



Clinical trial results:

A multicenter, randomized, double-blind, placebo-controlled, dose-response study to investigate the biological activity, safety, tolerability, and pharmacokinetics of ACT-334441 in subjects with systemic lupus erythematosus.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2014-002984-14 |
| Trial protocol | BG |
| Global end of trial date | 28 February 2017 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 07 November 2019 |
| First version publication date | 16 March 2018 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setChange of Sponsor |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AC-064A201 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02472795 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Idorsia Pharmaceuticals Ltd |
| Sponsor organisation address | Hegenheimermattweg 91, Allschwil , Switzerland, |
| Public contact | Global Clinical Study Disclosure, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com |
| Scientific contact | Global Clinical Study Disclosure, Idorsia Pharmaceuticals Ltd, clinical-trials-disclosure@idorsia.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 12 January 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 February 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the pharmacodynamics of ACT-334441, its safety and tolerability profile in adult systemic lupus erythematosus (SLE) subjects.

Protection of trial subjects:

Prior to the start of the study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety, and well being of human subjects involved in a clinical investigation. The sponsor and the investigators ensured that the study was conducted in full compliance with International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) Guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the countries in which the research was conducted.

Background therapy:

Standard of care therapies for SLE were allowed

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 01 June 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Bulgaria: 19 |
| Country: Number of subjects enrolled | Belarus: 7 |
| Country: Number of subjects enrolled | Georgia: 6 |
| Country: Number of subjects enrolled | Russian Federation: 22 |
| Country: Number of subjects enrolled | Ukraine: 9 |
| Country: Number of subjects enrolled | United States: 4 |
| Worldwide total number of subjects | 67 |
| EEA total number of subjects | 19 |

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) | 67 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 18 sites in 6 countries (BLR, BGR, GEO, RUS, UKR, and USA) from 1 Jun 2015 to 28 Feb 2017 (First subject, first visit to last subject, last visit)

Pre-assignment

Screening details:

The screening period started at the time the ICF was signed (up to 30 days before Randomization), and ended with subject randomization. The period included Visit 1 (Screening) and the pre-randomization (pre-dose) assessments at Visit 2 (Day 1).

Period 1

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

Arms

| | |
|--|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ACT-334441 - 0.5 mg |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | ACT-334441 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One capsule of cenerimod was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

| | |
|--|---------------------|
| Arm title | ACT-334441 - 1.0 mg |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | ACT-334441 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One capsule of cenerimod was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

| | |
|--------------------|---------------------|
| Arm title | ACT-334441 - 2.0 mg |
| Arm description: - | |
| Arm type | Experimental |

| | |
|--|------------|
| Investigational medicinal product name | ACT-334441 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One capsule of cenerimod was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

| | |
|--|---------------------|
| Arm title | ACT-334441 - 4.0 mg |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | ACT-334441 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One capsule of cenerimod was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

| | |
|--|----------|
| Arm title | Placebo |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One capsule of placebo was taken orally o.d. irrespective of food intake. The capsule was to be swallowed whole. It was preferable that the capsule was taken each day at approximately the same time (preferably each morning).

| Number of subjects in period 1 | ACT-334441 - 0.5 mg | ACT-334441 - 1.0 mg | ACT-334441 - 2.0 mg |
|---------------------------------------|---------------------|---------------------|---------------------|
| Started | 12 | 12 | 13 |
| Completed | 12 | 11 | 13 |
| Not completed | 0 | 1 | 0 |
| Consent withdrawn by subject | - | - | - |
| Adverse event, non-fatal | - | 1 | - |

| Number of subjects in period 1 | ACT-334441 - 4.0 mg | Placebo |
|---------------------------------------|---------------------|---------|
| Started | 13 | 17 |
| Completed | 13 | 14 |
| Not completed | 0 | 3 |
| Consent withdrawn by subject | - | 1 |
| Adverse event, non-fatal | - | 2 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------------|
| Reporting group title | ACT-334441 - 0.5 mg |
| Reporting group description: - | |
| Reporting group title | ACT-334441 - 1.0 mg |
| Reporting group description: - | |
| Reporting group title | ACT-334441 - 2.0 mg |
| Reporting group description: - | |
| Reporting group title | ACT-334441 - 4.0 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | ACT-334441 - 0.5 mg | ACT-334441 - 1.0 mg | ACT-334441 - 2.0 mg |
|---------------------------------------|---------------------|---------------------|---------------------|
| Number of subjects | 12 | 12 | 13 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 12 | 12 | 13 |
| Age continuous Units: years | | | |
| arithmetic mean | 41.4 | 37.0 | 39.2 |
| standard deviation | ± 13.2 | ± 6.4 | ± 11.8 |
| Gender categorical Units: Subjects | | | |
| Female | 11 | 12 | 12 |
| Male | 1 | 0 | 1 |
| Race Units: Subjects | | | |
| Black or African American | 0 | 0 | 0 |
| White | 12 | 12 | 13 |
| Body mass index Units: kg/m2 | | | |
| arithmetic mean | 25.2 | 27.4 | 26.0 |
| standard deviation | ± 5.1 | ± 8.0 | ± 5.1 |

| Reporting group values | ACT-334441 - 4.0 mg | Placebo | Total |
|------------------------------------|---------------------|---------|-------|
| Number of subjects | 13 | 17 | 67 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 13 | 17 | 67 |
| Age continuous Units: years | | | |
| arithmetic mean | 41.7 | 41.0 | - |
| standard deviation | ± 8.1 | ± 9.5 | - |

| | | | |
|---------------------------|-------|-------|----|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 16 | 61 |
| Male | 3 | 1 | 6 |
| Race | | | |
| Units: Subjects | | | |
| Black or African American | 0 | 2 | 2 |
| White | 13 | 15 | 65 |
| Body mass index | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 27.5 | 25.4 | |
| standard deviation | ± 4.7 | ± 6.8 | - |

Subject analysis sets

| | |
|---|----------------------|
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The Full analysis set included all subjects randomized to a study treatment. | |
| Subject analysis set title | Pharmacodynamics set |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| The PD set included all subjects who received at least 21 days of study treatment, with lymphocyte count measurements at baseline and post-baseline | |
| Subject analysis set title | Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The Safety set included all subjects who received at least one dose of study treatment. Unless otherwise stated, any analysis using the Safety set used all available safety data up to EOS | |

| Reporting group values | Full analysis set | Pharmacodynamics set | Safety set |
|---------------------------|-------------------|----------------------|------------|
| Number of subjects | 67 | 64 | 67 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 67 | 64 | 67 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 40.1 | 40.6 | 40.1 |
| standard deviation | ± 9.9 | ± 9.8 | ± 9.9 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 61 | 59 | 61 |
| Male | 6 | 5 | 6 |
| Race | | | |
| Units: Subjects | | | |
| Black or African American | 2 | 2 | 2 |
| White | 65 | 62 | 65 |
| Body mass index | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 26.2 | 26.5 | 26.2 |
| standard deviation | ± 6.0 | ± 6.0 | ± 6.0 |

End points

End points reporting groups

| | |
|---|----------------------|
| Reporting group title | ACT-334441 - 0.5 mg |
| Reporting group description: - | |
| Reporting group title | ACT-334441 - 1.0 mg |
| Reporting group description: - | |
| Reporting group title | ACT-334441 - 2.0 mg |
| Reporting group description: - | |
| Reporting group title | ACT-334441 - 4.0 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The Full analysis set included all subjects randomized to a study treatment. | |
| Subject analysis set title | Pharmacodynamics set |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| The PD set included all subjects who received at least 21 days of study treatment, with lymphocyte count measurements at baseline and post-baseline | |
| Subject analysis set title | Safety set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The Safety set included all subjects who received at least one dose of study treatment. Unless otherwise stated, any analysis using the Safety set used all available safety data up to EOS | |

Primary: Total lymphocyte count, absolute change from baseline to EOT

| | |
|-----------------------------------|--|
| End point title | Total lymphocyte count, absolute change from baseline to EOT |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| From baseline to End of Treatment | |

| End point values | ACT-334441 - 0.5 mg | ACT-334441 - 1.0 mg | ACT-334441 - 2.0 mg | ACT-334441 - 4.0 mg |
|--------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 10 | 13 | 13 |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | -0.26 (± 0.48) | -0.96 (± 0.68) | -0.86 (± 0.61) | -0.87 (± 1.24) |

| | | | | |
|------------------|---------|--|--|--|
| End point values | Placebo | | | |
|------------------|---------|--|--|--|

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | -0.33 (± 0.72) | | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Lymphocyte count analysis 0.5 mg vs placebo |
| Comparison groups | ACT-334441 - 0.5 mg v Placebo |
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.39 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.56 |
| upper limit | 0.22 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2 |

| | |
|---|---|
| Statistical analysis title | Lymphocyte count analysis 1 mg vs placebo |
| Comparison groups | ACT-334441 - 1.0 mg v Placebo |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.91 |
| upper limit | -0.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Lymphocyte count analysis 2 mg vs placebo |
| Comparison groups | ACT-334441 - 2.0 mg v Placebo |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.95 |
| upper limit | -0.19 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.19 |

| | |
|---|---|
| Statistical analysis title | Lymphocyte count analysis 4 mg vs placebo |
| Comparison groups | ACT-334441 - 4.0 mg v Placebo |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.06 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.75 |
| upper limit | 0.02 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.19 |

Primary: Total lymphocyte count, absolute change from baseline to each post-baseline analysis visit

| | |
|-----------------|---|
| End point title | Total lymphocyte count, absolute change from baseline to each post-baseline analysis visit ^[1] |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From baseline to End of Treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Not applicable.

| End point values | ACT-334441 - 0.5 mg | ACT-334441 - 1.0 mg | ACT-334441 - 2.0 mg | ACT-334441 - 4.0 mg |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 12 | 13 | 13 |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 1.37 (± 0.52) | 1.71 (± 0.82) | 1.62 (± 0.75) | 1.88 (± 0.77) |
| Week 2 | -0.13 (± 0.56) | -0.48 (± 0.56) | -0.52 (± 1.03) | -1.09 (± 0.65) |
| Week 4 | -0.28 (± 0.42) | -0.69 (± 0.76) | -0.86 (± 0.63) | -0.68 (± 1.32) |
| Week 8 | -0.28 (± 0.60) | -0.92 (± 0.60) | -0.89 (± 0.68) | -1.03 (± 1.12) |
| Week 12 | -0.26 (± 0.48) | -0.72 (± 1.03) | -0.86 (± 0.61) | -0.87 (± 1.24) |
| End of Treatment | -0.26 (± 0.48) | -0.72 (± 1.03) | -0.86 (± 0.61) | -0.87 (± 1.24) |

| End point values | Placebo | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 17 | | | |
| Units: 10 ⁹ /L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 1.65 (± 0.88) | | | |
| Week 2 | -0.16 (± 0.75) | | | |
| Week 4 | -0.33 (± 0.69) | | | |
| Week 8 | -0.09 (± 0.82) | | | |
| Week 12 | -0.29 (± 0.73) | | | |
| End of Treatment | -0.30 (± 0.71) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Enter description here

Adverse event reporting additional description:

Enter description here

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

Dictionary used

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

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

Reporting groups

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

Reporting group description:

Placebo

| | |
|-----------------------|-------------------|
| Reporting group title | ACT-334441 0.5 mg |
|-----------------------|-------------------|

Reporting group description:

ACT-334441 0.5 mg

| | |
|-----------------------|-------------------|
| Reporting group title | ACT-334441 1.0 mg |
|-----------------------|-------------------|

Reporting group description:

ACT-334441 1.0 mg

| | |
|-----------------------|-------------------|
| Reporting group title | ACT-334441 2.0 mg |
|-----------------------|-------------------|

Reporting group description:

ACT-334441 2.0 mg

| | |
|-----------------------|-------------------|
| Reporting group title | ACT-334441 4.0 mg |
|-----------------------|-------------------|

Reporting group description:

ACT-334441 4.0 mg

| Serious adverse events | Placebo | ACT-334441 0.5 mg | ACT-334441 1.0 mg |
|---|----------------|-------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| Post cholecystectomy syndrome | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (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 | ACT-334441 2.0 mg | ACT-334441 4.0 mg | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post cholecystectomy syndrome | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Placebo | ACT-334441 0.5 mg | ACT-334441 1.0 mg |
|---|-----------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 17 (52.94%) | 5 / 12 (41.67%) | 5 / 12 (41.67%) |
| Surgical and medical procedures | | | |

| | | | |
|--------------------------------------|----------------|-----------------|----------------|
| decreased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laboratory test abnormal | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 12 (16.67%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 12 (16.67%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Eye disorders | | | |
| Age-related macular degeneration | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cataract | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry age-related macular | | | |

| | | | |
|--|----------------|----------------|----------------|
| degeneration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastroduodenitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Hepatobiliary disorders | | | |
| Chronic hepatitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nail dystrophy | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|----------------|----------------|
| Nitrituria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Asymptomatic bacteriuria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tracheobronchitis | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | ACT-334441 2.0 mg | ACT-334441 4.0 mg | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | 5 / 13 (38.46%) | |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Bilirubin conjugated increased | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood fibrinogen decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Electrocardiogram T wave amplitude decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Laboratory test abnormal | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|--------------------------------------|----------------|----------------|--|
| Anaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eye disorders | | | |
| Age-related macular degeneration | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cataract | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Dry age-related macular degeneration | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastroduodenitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hepatobiliary disorders | | | |
| Chronic hepatitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nail dystrophy | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Renal and urinary disorders | | | |
| Nitrituria | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Asymptomatic bacteriuria | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Erysipelas | | | |

| | | | |
|------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 13 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 25 March 2015 | <p>Summary of most relevant changes:</p> <ul style="list-style-type: none">• Study-specific stopping rules per FDA recommendations were introduced,• ECG discharge criteria from hospital on Day 1 and on the first day of re-initiation following treatment interruption were clarified,• Respiratory system criteria for interruption / premature discontinuation of study treatment per FDA recommendations were revised,• The safety endpoint/variable Occurrence of treatment-emergent decrease of FEV1 or FVC was modified,• Analysis of pulmonary safety events was to include treatment-emergent decrease of FEV1 or FVC to < 85% of baseline values instead of < 80% of baseline values,• Since at Visit 3 and re-initiation visits, study drug was not to be allocated by the IRT system, the compliance could not be calculated automatically in the eCRF. During these visits, a compliance review based on study drug accountability was to be performed by the investigator (or delegate) and recorded in the eCRF,• In case of no medical justification available for study treatment interruption, compliance < 80% was to be reported as a protocol deviation,• Clarifications were added in the laboratory sections,• In order to shorten the time window between assessments during the follow-up period (at 6 and 16 weeks after last dose of study treatment intake), a follow-up assessment via telephone was added at 11 weeks after last dose of study treatment intake to collect SAEs and pregnancy test results,• Informed Consent Form was amended to reflect the changes introduced by the amendment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported