



Clinical trial results:

Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy (Maintenance of Remission) and Safety of Etrolizumab Compared With Placebo in Patients With Moderate to Severe Active Ulcerative Colitis Who Are Naive to TNF Inhibitors

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-004280-31 |
| Trial protocol | CZ DK DE HU SK PL |
| Global end of trial date | 06 April 2020 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v2 (current) |
| This version publication date | 12 August 2021 |
| First version publication date | 15 April 2021 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | GA29102 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02165215 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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 | 04 November 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 April 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of etrolizumab compared with placebo for remission of Ulcerative Colitis (UC) at Week 62 among patients with a clinical response at Week 10

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 12 August 2014 |
| 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 | Brazil: 43 |
| Country: Number of subjects enrolled | Canada: 20 |
| Country: Number of subjects enrolled | Czechia: 15 |
| Country: Number of subjects enrolled | Germany: 18 |
| Country: Number of subjects enrolled | Denmark: 4 |
| Country: Number of subjects enrolled | Hungary: 21 |
| Country: Number of subjects enrolled | India: 53 |
| Country: Number of subjects enrolled | Israel: 14 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Mexico: 7 |
| Country: Number of subjects enrolled | Poland: 9 |
| Country: Number of subjects enrolled | Slovakia: 4 |
| Country: Number of subjects enrolled | Ukraine: 25 |
| Country: Number of subjects enrolled | United States: 106 |
| Country: Number of subjects enrolled | South Africa: 15 |
| Worldwide total number of subjects | 359 |
| EEA total number of subjects | 76 |

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) | 343 |
| From 65 to 84 years | 16 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

359 patients entered the Induction phase of the study. For the double-blind maintenance phase, 102 patients were randomized and dosed to the Placebo arm and 108 to the Etrolizumab arm.

Period 1

| | |
|------------------------------|-----------------|
| Period 1 title | Induction Phase |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|---|
| Arm title | Open-Label Induction Phase: Etrolizumab |
|-----------|---|

Arm description:

All participants will receive treatment with open-label etrolizumab 105 milligrams (mg) subcutaneous (SC) injection once every 4 weeks (Q4W) up to Week 10.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Etrolizumab |
| Investigational medicinal product code | |
| Other name | RG7413, RO5490261, PRO145223, rhuMAb Beta7 |
| Pharmaceutical forms | Solution for injection/infusion in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

105 mg once every 4 weeks (Q4W)

| Number of subjects in period 1 | Open-Label Induction Phase: Etrolizumab |
|--------------------------------|---|
| Started | 359 |
| Dosed | 358 |
| Completed | 336 |
| Not completed | 23 |
| Consent withdrawn by subject | 10 |
| Physician decision | 1 |
| Non-Compliance | 2 |
| Adverse event, non-fatal | 1 |
| Lost to follow-up | 6 |
| Lack of efficacy | 2 |
| Protocol deviation | 1 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Maintenance Phase |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Double-Blind Maintenance Phase: Etrolizumab |

Arm description:

Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive etrolizumab 105 mg SC injection Q4W from Week 12 up to Week 62.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Etrolizumab |
| Investigational medicinal product code | |
| Other name | RG7413, RO5490261, PRO145223, rhuMAb Beta7 |
| Pharmaceutical forms | Solution for injection/infusion in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

105 mg once every 4 weeks (Q4W)

| | |
|------------------|---|
| Arm title | Double-Blind Maintenance Phase: Placebo |
|------------------|---|

Arm description:

Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive placebo (matched to etrolizumab) SC injection Q4W from Week 12 up to Week 62.

| | |
|--|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Matched to etrolizumab

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 was an induction phase of the study and all participants received the same treatment. The Maintenance phase (during which the test product was compared to placebo) has been reported as the baseline period to provide more relevant comparative data.

| Number of subjects in period 2^{[2][3]} | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo |
|--|---|---|
| Started | 108 | 106 |
| Dosed | 108 | 102 |
| Completed | 96 | 101 |
| Not completed | 12 | 5 |
| Consent withdrawn by subject | 7 | 3 |

| | | |
|--------------------------|---|---|
| Adverse event, non-fatal | 1 | 1 |
| Lost to follow-up | 2 | - |
| Multiple reasons | 2 | 1 |

Notes:

[2] - 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: 210 participants were enrolled and dosed in the Maintenance phase. The worldwide number includes all participants in the Induction phase (n=359).

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Out of the participants that completed the Induction phase, only 210 met all criteria for dosing in the Maintenance phase.

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Double-Blind Maintenance Phase: Etrolizumab |
| Reporting group description: | |
| Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive etrolizumab 105 mg SC injection Q4W from Week 12 up to Week 62. | |
| Reporting group title | Double-Blind Maintenance Phase: Placebo |
| Reporting group description: | |
| Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive placebo (matched to etrolizumab) SC injection Q4W from Week 12 up to Week 62. | |

| Reporting group values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | Total |
|--|---|---|-------|
| Number of subjects | 108 | 106 | 214 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 104 | 104 | 208 |
| From 65-84 years | 4 | 2 | 6 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 38.3 | 39.2 | |
| standard deviation | ± 13.7 | ± 13.5 | - |
| Sex: Female, Male | | | |
| Maintenance Phase | | | |
| Units: | | | |
| Female | 48 | 54 | 102 |
| Male | 60 | 52 | 112 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 2 | 2 | 4 |
| Asian | 21 | 13 | 34 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 2 | 6 | 8 |
| White | 79 | 78 | 157 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 4 | 7 | 11 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Open-Label Induction Phase: Etrolizumab |
| Reporting group description: All participants will receive treatment with open-label etrolizumab 105 milligrams (mg) subcutaneous (SC) injection once every 4 weeks (Q4W) up to Week 10. | |
| Reporting group title | Double-Blind Maintenance Phase: Etrolizumab |
| Reporting group description: Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive etrolizumab 105 mg SC injection Q4W from Week 12 up to Week 62. | |
| Reporting group title | Double-Blind Maintenance Phase: Placebo |
| Reporting group description: Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive placebo (matched to etrolizumab) SC injection Q4W from Week 12 up to Week 62. | |

Primary: Maintenance Phase: Percentage of Participants in Remission at Week 62 Among Randomized Participants with a Clinical Response at Week 10, as Determined by the Mayo Clinic Score (MCS)

| | |
|--|---|
| End point title | Maintenance Phase: Percentage of Participants in Remission at Week 62 Among Randomized Participants with a Clinical Response at Week 10, as Determined by the Mayo Clinic Score (MCS) |
| End point description: MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment. Clinical Response is MCS with ≥ 3 -point decrease and 30% reduction from baseline as well as ≥ 1 -point decrease in rectal bleeding subscore or an absolute rectal bleeding score of 0 or 1. Remission is MCS ≤ 2 with individual subscores ≤ 1 and a rectal bleeding subscore of 0. | |
| End point type | Primary |
| End point timeframe: Week 62 | |

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 102 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 29.6 | 20.6 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1942 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in response rates |
| Point estimate | 7.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.2 |
| upper limit | 19.2 |

Secondary: Maintenance Phase: Percentage of Participants Who Maintained Clinical Remission at Week 62 Among Randomized Participants in Clinical Remission at Week 10, as Determined by the MCS

| | |
|---|---|
| End point title | Maintenance Phase: Percentage of Participants Who Maintained Clinical Remission at Week 62 Among Randomized Participants in Clinical Remission at Week 10, as Determined by the MCS |
| End point description: | |
| MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment. | |
| Clinical Remission is MCS ≤ 2 with individual subscores ≤ 1 . | |
| End point type | Secondary |
| End point timeframe: | |
| Week 62 | |

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 44 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 44.4 | 27.3 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|--|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1524 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in remission rates |
| Point estimate | 14.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.55 |
| upper limit | 33.15 |

Notes:

[1] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Percentage of Participants in Clinical Remission at Week 62, as Determined by the MCS

| | |
|-----------------|--|
| End point title | Maintenance Phase: Percentage of Participants in Clinical Remission at Week 62, as Determined by the MCS |
|-----------------|--|

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Clinical Remission is MCS ≤ 2 with individual subscores ≤ 1 .

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

End point timeframe:

Week 62

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 102 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 30.6 | 20.6 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|--|
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1466 ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in remission rates |
| Point estimate | 8.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.26 |
| upper limit | 20.21 |

Notes:

[2] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Percentage of Participants in Remission at Week 62 Among Randomized Participants in Remission at Week 10, as Determined by the MCS

| | |
|-----------------|---|
| End point title | Maintenance Phase: Percentage of Participants in Remission at Week 62 Among Randomized Participants in Remission at Week 10, as Determined by the MCS |
|-----------------|---|

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Remission is MCS ≤ 2 with individual subscores ≤ 1 and a rectal bleeding subscore of 0.

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

End point timeframe:

Week 62

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 41 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 40.0 | 26.8 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|--|
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3083 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in remission rates |
| Point estimate | 10.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.72 |
| upper limit | 30.49 |

Notes:

[3] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Percentage of Participants with Improvement from Baseline in Endoscopic Appearance of the Mucosa at Week 62, as Determined by the MCS Endoscopic Subscore

| | |
|-----------------|--|
| End point title | Maintenance Phase: Percentage of Participants with Improvement from Baseline in Endoscopic Appearance of the Mucosa at Week 62, as Determined by the MCS Endoscopic Subscore |
|-----------------|--|

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Improvement in endoscopic appearance of the mucosa is Endoscopy subscore ≤ 1 .

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

End point timeframe:

Baseline, Week 62

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 102 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 38.0 | 22.5 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0235 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in response rates |
| Point estimate | 14.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.84 |
| upper limit | 26.28 |

Notes:

[4] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Percentage of Participants with Endoscopic Remission at Week 62, as Determined by the MCS Endoscopic Subscore

| | |
|-----------------|--|
| End point title | Maintenance Phase: Percentage of Participants with Endoscopic Remission at Week 62, as Determined by the MCS Endoscopic Subscore |
|-----------------|--|

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Endoscopic Remission is Endoscopy subscore = 0.

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

End point timeframe:

Week 62

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 102 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 30.6 | 16.7 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|--|
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0293 ^[5] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in remission rates |
| Point estimate | 12.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.13 |
| upper limit | 23.89 |

Notes:

[5] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Percentage of Participants with Histologic Remission at Week 62, as Determined by the Nancy Histological Index

| | |
|-----------------|---|
| End point title | Maintenance Phase: Percentage of Participants with Histologic Remission at Week 62, as Determined by the Nancy Histological Index |
|-----------------|---|

End point description:

Nancy Histological Index (NHI) is a 5-level classification ranging from grade 0 (No histologically significant disease) to grade 4 (severely active disease). Histologic remission is defined as a Nancy histological index of 0 or 1.

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

End point timeframe:

Week 62

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 85 | 78 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 42.4 | 21.8 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|--|
| Number of subjects included in analysis | 163 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0075 ^[6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in remission rates |
| Point estimate | 19.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.16 |
| upper limit | 33.11 |

Notes:

[6] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Percentage of Participants with Corticosteroid-Free Clinical Remission at Week 62 Among Participants Who Were Receiving Corticosteroids at Baseline, as Determined by the MCS

| | |
|-----------------|--|
| End point title | Maintenance Phase: Percentage of Participants with Corticosteroid-Free Clinical Remission at Week 62 Among Participants Who Were Receiving Corticosteroids at Baseline, as Determined by the MCS |
|-----------------|--|

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Clinical Remission is MCS ≤ 2 with individual subscores ≤ 1 .

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

End point timeframe:

Baseline, Week 62

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 50 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 18.2 | 8.0 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|--|
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1415 ^[7] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in remission rates |
| Point estimate | 9.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.47 |
| upper limit | 23.13 |

Notes:

[7] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Percentage of Participants with Corticosteroid-Free Remission at Week 62 Among Participants Who Were Receiving Corticosteroids at Baseline, as Determined by the MCS

| | |
|-----------------|---|
| End point title | Maintenance Phase: Percentage of Participants with Corticosteroid-Free Remission at Week 62 Among Participants Who Were Receiving Corticosteroids at Baseline, as Determined by the MCS |
|-----------------|---|

End point description:

MCS is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment.

Remission is MCS ≤ 2 with individual subscores ≤ 1 and a rectal bleeding subscore of 0.

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

End point timeframe:

Baseline, Week 62

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 50 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 18.2 | 8.0 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|--|
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1415 ^[8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted difference in remission rates |
| Point estimate | 9.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.47 |
| upper limit | 23.13 |

Notes:

[8] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Change from Baseline to Week 62 in UC Bowel Movement Signs and Symptoms, as Assessed by the Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS) Questionnaire

| | |
|-----------------|---|
| End point title | Maintenance Phase: Change from Baseline to Week 62 in UC Bowel Movement Signs and Symptoms, as Assessed by the Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS) Questionnaire |
|-----------------|---|

End point description:

The UC-PRO questionnaire is collected in the e-diary and completed by participants for at least 9-12 consecutive days prior to a study visit. The UC-PRO is being reported in three domains; two domains are key endpoints and reported as UC-PRO Signs and Symptoms (UC-PRO/SS).

The bowel domain score ranges from 0-27, with a higher score indicating a worse disease state.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 62 | |

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68 | 73 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -9.6 (± 0.8) | -6.7 (± 0.9) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|----------------------------------|
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0266 ^[9] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Least Square Means |
| Point estimate | -2.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.3 |
| upper limit | -0.4 |

Notes:

[9] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Change from Baseline to Week 62 in UC Functional Symptoms, as Assessed by the UC-PRO/SS Questionnaire

| | |
|-----------------|--|
| End point title | Maintenance Phase: Change from Baseline to Week 62 in UC Functional Symptoms, as Assessed by the UC-PRO/SS Questionnaire |
|-----------------|--|

End point description:

The UC-PRO questionnaire is collected in the e-diary and completed by participants for at least 9-12 consecutive days prior to a study visit. The UC-PRO is being reported in three domains; two domains are key endpoints and reported as UC-PRO Signs and Symptoms (UC-PRO/SS).

The functional domain score ranges from 0-12, with a higher score indicating a worse disease state.

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

End point timeframe:

Baseline, Week 62

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68 | 73 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -3.0 (± 0.3) | -1.8 (± 0.4) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etrolizumab vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|----------------------------------|
| Number of subjects included in analysis | 141 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0175 ^[10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in Least Square Means |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | -0.2 |

Notes:

[10] - p-value has not been adjusted for multiplicity

Secondary: Maintenance Phase: Change from Baseline to Week 62 in Health-Related Quality of Life, as Assessed by the Overall Score of the Inflammatory Bowel Disease Questionnaire (IBDQ)

| | |
|-----------------|---|
| End point title | Maintenance Phase: Change from Baseline to Week 62 in Health-Related Quality of Life, as Assessed by the Overall Score of the Inflammatory Bowel Disease Questionnaire (IBDQ) |
|-----------------|---|

End point description:

The IBDQ is used to assess participant's health-related quality of life (QOL). The 32-item questionnaire contains four domains: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). The items are scored on a 7-point Likert scale with a higher score indicating better health-related QOL.

IBDQ score is a total score summed up from across all 32 questions on the questionnaire. The score can range from 32-224 and the higher score indicates a better quality of life.

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

End point timeframe:

Baseline, Week 62

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 102 | | |
| Units: scores on a scale | | | | |
| least squares mean (standard error) | 66.9 (± 3.39) | 64.8 (± 3.45) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Etro vs. Placebo |
| Comparison groups | Double-Blind Maintenance Phase: Etrolizumab v Double-Blind Maintenance Phase: Placebo |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6331 ^[11] |
| Method | ANCOVA |
| Parameter estimate | Difference in Adjusted Mean |
| Point estimate | 2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.6 |
| upper limit | 10.8 |

Notes:

[11] - p-value has not been adjusted for multiplicity

Secondary: Number of Participants with at Least One Adverse Event by Severity, According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0)

| | |
|-----------------|---|
| End point title | Number of Participants with at Least One Adverse Event by Severity, According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0) |
|-----------------|---|

End point description:

All adverse events (AEs) were graded for severity using the NCI-CTCAE v4.0. Any AE not specifically listed was assessed per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 3 = severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. Not all grades are appropriate for all AEs; some AEs have fewer than 5 options. The terms "severe" and "serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

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

End point timeframe:

From Baseline up to Week 74

| End point values | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | |
|-----------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 358 | 108 | 102 | |
| Units: participants | | | | |
| Grade 1 | 95 | 24 | 23 | |
| Grade 2 | 58 | 30 | 44 | |
| Grade 3 | 24 | 14 | 15 | |
| Grade 4 | 3 | 2 | 0 | |
| Grade 5 | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events Leading to Study Drug Discontinuation

| | |
|-----------------|--|
| End point title | Number of Participants with Adverse Events Leading to Study Drug Discontinuation |
|-----------------|--|

End point description:

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

End point timeframe:

From Baseline up to Week 74

| End point values | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | |
|-----------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 358 | 108 | 102 | |
| Units: participants | 9 | 5 | 9 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Serious Infection-Related Adverse Events

| | |
|-----------------|--|
| End point title | Number of Participants with Serious Infection-Related Adverse Events |
|-----------------|--|

End point description:

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

End point timeframe:

From Baseline up to Week 74

| End point values | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | |
|-----------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 358 | 108 | 102 | |
| Units: participants | 6 | 2 | 2 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Infection-Related Adverse Events by Severity, According to NCI-CTCAE v4.0

| | |
|-----------------|---|
| End point title | Number of Participants with Infection-Related Adverse Events by Severity, According to NCI-CTCAE v4.0 |
|-----------------|---|

End point description:

All adverse events (AEs) were graded for severity using the NCI-CTCAE v4.0. Any AE not specifically listed was assessed per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 3 = severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. Not all grades are appropriate for all AEs; some AEs have fewer than 5 options. The terms "severe" and "serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

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

End point timeframe:

From Baseline up to Week 74

| End point values | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | |
|-----------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 358 | 108 | 102 | |
| Units: participants | | | | |
| Grade 1 | 39 | 18 | 22 | |
| Grade 2 | 21 | 17 | 10 | |
| Grade 3 | 6 | 1 | 1 | |
| Grade 4 | 0 | 1 | 0 | |
| Grade 5 | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Injection-Site Reactions by Severity, According to NCI-CTCAE v4.0

| | |
|-----------------|---|
| End point title | Number of Participants with Injection-Site Reactions by Severity, According to NCI-CTCAE v4.0 |
|-----------------|---|

End point description:

All adverse events (AEs) were graded for severity using the NCI-CTCAE v4.0. Any AE not specifically listed was assessed per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 3 = severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. Not all grades are appropriate for all AEs; some AEs have fewer than 5 options. The terms "severe" and

"serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline up to Week 74 | |

| End point values | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | |
|-----------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 358 | 108 | 102 | |
| Units: participants | | | | |
| Grade 1 | 8 | 4 | 3 | |
| Grade 2 | 0 | 0 | 0 | |
| Grade 3 | 0 | 0 | 0 | |
| Grade 4 | 0 | 0 | 0 | |
| Grade 5 | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Hypersensitivity Reaction Events by Severity, According to NCI-CTCAE v4.0

| | |
|-----------------|---|
| End point title | Number of Participants with Hypersensitivity Reaction Events by Severity, According to NCI-CTCAE v4.0 |
|-----------------|---|

End point description:

All adverse events (AEs) were graded for severity using the NCI-CTCAE v4.0. Any AE not specifically listed was assessed per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 3 = severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. Not all grades are appropriate for all AEs; some AEs have fewer than 5 options. The terms "severe" and "serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline up to Week 74 | |

| End point values | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | |
|-----------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 358 | 108 | 102 | |
| Units: participants | | | | |
| Grade 1 | 0 | 0 | 0 | |
| Grade 2 | 1 | 0 | 0 | |
| Grade 3 | 0 | 0 | 0 | |
| Grade 4 | 0 | 0 | 0 | |
| Grade 5 | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Malignancies

| | |
|-----------------------------|--|
| End point title | Number of Participants with Malignancies |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline up to Week 74 | |

| End point values | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | |
|-----------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 358 | 108 | 102 | |
| Units: participants | 0 | 2 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-Therapeutic Antibodies (ATAs) to Etrolizumab

| | |
|--|---|
| End point title | Number of Participants with Anti-Therapeutic Antibodies (ATAs) to Etrolizumab |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 4, 12, 24, 44, and 62, and and Early Termination/End of Safety Follow-Up (up to Week | |

| End point values | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | |
|-----------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 337 | 108 | 102 | |
| Units: participants | 62 | 35 | 33 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Etrolizumab Serum Trough Concentration

| | |
|---|---|
| End point title | Maintenance Phase: Etrolizumab Serum Trough Concentration |
| End point description: Here 99999 represents data that were not analyzed as more than a third of the samples were below the lower limit of quantitation (LLOQ) | |
| End point type | Secondary |
| End point timeframe: Pre-dose (0 hour) at Baseline and Weeks 12, 24, 44, and 62 | |

| End point values | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo | | |
|--|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 | 100 | | |
| Units: micrograms per millilitre (µg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 | 7.66 (± 4.21) | 7.63 (± 3.67) | | |
| Week 24 | 10 (± 4.86) | 99999 (± 99999) | | |
| Week 44 | 10 (± 4.88) | 99999 (± 99999) | | |
| Week 62 | 15.4 (± 7.46) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to Week 74

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Open-Label Induction Phase: Etrolizumab |
|-----------------------|---|

Reporting group description:

All participants will receive treatment with open-label etrolizumab 105 milligrams (mg) subcutaneous (SC) injection once every 4 weeks (Q4W) up to Week 10.

| | |
|-----------------------|---|
| Reporting group title | Double-Blind Maintenance Phase: Etrolizumab |
|-----------------------|---|

Reporting group description:

Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive etrolizumab 105 mg SC injection Q4W from Week 12 up to Week 62.

| | |
|-----------------------|---|
| Reporting group title | Double-Blind Maintenance Phase: Placebo |
|-----------------------|---|

Reporting group description:

Participants who achieved a clinical response at Week 10 during the induction phase and randomized to this arm for the double-blind maintenance phase will receive placebo (matched to etrolizumab) SC injection Q4W from Week 12 up to Week 62.

| Serious adverse events | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 358 (4.75%) | 10 / 108 (9.26%) | 8 / 102 (7.84%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 1 / 108 (0.93%) | 0 / 102 (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 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 358 (0.00%) | 1 / 108 (0.93%) | 0 / 102 (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 |
| Gallbladder cancer | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 1 / 108 (0.93%) | 0 / 102 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 0 / 108 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Bone marrow failure | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Iron deficiency anaemia | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 358 (0.00%) | 1 / 108 (0.93%) | 0 / 102 (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 |
| General disorders and administration site conditions | | | |
| Systemic inflammatory response syndrome | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 0 / 108 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Anal fistula | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Colitis ulcerative | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 6 / 358 (1.68%) | 2 / 108 (1.85%) | 2 / 102 (1.96%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Diarrhoea haemorrhagic | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 0 / 108 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Intestinal perforation | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Pancreatitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 1 / 108 (0.93%) | 0 / 102 (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 |
| Hepatitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 0 / 108 (0.00%) | 2 / 102 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Pneumonitis | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Pulmonary embolism | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 0 / 108 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Exostosis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 1 / 108 (0.93%) | 0 / 102 (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 |
| Osteoarthritis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 1 / 108 (0.93%) | 0 / 102 (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 |
| Infections and infestations | | | |
| Appendicitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 1 / 108 (0.93%) | 0 / 102 (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 |
| Clostridium difficile colitis | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Hepatitis B | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Pulmonary tuberculosis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Rectal abscess | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |
| Upper respiratory tract infection | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 358 (0.00%) | 0 / 108 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 358 (0.28%) | 0 / 108 (0.00%) | 0 / 102 (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 |

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

| Non-serious adverse events | Open-Label Induction Phase: Etrolizumab | Double-Blind Maintenance Phase: Etrolizumab | Double-Blind Maintenance Phase: Placebo |
|---|---|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 64 / 358 (17.88%) | 30 / 108 (27.78%) | 54 / 102 (52.94%) |
| General disorders and administration site conditions Pyrexia alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 8 / 358 (2.23%) 9 | 0 / 108 (0.00%) 0 | 6 / 102 (5.88%) 6 |
| Gastrointestinal disorders Abdominal pain alternative assessment type: Systematic subjects affected / exposed occurrences (all) Colitis ulcerative alternative assessment type: Systematic subjects affected / exposed occurrences (all) Diarrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 1 / 358 (0.28%) 1 24 / 358 (6.70%) 24 5 / 358 (1.40%) 10 | 6 / 108 (5.56%) 9 14 / 108 (12.96%) 16 4 / 108 (3.70%) 4 | 9 / 102 (8.82%) 11 34 / 102 (33.33%) 35 8 / 102 (7.84%) 9 |
| Musculoskeletal and connective tissue disorders Arthralgia alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 9 / 358 (2.51%) 11 | 8 / 108 (7.41%) 10 | 11 / 102 (10.78%) 11 |
| Infections and infestations | | | |

| | | | |
|--|------------------|-----------------|-----------------|
| Nasopharyngitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 22 / 358 (6.15%) | 8 / 108 (7.41%) | 3 / 102 (2.94%) |
| occurrences (all) | 22 | 10 | 4 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 03 April 2014 | The definition of moderate to severe UC was updated to include stool frequency sub-score of ≥ 1 . Further, for MCS/pMCS calculation, the worst rectal bleeding score from the most recent 3 days prior to clinical visit was to be used; Endoscopy procedures for UC disease activity assessment were modified; further, in case of any discrepancy between local versus central endoscopy readers, an adjudication read was to be added; The dosage of etrolizumab to be administered was corrected from 100 mg to 105 mg. The dose of 100 mg was not administered to patients; PML assessment was modified to include the PML Subjective Checklist (symptom assessment) and the PML Objective Checklist (neurologic evaluation). The algorithm for evaluation of PML was updated; Exclusion criteria related to hepatitis C, CMV testing, patient's cancer history and stenosis and screening assessments related to JCV testing and the timing of endoscopy were revised; and The dosage and administration section was revised to include a 2-week window for delayed administration of study medication due to minor illness. |
| 08 July 2014 | The inclusion criterion regarding contraception use for women was amended to detail the use of spermicide and double barrier (rather than barrier alone) for acceptable methods of contraception during treatment period and for at least 24 weeks after the last dose (reflecting International Conference on Harmonisation (M3) guidance; A new exclusion criterion was added to exclude patients with suspicion of ischemic colitis, radiation colitis, or microscopic colitis; and The exclusion criterion regarding the history of moderate or severe allergic or anaphylactic/anaphylactoid reactions to chimeric, human, or humanized antibodies, fusion proteins, or murine proteins was updated to include hypersensitivity to etrolizumab (active drug substance) or any of the excipients (L-histidine, L-arginine, succinic acid, Polysorbate 20). |
| 22 August 2014 | Local amendment only (US and Canada). |
| 28 August 2015 | The protocol was amended to remove the previous requirement that immunosuppressant use stop at Week 10 in the U.S. and Canada based on HA feedback. Instead, patients were allowed to continue with immunosuppressant use from baseline throughout induction and maintenance (with dose reduction or discontinuation of immunosuppressant use permitted in the event of toxicity) in the U.S. and Canada; and Inclusion criteria were modified to allow patients with inadequate response to either immunosuppressants or corticosteroids to be eligible for the study (rather than the previous requirement for failure to immunosuppressants with or without failure to corticosteroids). |
| 24 August 2017 | The protocol was amended to update and align the safety section with information regarding potential risks for etrolizumab in the etrolizumab Investigator's Brochure, Version 10, as follows. Guidelines for managing specific AEs were updated to include hepatic effects as a potential risk for etrolizumab, to be in line with the safety profile of other anti-integrins, including vedolizumab, for which hepatic AEs have been reported; Changes were also made to enhance recruitment by reducing the complexity of the protocol, particularly at the time of screening and re-screening, as follows: The minimum time between the diagnosis of ulcerative colitis (UC) and enrollment (Day 1) was reduced from 6 months to 3 months. This allowed patients with a more recent diagnosis of UC to be enrolled; The window for performing the endoscopy prior to Day 1 was extended from 10 to 16 days. The requirement for Medical Monitor approval for endoscopies conducted during this window was eliminated; and The time qualification for derivation of Mayo Clinic Score (MCS) baseline stool frequency and rectal bleeding subscores was redefined to include subscores obtained within 22 days prior to Day 1. |

| | |
|----------------|---|
| 27 August 2018 | <p>The protocol was primarily amended to reflect changes in efficacy endpoints. The changes would not impact study conduct at site level. The primary efficacy endpoint was changed to remission at Week 62 for patients who achieved clinical response (rather than remission) at Week 10, to align with clinical practice standards whereby patients who experienced a clinical response during treatment induction continued on treatment and were assessed for remission at a later time point; Secondary and exploratory efficacy endpoints were amended to align with the revision of the primary efficacy endpoint; To assess the onset of action of etrolizumab, a secondary efficacy endpoint of change in MCS rectal bleeding and stool frequency subscores from baseline to Week 6 was added; Histologic remission, defined as a Nancy histological index of ≤ 1, was added as a secondary efficacy outcome measure. The definition is based on consensus guidelines recommending that histologic remission should be defined by the absence of neutrophils in the crypts and lamina propria; Derivation of the MCS endoscopic subscore at post-baseline timepoints was amended to be consistent with emerging normative standards of endoscopic assessment in clinical trials; The sigmoid colon MCS endoscopic subscore will be used (rather than the score from the worst affected segment, i.e., rectum, sigmoid colon, or descending colon) if the baseline sigmoid colon MCS endoscopic subscore is 2-3. The sigmoid colon MCS endoscopic subscore is considered to be more reliable in assessing earlier treatment response; and Histologic activity on colon biopsies would be primarily measured using the Nancy histological index instead of the Geboes scale. Language regarding local injection-site reactions was clarified.</p> |
|----------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported