# Clinical trial results:
# A Cluster Randomized Controlled Trial of an Enhanced Treatment Algorithm for the Management of Crohn's Disease

## Summary

| | |
|---|---|
| EudraCT number | 2014-001050-41 |
| Trial protocol | DE |
| Global end of trial date | 16 April 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 29 April 2022 |
| First version publication date | 29 April 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | RP1202 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01698307 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Alimentiv Inc (formerly Robarts Clinical Trials Inc) |
| Sponsor organisation address | 100 Dundas Street Suite 200, London, Canada, N6A-5B6 |
| Public contact | Joan Morris, Project Director, Alimentiv Inc (formerly Robarts Clinical Trials Inc), 01 226-270-7652, joan.morris@alimentiv.com |
| Scientific contact | Vipul Jairath, Chief Medical Officer, Alimentiv Inc (formerly Robarts Clinical Trials Inc), 01 226-270-7652, vipul.jairath@alimentiv.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 | 22 April 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 April 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 April 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the Randomized Evaluation of an Algorithm for Crohn's Treatment Study-2 (REACT-2) cluster-randomized trial was to compare the efficacy of enhanced care (early combination therapy with treatment intensification to a target of absence of ulcers [>5mm in size], or deep remission) and step-care (treatment intensification to a target of clinical remission [Harvey Bradshaw Index (HBI) score ≤4]) for the treatment of Crohn's disease (CD). The primary outcome compared the risk of the first chronological CD-related complication (defined as a composite of CD-related surgeries, non-surgical events, and hospitalizations, and complications, hospitalizations and surgeries related to CD medications or procedures) at 24 months between the 2 treatment approaches.

Protection of trial subjects:

All investigative sites obtained and maintained Ethics committee/Institutional Review Board approval. While investigators were asked to adhere to the treatment algorithms to the extent possible, treatment modification was allowed to ensure patient safety (e.g., avoiding use of a product contraindicated due to previous intolerance, or childbearing potential).

Background therapy: -

Evidence for comparator:

Clinical management of active Crohn's disease (CD) includes sequential introduction of corticosteroids, immunosuppressants and biological therapy (e.g, step-care). Advanced therapies are typically reserved for more refractory patients to balance the perceived risks of these agents compared to first line drugs. Societal guidelines recommend the introduction of monoclonal antibodies for patients with moderate-to-severe CD with inadequate response or intolerance to conventional therapy. However this approach can risk prolonged corticosteroid exposure and inadequate management of underlying inflammatory disease and associated complications. Treatment to an objective target of endoscopic healing (absence of ulcers) in addition to symptomatic improvement is also favored in contemporary guidelines. Deep (clinical and endoscopic) remission has been associated with significantly lower risk of new fistulas, abscesses, hospitalization, or surgery. Early aggressive treatment, including earlier initiation of biologic therapy, is recognized as a potential approach to improve outcomes for patients with CD. The REACT-1 randomized trial found a lower composite rate of major adverse outcomes (defined as occurrence of surgery, hospital admission, or serious disease-related complications) at 2 years with early combined treatment with a tumor necrosis factor agent and antimetabolite to conventional step-care however the trial design did not reflect current recommended treatment targets and ileocolonoscopy was not performed to assess disease activity.

| | |
|---|---|
| Actual start date of recruitment | 17 February 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 330 |
| Country: Number of subjects enrolled | United Kingdom: 282 |
| Country: Number of subjects enrolled | Germany: 103 |

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 379 |
| Worldwide total number of subjects | 1094 |
| EEA total number of subjects | 103 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 982 |
| From 65 to 84 years | 110 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

Trial recruitment began in March 2014.
Enrollment per territory:
Canada: first patient 28-Mar-2014; last patient 02-Mar-2018
United States: first patient 13-Aug-2014; last patient 13-Sep-2017
Germany: first patient 23-Jul-2015; last patient 27-Feb-2018
United Kingdom: first patient 20-May-2015; last patient 11-Apr-2018

### Pre-assignment

Screening details:

Eligible practices could: implement EC or SC; provide data for 40 patients; perform ileocolonoscopy; transfer ileocolonoscopy videos. Eligible patients: ≥18 years of age with CD and able to receive adalimumab; no condition preventing compliance; no prior failure of all anti-TNFs; no investigational trial within 24 months; no short bowel syndrome.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

The trial was open-label.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Enhanced care |

Arm description:

Patients with one large (>5 mm) ulcer. Combination therapy with adalimumab and azathioprine or methotrexate +/- glucocorticosteroids (GCS) as required with tapering. Ileocolonoscopy at 16 weeks to assess for remission (no large ulcer or GCS); if yes, continue current combination treatment; if no, increase to weekly adalimumab +/- GCS with tapering. Ileocolonoscopy at 16 weeks for those not in remission at prior assessment; if remission, continue combination treatment; if no remission, switch anti-metabolite +/- GCS with tapering. Ileocolonoscopy at 16 weeks for those not in remission at prior assessment; if remission, continue combination treatment; if no remission, switch tumor necrosis factor antagonist +/- GCS with tapering.

| | |
|---|---|
| Arm type | Early combination therapy |
| Investigational medicinal product name | Adalimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Indicated dose for Crohn's disease with dose escalation as needed for inadequate response

| | |
|---|---|
| **Arm title** | Step-care |

Arm description:

Patients with Harvey Bradshaw Index (HBI) score >4 + glucocorticosteroids (GCS) with tapering. Evaluate in 16 weeks; if remission (HBI≤4), no maintenance therapy; if no remission, add azathioprine or methotrexate +/- GCS with tapering. Evaluate in 16 weeks for patients not in remission at prior assessment; if remission, continue antimetabolite; if no remission, add adalimumab +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, increase to weekly adalimumab +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, switch anti-metabolite +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, switch tumor necrosis factor antagonist +/- GCS with tapering.

| Arm type | Standard of care |
|---|---|
| No investigational medicinal product assigned in this arm | |

| **Number of subjects in period 1** | Enhanced care | Step-care |
|---|---|---|
| Started | 525 | 569 |
| Completed | 415 | 397 |
| Not completed | 110 | 172 |
| Adverse event, serious fatal | 1 | 2 |
| Consent withdrawn by subject | 27 | 17 |
| Relocation/travel | 12 | 18 |
| Not Crohn's disease | 1 | 2 |
| Eligibility criteria violation | 2 | 4 |
| Other health condition | 3 | 3 |
| Pregnancy | 2 | - |
| Poor patient compliance | 21 | 8 |
| Changed or left practitioner | 3 | 5 |
| Lost to follow-up | 38 | 50 |
| Site closure | - | 63 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Enhanced care |
| Reporting group description: | |
| Patients with one large (>5 mm) ulcer. Combination therapy with adalimumab and azathioprine or methotrexate +/- glucocorticosteroids (GCS) as required with tapering. Ileocolonoscopy at 16 weeks to assess for remission (no large ulcer or GCS); if yes, continue current combination treatment; if no, increase to weekly adalimumab +/- GCS with tapering. Ileocolonoscopy at 16 weeks for those not in remission at prior assessment; if remission, continue combination treatment; if no remission, switch anti-metabolite +/- GCS with tapering. Ileocolonoscopy at 16 weeks for those not in remission at prior assessment; if remission, continue combination treatment; if no remission, switch tumor necrosis factor antagonist +/- GCS with tapering. | |
| Reporting group title | Step-care |
| Reporting group description: | |
| Patients with Harvey Bradshaw Index (HBI) score >4 + glucocorticosteroids (GCS) with tapering. Evaluate in 16 weeks; if remission (HBI≤4), no maintenance therapy; if no remission, add azathioprine or methotrexate +/- GCS with tapering. Evaluate in 16 weeks for patients not in remission at prior assessment; if remission, continue antimetabolite; if no remission, add adalimumab +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, increase to weekly adalimumab +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, switch anti-metabolite +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, switch tumor necrosis factor antagonist +/- GCS with tapering. | |

| **Reporting group values** | Enhanced care | Step-care | Total |
|---|---|---|---|
| Number of subjects | 525 | 569 | 1094 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 489 | 493 | 982 |
| From 65-84 years | 36 | 74 | 110 |
| 85 years and over | 0 | 2 | 2 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 310 | 324 | 634 |
| Male | 215 | 245 | 460 |
| Number of patients per practice<br>Units: Number | | | |
| arithmetic mean | 37.5 | 37.9 | |
| standard deviation | ± 12.1 | ± 9.8 | - |
| CD duration | | | |
| These are practice level summaries | | | |
| Units: Months | | | |
| arithmetic mean | 138.8 | 153.4 | |
| standard deviation | ± 43.8 | ± 37.0 | - |
| Current smoker | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 19.4 | 15.3 | |
| standard deviation | ± 9.6 | ± 10.3 | - |
| 5-ASA use | | | |
| These are practice level summaries | | | |

| | | | |
|---|---|---|---|
| Units: percent | | | |
| arithmetic mean | 12.6 | 21.8 | |
| standard deviation | ± 7.4 | ± 18.6 | - |
| Corticosteroid use | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 6.3 | 7.0 | |
| standard deviation | ± 4.0 | ± 5.5 | - |
| Any immunosuppressant use | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 31.6 | 34.8 | |
| standard deviation | ± 9.3 | ± 14.0 | - |
| Anti-TNF use | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 23.0 | 29.1 | |
| standard deviation | ± 15.9 | ± 18.8 | - |
| Combination therapy use | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 14.3 | 19.8 | |
| standard deviation | ± 14.6 | ± 14.3 | - |
| Prior surgery for CD | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 41.7 | 48.4 | |
| standard deviation | ± 14.1 | ± 11.9 | - |
| CD location: ileum | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 34.0 | 29.9 | |
| standard deviation | ± 17.9 | ± 12.5 | - |
| CD location: colon | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 23.1 | 24.0 | |
| standard deviation | ± 12.8 | ± 8.4 | - |
| CD location: ileocolonic | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 40.0 | 44.0 | |
| standard deviation | ± 19.4 | ± 15.3 | - |
| Active fistula | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 6.1 | 8.8 | |
| standard deviation | ± 5.2 | ± 6.0 | - |
| Harvery Bradshaw Index score | | | |
| These are practice level summaries | | | |
| Units: Score | | | |
| arithmetic mean | 4.2 | 3.4 | |

| | | | |
|---|---|---|---|
| standard deviation | ± 1.1 | ± 1.3 | - |
| Harvey Bradshaw Index score ≤ 4 | | | |
| These are practice level summaries | | | |
| Units: percent | | | |
| arithmetic mean | 62.7 | 70.3 | |
| standard deviation | ± 11.3 | ± 14.2 | - |
| EQ-5D index score | | | |
| These are practice level summaries | | | |
| Units: Score | | | |
| arithmetic mean | 0.73 | 0.74 | |
| standard deviation | ± 0.03 | ± 0.04 | - |
| EQ-5D visual analogue score | | | |
| These are practice level summaries | | | |
| Units: Score | | | |
| arithmetic mean | 71.9 | 75.4 | |
| standard deviation | ± 3.8 | ± 5.9 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Enhanced care |

Reporting group description:

Patients with one large (>5 mm) ulcer. Combination therapy with adalimumab and azathioprine or methotrexate +/- glucocorticosteroids (GCS) as required with tapering. Ileocolonoscopy at 16 weeks to assess for remission (no large ulcer or GCS); if yes, continue current combination treatment; if no, increase to weekly adalimumab +/- GCS with tapering. Ileocolonoscopy at 16 weeks for those not in remission at prior assessment; if remission, continue combination treatment; if no remission, switch anti-metabolite +/- GCS with tapering. Ileocolonoscopy at 16 weeks for those not in remission at prior assessment; if remission, continue combination treatment; if no remission, switch tumor necrosis factor antagonist +/- GCS with tapering.

| | |
|---|---|
| Reporting group title | Step-care |

Reporting group description:

Patients with Harvey Bradshaw Index (HBI) score >4 + glucocorticosteroids (GCS) with tapering. Evaluate in 16 weeks; if remission (HBI≤4), no maintenance therapy; if no remission, add azathioprine or methotrexate +/- GCS with tapering. Evaluate in 16 weeks for patients not in remission at prior assessment; if remission, continue antimetabolite; if no remission, add adalimumab +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, increase to weekly adalimumab +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, switch anti-metabolite +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, switch tumor necrosis factor antagonist +/- GCS with tapering.

### Primary: Patient-level risk of CD-related complications: 24 months

| | |
|---|---|
| End point title | Patient-level risk of CD-related complications: 24 months |

End point description:

Risk of the first chronological CD-related complication (defined as a composite of CD-related surgeries, non-surgical events, and hospitalizations, and complications, hospitalizations and surgeries related to CD medications or procedures) at 24 months

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

End point timeframe:

24 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 40.9 (33.3 to 50.1) | 43.1 (35.3 to 52.5) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Risk ratio |

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.59 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.15 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.73 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.2 |
| upper limit | 7.2 |

## Secondary: Patient-level risk of CD-related complications: 12 months

| End point title | Patient-level risk of CD-related complications: 12 months |
|---|---|

End point description:

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

End point timeframe:

12 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 29.7 (22.3 to 39.5) | 31.3 (23.6 to 41.5) | | |

## Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Step-care v Enhanced care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.19 |

| Statistical analysis title | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.86 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.7 |
| upper limit | 7.2 |

## Secondary: Patient-level risk of CD-related complications: 6 months

| End point title | Patient-level risk of CD-related complications: 6 months |
|---|---|

End point description:

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

End point timeframe:

6 months

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 18.0 (12.3 to 26.4) | 21.0 (14.6 to 30.2) | | |

**Statistical analyses**

| **Statistical analysis title** | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| Comparison groups | Enhanced care v Step-care |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.42 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.25 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -2.2 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.5 |
| upper limit | 6 |

## Secondary: Patient-level risk of CD-related surgery: 24 months

| | |
|---|---|
| End point title | Patient-level risk of CD-related surgery: 24 months |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 7.0 (3.8 to 12.8) | 6.4 (3.8 to 10.6) | | |

### Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|
| Statistical analysis description: | |
| Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.77 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 2.06 |

| Statistical analysis title | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.28 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 6.1 |

| Secondary: Patient-level risk of CD-related surgery: 12 months | |
|---|---|
| End point title | Patient-level risk of CD-related surgery: 12 months |
| End point description: | |

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| 12 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 5.2 (2.6 to 10.3) | 3.9 (2.1 to 7.0) | | |

**Statistical analyses**

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| Comparison groups | Enhanced care v Step-care |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.49 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 3.1 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.098 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 5.9 |

| **Secondary: Patient-level risk of CD-related surgery: 6 months** |
|---|
| End point title: Patient-level risk of CD-related surgery: 6 months |
| End point description: |
| End point type: Secondary |
| End point timeframe: 6 months |

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 2.4 (1.1 to 5.0) | 2.0 (1.0 to 3.7) | | |

## Statistical analyses

| **Statistical analysis title** | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.66 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 2.82 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.23 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 2.7 |

## Secondary: Patient-level risk of all-cause surgery: 24 months

| End point title | Patient-level risk of all-cause surgery: 24 months |
|---|---|

End point description:

| | |
|---|---|
| End point type | Secondary |
| End point timeframe:<br>24 months | |

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 7.6 (4.6 to 12.5) | 7.3 (4.6 to 11.6) | | |

**Statistical analyses**

| **Statistical analysis title** | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.82 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.53 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 1.3 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | 5.4 |

## Secondary: Patient-level risk of all-cause surgery: 12 months

| | |
|---|---|
| End point title | Patient-level risk of all-cause surgery: 12 months |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 5.4 (2.9 to 10.1) | 4.2 (2.4 to 7.2) | | |

### Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|
| Statistical analysis description: | |
| Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.48 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 2.66 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.19 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 5.3 |

## Secondary: Patient-level risk of all-cause surgery: 6 months

| End point title | Patient-level risk of all-cause surgery: 6 months |
|---|---|

End point description:

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

End point timeframe:

6 months

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 1.8 (0.6 to 4.9) | 1.7 (0.7 to 4.2) | | |

### Statistical analyses

| **Statistical analysis title** | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| Comparison groups | Enhanced care v Step-care |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.99 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 2.3 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.42 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 2.7 |

| **Secondary: Patient-level risk of CD-related hospitalization: 24 months** | |
|---|---|
| End point title | Patient-level risk of CD-related hospitalization: 24 months |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 14.4 (10.1 to 20.6) | 11.4 (7.8 to 16.9) | | |

### Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.99 |

| Statistical analysis title | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.28 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 3.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | 9.4 |

### Secondary: Clinical remission: 24 months

| End point title | Clinical remission: 24 months |
|---|---|

End point description:

Harvey Bradshaw Index score ≤ 4

| | |
|---|---|
| End point type | Secondary |
| End point timeframe:<br>24 months | |

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 32.3 (25.5 to 41.0) | 30.7 (21.9 to 42.9) | | |

**Statistical analyses**

| **Statistical analysis title** | Risk ratio |
|---|---|
| Statistical analysis description:<br>The risk ratio is estimated from individual-level data using a modified Poisson model for clustered binomial data adjusted for design elements. The proportions in each treatment algorithm are the associated least-squares means from this model. The comparisons are in reference to the step-care algorithm. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.75 |
| Method | Modified Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.46 |

**Secondary: Clinical remission: 12 months**

| End point title | Clinical remission: 12 months |
|---|---|
| End point description:<br>Harvey Bradshaw Index score ≤ 4 | |
| End point type | Secondary |
| End point timeframe:<br>12 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 45.2 (38.2 to 53.5) | 47.6 (38.6 to 58.8) | | |

### Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

The risk ratio is estimated from individual-level data using a modified Poisson model for clustered binomial data adjusted for design elements. The proportions in each treatment algorithm are the associated least-squares means from this model. The comparisons are in reference to the step-care algorithm.

| Comparison groups | Enhanced care v Step-care |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.68 |
| Method | Modified Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.22 |

### Secondary: Deep remission: 24 months

| End point title | Deep remission: 24 months |
|---|---|

End point description:

Deep remission defined as Harvey Bradshaw Index score ≤ 4, no corticosteroids for the treatment of Crohn's disease, and normal C-reactive protein

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

End point timeframe:

24 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 15.9 (10.3 to 24.5) | 13.5 (8.6 to 21.2) | | |

### Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

The risk ratio is estimated from individual-level data using a modified Poisson model for clustered binomial data adjusted for design elements. The proportions in each treatment algorithm are the associated least-squares means from this model. The comparisons are in reference to the step-care algorithm.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.55 |
| Method | Modified Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.99 |

### Secondary: Deep remission: 12 months

| End point title | Deep remission: 12 months |
|---|---|

End point description:

Deep remission defined as Harvey Bradshaw Index score ≤ 4, no corticosteroids for the treatment of Crohn's disease, and normal C-reactive protein

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

End point timeframe:

12 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 24.1 (17.8 to 32.7) | 24.7 (18.1 to 33.7) | | |

**Statistical analyses**

| **Statistical analysis title** | Risk ratio |
|---|---|

Statistical analysis description:

The risk ratio is estimated from individual-level data using a modified Poisson model for clustered binomial data adjusted for design elements. The proportions in each treatment algorithm are the associated least-squares means from this model. The comparisons are in reference to the step-care algorithm.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.91 |
| Method | Modified Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.5 |

**Secondary: Progression-free deep remission: 24 months**

| End point title | Progression-free deep remission: 24 months |
|---|---|

End point description:

Deep remission without disease progression, where disease progression is defined as the de novo development of strictures, fistula, the occurrence of an intra-abdominal abscess, or surgery for Crohn's disease (resection, bypass, stricturoplasty)

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

End point timeframe:

24 months

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 15.5 (10.0 to 24.0) | 13.2 (8.4 to 20.6) | | |

**Statistical analyses**

| **Statistical analysis title** | Risk ratio |
|---|---|

Statistical analysis description:

The risk ratio is estimated from individual-level data using a modified Poisson model for clustered binomial data adjusted for design elements. The proportions in each treatment algorithm are the associated least-squares means from this model. The comparisons are in reference to the

step-care algorithm.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.55 |
| Method | Modified Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 2 |

## Secondary: Progression-free deep remission: 12 months

| | |
|---|---|
| End point title | Progression-free deep remission: 12 months |

End point description:

Deep remission without disease progression, where disease progression is defined as the de novo development of strictures, fistula, the occurrence of an intra-abdominal abscess, or surgery for Crohn's disease (resection, bypass, stricturoplasty)

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

End point timeframe:

12 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 24.4 (18.0 to 33.0) | 23.8 (17.5 to 32.5) | | |

## Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

The risk ratio is estimated from individual-level data using a modified Poisson model for clustered binomial data adjusted for design elements. The proportions in each treatment algorithm are the associated least-squares means from this model. The comparisons are in reference to the step-care algorithm.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |

| | |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.91 |
| Method | Modified Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.57 |

## Secondary: Difference in change from baseline in C-reactive protein concentration between treatment groups at month 24

| | |
|---|---|
| End point title | Difference in change from baseline in C-reactive protein concentration between treatment groups at month 24 |

End point description:

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

End point timeframe:

24 months

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 327 | 323 | | |
| Units: mg/L | | | | |
| arithmetic mean (standard error) | 8.3 (± 1.2) | 5.0 (± 0.6) | | |

## Statistical analyses

| **Statistical analysis title** | Difference between treatment arms |
|---|---|

Statistical analysis description:

Analysis of change within visit was performed at the patient-level using linear mixed-model accounting for clusters and adjusting for design elements and baseline C-Reactive Protein [mg/L].

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 650 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |
| Point estimate | 2.2 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 6.6 |

## Secondary: Differerence in change from baseline in C-reactive protein concentration between treatment groups at month 12

| | |
|---|---|
| End point title | Differerence in change from baseline in C-reactive protein concentration between treatment groups at month 12 |

End point description:

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

End point timeframe:

12 months

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 339 | 363 | | |
| Units: mg/L | | | | |
| arithmetic mean (standard error) | 8.7 (± 2.1) | 6.5 (± 0.8) | | |

## Statistical analyses

| **Statistical analysis title** | Difference between treatment arms |
|---|---|

Statistical analysis description:

Analysis of change within visit was performed at the patient-level using linear mixed-model accounting for clusters and adjusting for design elements and baseline C-Reactive Protein [mg/L].

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 702 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.47 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |
| Point estimate | 3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.1 |
| upper limit | 11.1 |

## Secondary: Difference in change from baseline in C-reactive protein concentration between treatment groups at month 6

| End point title | Difference in change from baseline in C-reactive protein concentration between treatment groups at month 6 |
|---|---|

End point description:

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

End point timeframe:

6 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 262 | 212 | | |
| Units: mg/L | | | | |
| arithmetic mean (standard error) | 6.4 (± 0.9) | 6.1 (± 1.0) | | |

### Statistical analyses

| Statistical analysis title | Difference between treatment arms |
|---|---|

Statistical analysis description:

Analysis of change within visit was performed at the patient-level using linear mixed-model accounting for clusters and adjusting for design elements and baseline C-Reactive Protein [mg/L].

| Comparison groups | Step-care v Enhanced care |
|---|---|
| Number of subjects included in analysis | 474 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.42 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7 |
| upper limit | 6.5 |

## Secondary: Difference in change from baseline in Harvey Bradshaw Index score between treatment groups at month 24

| End point title | Difference in change from baseline in Harvey Bradshaw Index score between treatment groups at month 24 |
|---|---|

End point description:

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

End point timeframe:

24 months

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 419 | 384 | | |
| Units: score | | | | |
| arithmetic mean (standard error) | 2.4 (± 0.1) | 2.4 (± 0.2) | | |

**Statistical analyses**

| **Statistical analysis title** | Difference between treatment arms |
|---|---|

Statistical analysis description:

Analysis of change from baseline was performed at the patient-level using a linear mixed-model, modeling the change from baseline value, adjusting for design elements and clustering.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 803 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.017 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | -0.2 |

**Secondary: Difference in change from baseline in Harvey Bradshaw Index score between treatment groups at month 12**

| End point title | Difference in change from baseline in Harvey Bradshaw Index score between treatment groups at month 12 |
|---|---|

End point description:

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

End point timeframe:

12 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 427 | 456 | | |
| Units: score | | | | |
| arithmetic mean (standard error) | 2.8 (± 0.2) | 2.7 (± 0.2) | | |

**Statistical analyses**

| Statistical analysis title | Difference between treatment arms |
|---|---|
| Statistical analysis description: | |
| Analysis of change from baseline was performed at the patient-level using a linear mixed-model, modeling the change from baseline value, adjusting for design elements and clustering. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 883 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.14 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 0.2 |

**Secondary: Difference in change from baseline in Harvey Bradshaw Index score between treatment groups at month 6**

| End point title | Difference in change from baseline in Harvey Bradshaw Index score between treatment groups at month 6 |
|---|---|
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| 6 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 424 | 483 | | |
| Units: score | | | | |
| arithmetic mean (standard error) | 2.7 (± 0.1) | 2.8 (± 0.2) | | |

### Statistical analyses

| Statistical analysis title | Difference between treatment arms |
|---|---|
| Statistical analysis description: | |
| Analysis of change from baseline was performed at the patient-level using a linear mixed-model, modeling the change from baseline value, adjusting for design elements and clustering. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 907 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.017 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | -0.2 |

## Secondary: Difference in change from baseline in EQ-5D score between treatment groups at month 24

| End point title | Difference in change from baseline in EQ-5D score between treatment groups at month 24 |
|---|---|
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 416 | 381 | | |
| Units: score | | | | |
| arithmetic mean (standard error) | 0.77 (± 0.01) | 0.77 (± 0.01) | | |

### Statistical analyses

| **Statistical analysis title** | Difference between treatment arms |
|---|---|
| Statistical analysis description: | |
| Analysis of change within visit was performed at the patient-level using linear mixed-model accounting for clusters and adjusting for design elements and baseline EQ-5D single index. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 797 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.77 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.02 |

## Secondary: Difference in change from baseline in EQ-5D score between treatment groups at month 12

| End point title | Difference in change from baseline in EQ-5D score between treatment groups at month 12 |
|---|---|
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 428 | 453 | | |
| Units: score | | | | |
| arithmetic mean (standard error) | 0.76 (± 0.01) | 0.76 (± 0.01) | | |

### Statistical analyses

| **Statistical analysis title** | Difference between treatment arms |
|---|---|
| Statistical analysis description: | |
| Analysis of change within visit was performed at the patient-level using linear mixed-model accounting for clusters and adjusting for design elements and baseline EQ-5D single index. | |
| Comparison groups | Enhanced care v Step-care |

| | |
|---|---|
| Number of subjects included in analysis | 881 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.02 |

## Secondary: Difference in change from baseline in EQ-5D score between treatment groups at month 6

| | |
|---|---|
| End point title | Difference in change from baseline in EQ-5D score between treatment groups at month 6 |

End point description:

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

End point timeframe:

6 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 408 | 472 | | |
| Units: score | | | | |
| arithmetic mean (standard error) | 0.75 (± 0.01) | 0.76 (± 0.01) | | |

## Statistical analyses

| Statistical analysis title | Difference between treatment arms |
|---|---|

Statistical analysis description:

Analysis of change within visit was performed at the patient-level using linear mixed-model accounting for clusters and adjusting for design elements and baseline EQ-5D single index.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 880 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.34 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |
| Point estimate | -0.01 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.01 |

## Secondary: Patient-level risk of CD-related hospitalization: 12 months

| | |
|---|---|
| End point title | Patient-level risk of CD-related hospitalization: 12 months |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 12.4 (8.8 to 17.5) | 8.2 (5.6 to 12.1) | | |

### Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|
| Statistical analysis description: | |
| Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.073 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 2.35 |

| Statistical analysis title | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.044 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 4.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1 |
| upper limit | 8.4 |

| Secondary: Patient-level risk of CD-related hospitalization: 6 months | |
|---|---|
| End point title | Patient-level risk of CD-related hospitalization: 6 months |
| End point description: | |

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| 6 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 7.3 (4.5 to 11.9) | 4.8 (2.7 to 8.5) | | |

## Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| Comparison groups | Enhanced care v Step-care |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.23 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 3.05 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.15 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 6.1 |

**Secondary: Patient satisfaction**

| | |
|---|---|
| End point title | Patient satisfaction |

End point description:

How satisfied are you with the management of your Crohn's Disease during the course of participation in the study?

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

End point timeframe:

24 months

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 412 | 408 | | |
| Units: none | | | | |
| arithmetic mean (standard deviation) | 9.3 (± 1.3) | 9.2 (± 1.5) | | |

### Statistical analyses

| Statistical analysis title | Difference between treatment arms |
|---|---|
| Statistical analysis description:<br>Linear-mixed model adjusted for stratification factors, caseload, and region. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 820 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.758 |
| Method | Mixed models analysis |

### Secondary: Patient-level time to first CD-related complication

| End point title | Patient-level time to first CD-related complication |
|---|---|
| End point description: | |
| End point type | Secondary |
| End point timeframe:<br>From randomization to end of study | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 18.7 (5 to 24.4) | 12.5 (4.5 to 24.3) | | |

### Statistical analyses

| Statistical analysis title | Treatment effect |
|---|---|
| Statistical analysis description:<br>Individual-level data were analyzed by a Cox proportional hazards regression, adjusting for design elements and clustering | |
| Comparison groups | Enhanced care v Step-care |

| | |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.62 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.23 |

## Secondary: Patient-level risk of all cause hospitalization: 24 months

| | |
|---|---|
| End point title | Patient-level risk of all cause hospitalization: 24 months |

End point description:

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

End point timeframe:

24 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 22.2 (18.0 to 27.3) | 22.6 (19.1 to 26.8) | | |

### Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.89 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.98 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.31 |

| | |
|---|---|
| **Statistical analysis title** | Risk difference |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.94 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.1 |
| upper limit | 6.6 |

| **Secondary: Patient-level risk of all cause hospitalization: 12 months** | |
|---|---|
| End point title | Patient-level risk of all cause hospitalization: 12 months |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 18.1 (14.5 to 22.5) | 15.1 (12.7 to 17.9) | | |

**Statistical analyses**

| **Statistical analysis title** | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted

for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.25 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.62 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.23 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 7.7 |

## Secondary: Patient-level risk of all cause hospitalization: 6 months

| | |
|---|---|
| End point title | Patient-level risk of all cause hospitalization: 6 months |

End point description:

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

End point timeframe:

6 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 11.7 (8.2 to 16.5) | 7.9 (5.9 to 10.5) | | |

**Statistical analyses**

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.13 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 2.47 |

| Statistical analysis title | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.13 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 3.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 7.8 |

**Secondary: Patient-level risk of non-surgical CD-related complications: 24 months**

| End point title | Patient-level risk of non-surgical CD-related complications: 24 months |
|---|---|

End point description:

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

End point timeframe:

24 months

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 37.9 (30.4 to 47.3) | 41.8 (33.9 to 51.6) | | |

**Statistical analyses**

| **Statistical analysis title** | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| Comparison groups | Enhanced care v Step-care |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.33 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.11 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |

| | |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.45 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -3.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.1 |
| upper limit | 5.4 |

## Secondary: Patient-level risk of non-surgical CD-related complications: 12 months

| | |
|---|---|
| End point title | Patient-level risk of non-surgical CD-related complications: 12 months |

End point description:

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

End point timeframe:

12 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 26.4 (19.0 to 36.7) | 29.3 (21.7 to 39.4) | | |

### Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.44 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.9 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.17 |

| | |
|---|---|
| **Statistical analysis title** | Risk difference |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.62 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.5 |
| upper limit | 6.3 |

| **Secondary: Patient-level risk of non-surgical CD-related complications: 6 months** | |
|---|---|
| End point title | Patient-level risk of non-surgical CD-related complications: 6 months |
| End point description: | |
| End point type | Secondary |
| End point timeframe: 6 months | |

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 14.9 (9.7 to 22.9) | 19.1 (13.1 to 28.0) | | |

**Statistical analyses**

| | |
|---|---|
| **Statistical analysis title** | Risk ratio |

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.23 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.17 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.36 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -3.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.8 |
| upper limit | 4.3 |

## Secondary: Patient-level risk of CD medication-related complications: 24 months

| | |
|---|---|
| End point title | Patient-level risk of CD medication-related complications: 24 months |

End point description:

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

End point timeframe:

24 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 18.8 (11.8 to 29.8) | 20.3 (12.4 to 33.2) | | |

## Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.37 |

| Statistical analysis title | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.82 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.6 |
| upper limit | 7.6 |

## Secondary: Patient-level risk of CD medication-related complications: 12 months

| End point title | Patient-level risk of CD medication-related complications: 12 months |
|---|---|

End point description:

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

End point timeframe:

12 months

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 13.1 (8.3 to 20.9) | 13.0 (7.6 to 22.1) | | |

**Statistical analyses**

| **Statistical analysis title** | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| Comparison groups | Enhanced care v Step-care |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.96 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.53 |

| **Statistical analysis title** | Risk difference |
|---|---|
| Comparison groups | Enhanced care v Step-care |

| | |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.82 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.6 |
| upper limit | 7.1 |

## Secondary: Patient-level risk of CD medication-related complications: 6 months

| | |
|---|---|
| End point title | Patient-level risk of CD medication-related complications: 6 months |

End point description:

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

End point timeframe:

6 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 7.5 (3.8 to 14.8) | 8.9 (4.6 to 17.2) | | |

### Statistical analyses

| Statistical analysis title | Risk ratio |
|---|---|

Statistical analysis description:

Risk estimates from a GEE marginal risk model for clustered time-to-event data with censoring, adjusted for clustering, design elements and treatment allocation. Treatment effect is estimated both in terms of the risk ratio and risk difference estimated from a GEE model. All analyses conducted at level of the individual.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.59 |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.85 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 1.55 |

| | |
|---|---|
| **Statistical analysis title** | Risk difference |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.85 |
| Method | GEE |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.9 |
| upper limit | 4.9 |

| **Secondary: Physician satisfaction (1)** | |
|---|---|
| End point title | Physician satisfaction (1) |
| End point description: | |
| How effective do you feel the treatment algorithm is in managing your patients with Crohn’s Disease? | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 11 | | |
| Units: none | | | | |
| arithmetic mean (standard deviation) | 7.1 (± 1.9) | 6.0 (± 2.6) | | |

**Statistical analyses**

| **Statistical analysis title** | Difference between treatment arms |
|---|---|
| Statistical analysis description: | |
| Linear-mixed model adjusted for stratification factors, caseload, and region. | |
| Comparison groups | Enhanced care v Step-care |

| | |
|---|---|
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.213 |
| Method | Mixed models analysis |
| Parameter estimate | Slope |

## Secondary: Physician satisfaction (2)

| | |
|---|---|
| End point title | Physician satisfaction (2) |

End point description:

How feasible do you think it is to sustain the treatment algorithm within your practice setting?

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

End point timeframe:

24 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 11 | | |
| Units: none | | | | |
| arithmetic mean (standard deviation) | 7.6 (± 1.8) | 6.0 (± 2.9) | | |

### Statistical analyses

| Statistical analysis title | Difference between treatment arms |
|---|---|

Statistical analysis description:

Linear-mixed model adjusted for stratification factors, caseload, and region.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.057 |
| Method | Mixed models analysis |

## Secondary: Physician satisfaction (3)

| | |
|---|---|
| End point title | Physician satisfaction (3) |

End point description:

How satisfied are you with the information given to you regarding the use of the treatment algorithm in your practice setting?

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

End point timeframe:

24 months

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 11 | | |
| Units: none | | | | |
| arithmetic mean (standard deviation) | 8.1 (± 1.3) | 6.8 (± 2.8) | | |

**Statistical analyses**

| Statistical analysis title | Difference between treatment arms |
|---|---|
| Statistical analysis description:<br>Linear-mixed model adjusted for stratification factors, caseload, and region. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.095 |
| Method | Mixed models analysis |

**Secondary: Physician satisfaction (4)**

| End point title | Physician satisfaction (4) |
|---|---|
| End point description:<br>How likely would you be to recommend the treatment algorithm to a colleague? | |
| End point type | Secondary |
| End point timeframe:<br>24 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 11 | | |
| Units: none | | | | |
| arithmetic mean (standard deviation) | 7.6 (± 2.2) | 6.2 (± 3.0) | | |

**Statistical analyses**

| Statistical analysis title | Difference between treatment arms |
|---|---|
| Statistical analysis description:<br>Linear-mixed model adjusted for stratification factors, caseload, and region. | |

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.174 |
| Method | Mixed models analysis |

## Secondary: Physician satisfaction (5)

| | |
|---|---|
| End point title | Physician satisfaction (5) |
| End point description:<br>Overall how satisfied are you with the treatment algorithm to Crohn’s Disease management? | |
| End point type | Secondary |
| End point timeframe:<br>24 months | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 11 | | |
| Units: none | | | | |
| arithmetic mean (standard deviation) | 7.1 (± 2.4) | 6.2 (± 3.3) | | |

### Statistical analyses

| Statistical analysis title | Difference between treatment arms |
|---|---|
| Statistical analysis description:<br>Linear-mixed model adjusted for stratification factors, caseload, and region. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 25 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.385 |
| Method | Mixed models analysis |

## Secondary: Patient-level time to first CD-related surgery

| | |
|---|---|
| End point title | Patient-level time to first CD-related surgery |
| End point description: | |
| End point type | Secondary |
| End point timeframe:<br>From randomization to study end | |

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 24.3 (18.6 to 24.7) | 24.1 (12.2 to 24.6) | | |

**Statistical analyses**

| **Statistical analysis title** | Treatment effect |
|---|---|
| Statistical analysis description: | |
| Individual-level data were analyzed by a Cox proportional hazards regression, adjusting for design elements and clustering. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.37 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 2.64 |

**Secondary: Patient-level time to first CD-related hospitalization**

| End point title | Patient-level time to first CD-related hospitalization |
|---|---|
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization to study end | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 24.2 (12.4 to 24.7) | 24.1 (11.0 to 24.5) | | |

**Statistical analyses**

| Statistical analysis title | Treatment effect |
|---|---|
| Statistical analysis description: | |
| Individual-level data were analyzed by a Cox proportional hazards regression, adjusting for design elements and clustering. | |
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.35 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 2.09 |

**Secondary: Patient level time to first non-surgical CD-related complication**

| End point title | Patient level time to first non-surgical CD-related complication |
|---|---|
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization to study end | |

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 20.2 (6.1 to 24.4) | 12.8 (4.7 to 24.3) | | |

**Statistical analyses**

| **Statistical analysis title** | Treatment effect |
|---|---|

Statistical analysis description:

Individual-level data were analyzed by a Cox proportional hazards regression, adjusting for design elements and clustering.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.36 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 1.17 |

**Secondary: Patient-level time to first CD medication-related complication**

| | |
|---|---|
| End point title | Patient-level time to first CD medication-related complication |

End point description:

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

End point timeframe:

From randomization to study end

| **End point values** | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 24.1 (11.7 to 24.6) | 22.9 (8.2 to 24.5) | | |

**Statistical analyses**

| **Statistical analysis title** | Treatment effect |
|---|---|

Statistical analysis description:

Individual-level data were analyzed by a Cox proportional hazards regression, adjusting for design elements and clustering.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |

| | |
|---|---|
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.4 |

## Secondary: Patient-level time to first all-cause surgery

| | |
|---|---|
| End point title | Patient-level time to first all-cause surgery |

End point description:

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

End point timeframe:

From randomization to study end

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 24.3 (18.6 to 24.8) | 24.1 (12.2 to 24.6) | | |

### Statistical analyses

| Statistical analysis title | Treatment effect |
|---|---|

Statistical analysis description:

Individual-level data were analyzed by a Cox proportional hazards regression, adjusting for design elements and clustering.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.58 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.19 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 2.2 |

## Secondary: Patient-level time to first all-cause hospitalization

| | |
|---|---|
| End point title | Patient-level time to first all-cause hospitalization |

End point description:

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

End point timeframe:

From randomization to study end

| End point values | Enhanced care | Step-care | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 525 | 569 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 24.1 (9.8 to 24.6) | 23.0 (9.1 to 24.5) | | |

### Statistical analyses

| Statistical analysis title | Treatment effect |
|---|---|

Statistical analysis description:

Individual-level data were analyzed by a Cox proportional hazards regression, adjusting for design elements and clustering.

| | |
|---|---|
| Comparison groups | Enhanced care v Step-care |
| Number of subjects included in analysis | 1094 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.46 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 months

Adverse event reporting additional description:

Adverse events (serious and non-serious) reflect those occurring in >5% of patients

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Enhanced care |

Reporting group description:

Patients with one large (>5 mm) ulcer. Combination therapy with adalimumab and azathioprine or methotrexate +/- glucocorticosteroids (GCS) as required with tapering. Ileocolonoscopy at 16 weeks to assess for remission (no large ulcer or GCS); if yes, continue current combination treatment; if no, increase to weekly adalimumab +/- GCS with tapering. Ileocolonoscopy at 16 weeks for those not in remission at prior assessment; if remission, continue combination treatment; if no remission, switch anti-metabolite +/- GCS with tapering. Ileocolonoscopy at 16 weeks for those not in remission at prior assessment; if remission, continue combination treatment; if no remission, switch tumor necrosis factor antagonist +/- GCS with tapering.

| | |
|---|---|
| Reporting group title | Step-care |

Reporting group description:

Patients with Harvey Bradshaw Index (HBI) score >4 + glucocorticosteroids (GCS) with tapering. Evaluate in 16 weeks; if remission (HBI≤4), no maintenance therapy; if no remission, add azathioprine or methotrexate +/- GCS with tapering. Evaluate in 16 weeks for patients not in remission at prior assessment; if remission, continue antimetabolite; if no remission, add adalimumab +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, increase to weekly adalimumab +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, switch anti-metabolite +/- GCS with tapering. Evaluate at 16 weeks for those not in remission at prior assessment; if remission, continue combination therapy; if no remission, switch tumor necrosis factor antagonist +/- GCS with tapering.

| **Serious adverse events** | Enhanced care | Step-care | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 37 / 530 (6.98%) | 31 / 572 (5.42%) | |
| number of deaths (all causes) | 1 | 2 | |
| number of deaths resulting from adverse events | | | |
| Gastrointestinal disorders | | | |
| Crohn's disease | | | |
| subjects affected / exposed | 36 / 530 (6.79%) | 28 / 572 (4.90%) | |
| occurrences causally related to treatment / all | 0 / 41 | 0 / 34 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |

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

| **Non-serious adverse events** | Enhanced care | Step-care | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 276 / 530 (52.08%) | 236 / 572 (41.26%) | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 34 / 530 (6.42%) | 35 / 572 (6.12%) | |
| occurrences (all) | 35 | 38 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 62 / 530 (11.70%) | 37 / 572 (6.47%) | |
| occurrences (all) | 73 | 41 | |
| Crohn's disease | | | |
| subjects affected / exposed | 87 / 530 (16.42%) | 111 / 572 (19.41%) | |
| occurrences (all) | 102 | 133 | |
| Diarrhoea | | | |
| subjects affected / exposed | 49 / 530 (9.25%) | 32 / 572 (5.59%) | |
| occurrences (all) | 55 | 32 | |
| Nausea | | | |
| subjects affected / exposed | 43 / 530 (8.11%) | 28 / 572 (4.90%) | |
| occurrences (all) | 47 | 29 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 27 / 530 (5.09%) | 15 / 572 (2.62%) | |
| occurrences (all) | 30 | 17 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 112 / 530 (21.13%) | 71 / 572 (12.41%) | |
| occurrences (all) | 125 | 73 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 45 / 530 (8.49%) | 22 / 572 (3.85%) | |
| occurrences (all) | 53 | 26 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 03 June 2019 | The study was extended from 1 to 2 years of follow-up. An extended follow up period was implemented in response to regulatory (FDA) recommendations and to enhance the scientific merit of the study. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported