: Score on a scale | | | |
| arithmetic mean | 5.9 | | |
| standard deviation | ± 2.24 | - | |

End points

End points reporting groups

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Reporting group title | Filgotinib |
| Reporting group description: Filgotinib (1 x 200 mg) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks | |
| Reporting group title | Lanraplenib |
| Reporting group description: Lanraplenib (1 x 30 mg) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks | |
| Reporting group title | Tirabrutinib |
| Reporting group description: Tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet) orally once daily for 48 weeks | |
| Reporting group title | Placebo |
| Reporting group description: Participants received filgotinib placebo + lanraplenib placebo + tirabrutinib placebo tablets orally once daily for 24 weeks. At Week 24 Visit, participants were rerandomised 1:1:1, in a blinded fashion and received either of the three experimental study drugs orally once daily through Week 48: <ul style="list-style-type: none">• filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)• lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)• tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet) | |

Primary: Percentage of Participants Fulfilling Protocol-Specified Response Criteria at Week 12, as Compared to Baseline

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Fulfilling Protocol-Specified Response Criteria at Week 12, as Compared to Baseline |
| End point description: Response was defined as: Improvement $\geq 20\%$ in ≥ 3 of 5 participant-reported Sjogren's syndrome (SjS) related visual analogue score (VAS) measures (participant's assessment of global disease, pain, oral dryness, ocular dryness and fatigue), with no increase defined as > 30 mm from baseline (Day 1) in any of the above 5 VAS measures, AND either $\geq 20\%$ improvement in high sensitivity C-reactive protein (hsCRP) (if hsCRP $\geq 1.5 \times$ ULN on Day 1) or no increase in hsCRP to $\geq 1.5 \times$ ULN (if hsCRP $< 1.5 \times$ ULN on Day 1). Missing data were imputed using multiple imputations with logistic regression. The Full Analysis Set included all randomised participants who received at least one dose of study drug. | |
| End point type | Primary |
| End point timeframe: Week 12 | |

| End point values | Filgotinib | Lanraplenib | Tirabrutinib | Placebo |
|-----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 37 | 39 | 36 |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 43.0 (27.1 to 59.0) | 42.3 (25.9 to 58.7) | 34.7 (19.6 to 49.9) | 26.4 (11.5 to 41.3) |

Statistical analyses

| | |
|-----------------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Filgotinib v Placebo |
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2082 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Lanraplenib v Placebo |
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1373 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 3 |
| Comparison groups | Tirabrutinib v Placebo |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3732 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Change From Baseline in European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) at Week 12

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) at Week 12 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

The ESSDAI is a physician-administered tool designed to measure disease activity. It consists of 12 organ-specific 'domains' contributing to disease activity associated with the patient's Sjogren's Syndrome only (constitutional, lymphadenopathy, articular, muscular, cutaneous, glandular, pulmonary, renal, peripheral nervous system, central nervous system, hematological, biological). Each domain is assessed for activity level (i.e., no, low, moderate, high) and assigned a numerical score based on pre-determined weighting of each individual domain. Overall score (ranges from 0 (best) to 123 (worst activity)) is calculated as sum of all individual weighted domain scores. Participants in the Full Analysis Set were analyzed.

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

End point timeframe:

Baseline; Week 12

| End point values | Filgotinib | Lanraplenib | Tirabrutinib | Placebo |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 37 | 39 | 36 |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | -4.7 (± 0.73) | -2.6 (± 0.76) | -3.2 (± 0.73) | -3.8 (± 0.76) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) at Week 12

| | |
|-----------------|---------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) at Week 12 |
|-----------------|---------------------------------------------------------------------------------------------|

End point description:

The ESSPRI is a patient-reported questionnaire to assess subjective patient symptoms and includes 3 domains (dryness, pain, and fatigue). Each domain scored on scale of 0-10 (0 = no symptom at all and 10 = worst symptom imaginable), and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Minimum score can be 0 and maximum score can be 10. Participants in the Full Analysis Set were analyzed.

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

End point timeframe:

Baseline; Week 12

| End point values | Filgotinib | Lanraplenib | Tirabrutinib | Placebo |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 37 | 39 | 36 |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | -1.4 (± 0.33) | -1.0 (± 0.34) | -1.3 (± 0.33) | -1.0 (± 0.35) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESSDAI at Week 24

| | |
|-----------------|-------------------------------------------|
| End point title | Change From Baseline in ESSDAI at Week 24 |
|-----------------|-------------------------------------------|

End point description:

The ESSDAI is a physician-administered tool designed to measure disease activity. It consists of 12 organ-specific 'domains' contributing to disease activity associated with the patient's Sjogren's Syndrome only (constitutional, lymphadenopathy, articular, muscular, cutaneous, glandular, pulmonary, renal, peripheral nervous system, central nervous system, hematological, biological). Each domain is assessed for activity level (i.e., no, low, moderate, high) and assigned a numerical score based on pre-determined weighting of each individual domain. An overall score is then calculated as the sum of all individual weighted domain scores. Overall score (ranges from 0 (best) to 123 (worst activity)) is calculated as sum of all individual weighted domain scores. Participants in the Full Analysis Set were analyzed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Week 24 | |

| End point values | Filgotinib | Lanraplenib | Tirabrutinib | Placebo |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 37 | 39 | 36 |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | -5.4 (± 0.75) | -4.3 (± 0.81) | -4.0 (± 0.75) | -4.2 (± 0.79) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESSPRI at Week 24

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| End point title | Change From Baseline in ESSPRI at Week 24 |
| End point description: | |
| The ESSPRI is a patient-reported questionnaire to assess subjective patient symptoms and includes 3 domains (dryness, pain, and fatigue). Each domain scored on scale of 0-10 (0 = no symptom at all and 10 = worst symptom imaginable), and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Minimum score can be 0 and maximum score can be 10. Participants in the Full Analysis Set were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Week 24 | |

| End point values | Filgotinib | Lanraplenib | Tirabrutinib | Placebo |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 37 | 39 | 36 |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | -0.8 (± 0.31) | -1.1 (± 0.35) | -1.2 (± 0.31) | -0.8 (± 0.33) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose date up to Week 24

Adverse event reporting additional description:

The Safety Analysis Set included participants who received at least one dose of study drug.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.1 |
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Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Filgotinib |
|-----------------------|------------|

Reporting group description:

Filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks

| | |
|-----------------------|-------------|
| Reporting group title | Lanraplenib |
|-----------------------|-------------|

Reporting group description:

Lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks

| | |
|-----------------------|--------------|
| Reporting group title | Tirabrutinib |
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Reporting group description:

Tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet) orally once daily for 48 weeks

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

Reporting group description:

Participants received filgotinib placebo + lanraplenib placebo + tirabrutinib placebo tablets orally once daily for 24 weeks. At Week 24 Visit, participants were rerandomised 1:1:1, in a blinded fashion and received either of the three experimental study drugs orally once daily through Week 48:

- filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
- lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
- tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)

| Serious adverse events | Filgotinib | Lanraplenib | Tirabrutinib |
|---------------------------------------------------|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 3 / 37 (8.11%) | 1 / 39 (2.56%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 37 (2.70%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|----------------------------------------------------------------|----------------|----------------|----------------|
| Gastroesophageal reflux disease subjects affected / exposed | 0 / 38 (0.00%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute subjects affected / exposed | 0 / 38 (0.00%) | 1 / 37 (2.70%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease subjects affected / exposed | 1 / 38 (2.63%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicidal ideation subjects affected / exposed | 0 / 38 (0.00%) | 1 / 37 (2.70%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure subjects affected / exposed | 1 / 38 (2.63%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed | 0 / 38 (0.00%) | 0 / 37 (0.00%) | 1 / 39 (2.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis subjects affected / exposed | 0 / 38 (0.00%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Diverticulitis | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Placebo | | |
|---------------------------------------------------|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |

| | | | |
|--------------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Filgotinib | Lanraplenib | Tirabrutinib |
|--------------------------------------------------------------|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 38 (60.53%) | 16 / 37 (43.24%) | 22 / 39 (56.41%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 4 / 37 (10.81%) | 1 / 39 (2.56%) |
| occurrences (all) | 1 | 5 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 4 / 37 (10.81%) | 1 / 39 (2.56%) |
| occurrences (all) | 1 | 5 | 1 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 37 (0.00%) | 2 / 39 (5.13%) |
| occurrences (all) | 2 | 0 | 2 |

| | | | |
|------------------------------------------------------|----------------|----------------|----------------|
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 37 (0.00%) | 1 / 39 (2.56%) |
| occurrences (all) | 2 | 0 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 37 (5.41%) | 1 / 39 (2.56%) |
| occurrences (all) | 0 | 2 | 1 |
| Headache | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 37 (0.00%) | 2 / 39 (5.13%) |
| occurrences (all) | 2 | 0 | 3 |
| Sciatica | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 37 (5.41%) | 0 / 39 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 37 (5.41%) | 2 / 39 (5.13%) |
| occurrences (all) | 0 | 2 | 3 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 3 / 37 (8.11%) | 0 / 39 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 37 (2.70%) | 1 / 39 (2.56%) |
| occurrences (all) | 3 | 1 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 37 (0.00%) | 2 / 39 (5.13%) |
| occurrences (all) | 0 | 0 | 2 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|----------------|-----------------|
| Rash | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 37 (5.41%) | 3 / 39 (7.69%) |
| occurrences (all) | 2 | 2 | 3 |
| Alopecia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 37 (0.00%) | 2 / 39 (5.13%) |
| occurrences (all) | 2 | 0 | 2 |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 37 (5.41%) | 0 / 39 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 37 (2.70%) | 2 / 39 (5.13%) |
| occurrences (all) | 0 | 1 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 37 (5.41%) | 4 / 39 (10.26%) |
| occurrences (all) | 1 | 2 | 4 |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 37 (0.00%) | 1 / 39 (2.56%) |
| occurrences (all) | 2 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 2 / 37 (5.41%) | 4 / 39 (10.26%) |
| occurrences (all) | 7 | 2 | 4 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 2 / 37 (5.41%) | 4 / 39 (10.26%) |
| occurrences (all) | 4 | 2 | 5 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 37 (0.00%) | 1 / 39 (2.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 37 (2.70%) | 1 / 39 (2.56%) |
| occurrences (all) | 1 | 1 | 1 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Gastroenteritis viral | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 37 (2.70%) | 3 / 39 (7.69%) |
| occurrences (all) | 2 | 1 | 3 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 37 (5.41%) | 1 / 39 (2.56%) |
| occurrences (all) | 0 | 2 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 37 (2.70%) | 0 / 39 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 37 (0.00%) | 0 / 39 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| Non-serious adverse events | Placebo | | |
|-------------------------------------------------------|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 36 (58.33%) | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences (all) | 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|--|--|
| Dizziness subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 4 | | |
| Headache subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | | |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | | |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 0 / 36 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Alopecia | 2 / 36 (5.56%) 2 | | |

| | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed occurrences (all) Pruritus generalised subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 0 / 36 (0.00%) 0 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 0 / 36 (0.00%) 0 0 / 36 (0.00%) 0 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Gastroenteritis viral subjects affected / exposed occurrences (all) Sinusitis | 4 / 36 (11.11%) 5 4 / 36 (11.11%) 5 6 / 36 (16.67%) 6 3 / 36 (8.33%) 3 0 / 36 (0.00%) 0 0 | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 3 / 36 (8.33%) | | |
| occurrences (all) | 3 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | | |
| occurrences (all) | 2 | | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12 July 2018 | <p>- Protocol Amendment included:</p> <ol style="list-style-type: none">1) Addition of biomarker sample collection at Day 1 and Week 18 visits.2) Addition of a primary and secondary analysis to be conducted after all subjects either complete Week 24 visit or prematurely discontinue from the study.3) Assembly of an internal unblinded team independent of the blinded study team to closely monitor study progress and drug safety. <p>- "Pharmacogenomic" was changed to "Genomic" for consistency with the Patient Information Sheet/Informed Consent Form.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study.

Notes: