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 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 Units: Subjects			
Female	310	324	634
Male	215	245	460
Number of patients per practice 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: 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: 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: 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: Harvey Bradshaw Index score ≤ 4	
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%)	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: 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: 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: 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: 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: How likely would you be to recommend the treatment algorithm to a colleague?	
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 (± 2.2)	6.2 (± 3.0)		

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	= 0.174
Method	Mixed models analysis

Secondary: Physician satisfaction (5)

End point title	Physician satisfaction (5)
End point description: Overall how satisfied are you with the treatment algorithm to Crohn’s Disease management?	
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 (± 2.4)	6.2 (± 3.3)		

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	= 0.385
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: 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