



Clinical trial results:

Randomised, open, non-inferiority within patient-controlled trial evaluating the diagnostic usefulness of Lumentin® 44 when used as contrast agent in CT-enterography as compared to MRI- enterography in patients with small bowel Crohn's disease.

Summary

EudraCT number	2019-002093-32
Trial protocol	SE
Global end of trial date	24 May 2022

Results information

Result version number	v1 (current)
This version publication date	19 April 2023
First version publication date	22 March 2023

Trial information

Trial identification

Sponsor protocol code	LUM-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04321941
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lument AB
Sponsor organisation address	Scheelevägen 22, LUND, Sweden, SE-223 63
Public contact	Olof Bööck, CEO, Lument AB, olof.book@lumentab.com
Scientific contact	Jan Marsal, CMO, Lument AB, jan.marsal@med.lu.se

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 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 May 2022
Global end of trial reached?	Yes
Global end of trial date	24 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the Radiological Crohn's disease Activity Score (RCDAS) of a CT-enterography performed with Lumentin® 44 as a bowel filling contrast agent with the RCDAS of a routinely performed MR-enterography.

This was a phase II randomised, open, non-inferiority within patient-controlled multi-centre trial. Male and female subjects with a diagnosis of CD and a clinical indication for MRE examination were included. The subjects attended a CTE and an MRE examination in randomised order.

The assessments, according to the RCDAS, of the CTE and MRE were performed by radiologists specialised in abdominal imaging. The assessments of each patient's CTE and MRE examinations were performed by 2 radiologists in randomised order. For each radiologist, the 2 examinations were separated in time.

After CTE and MRE, a voluntary endoscopic examination (PillCam Crohn's capsule) and/or a voluntary ultrasound examination of the bowel were included and compared with CTE for a subset of patients.

Protection of trial subjects:

The trial was conducted in compliance with the protocol, the International Conference on Harmonisation (ICH) guidelines on good clinical practice (GCP), the applicable European Directives and local legal requirements, and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

All information containing personal data were handled in accordance with Swedish data protection legislation and with the EU Data Protection Directive (95/46/EC). In accordance with the legislation, the data do not identify any persons taking part in the trial.

Due to the long duration (30-60 min) of the MRE, taking place in a very narrow space within the instrument, a sedating medication, usually 5 mg Diazepam, may be given in connection with this examination in order to relax the subject.

Background therapy:

During the first year of the trial, the subjects were pre-treated with a bowel cleansing regimen before both CTE and MRE examinations. The subjects were given 2 entero-tablets of 5 mg bisacodyl times two with 8-10 hours in between. A small rectal bowel cleansing treatment with sorbitol (Klyx® Ferring) was self-administered at home in the morning of scheduled enterography. The subjects were fasting (including drinking) for 4 hours.

In November 2020, new routines which did not require bowel cleansing before MRE were implemented. Subjects only had to fast for 6 hours prior to the examination. Clear liquid was allowed. For CTE, the procedure was unchanged.

Filling of the terminal ileum was checked before starting any of the abdominal scans.

Before the CTE examination started, an IV injection of the contrast agent Omnipaque 350 mg I/mL was given. The dose was adjusted to body weight and kidney function. 20 mg of Buscopan® was injected IV to reduce bowel motility.

Before the MRE examination 0.2 mmol/kg of the contrast agent Dotarem® (279.3 mg/ml), and 20 mg of Buscopan® (20 mg) (to reduce bowel motility) were administered IV. To relax the subject, a sedating medication, usually 5 mg Diazepam, either as a tablet or a suppository, may be given in connection with the examination.

Evidence for comparator:

Evidence for Comparators

The comparator, Movprep® used in the trial is standard of care treatment, commonly used as contrast agent in patients referred to MRE examinations.

Abbreviations used:

CD: Crohn's disease

CDMRIS: Crohn's disease magnetic resonance index of inflammatory severity

CTE: Computerised tomography enterography

ID: Identification details

IV: intravenous

LS: Lewis score

MRE: Magnetic resonance enterography

RCDAS: Radiological Crohn's disease activity score

SB: Small bowel

US: Ultrasound

Actual start date of recruitment	02 September 2019
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	Sweden: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	51
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female subjects with a diagnosis of CD and a clinical indication for an MRE examination were informed of the trial.

Pre-assignment

Screening details:

The study had a Screening Phase of 14 days. After receiving information about the trial according to the procedures for patient information, and consent, eligible patients were included in the trial and randomised. After randomisation, the patient's demography, medical history and concomitant illness, and medical treatment were recorded.

Period 1

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

Blinding implementation details:

The subjects were examined both by CTE and MRE. To avoid cross-influencing, the assessments according to the RCDAS of a patient's CTE and MRE scans were performed by different radiologists. Appointment of assessor for each examination was performed by randomisation.

Pseudonymised assessments of CTE and MRE scans were performed in batches of 5 scans. Patient ID was exchanged for a code and the scans were saved in a separate archive. The assessors did not have access to the code list.

Arms

Are arms mutually exclusive?	No
Arm title	CTE – Lumentin® 44

Arm description:

Before CTE-examination, subjects received Lumentin 44 in volumes of 1.3-1.8 L (sufficient volume of contrast agent to fill the terminal ileum and cecum), which should be taken orally within 1-1.5 hour prior to examination. The final dose and time of administration depended on the time to fill the terminal ileum. Low radiation scout views on CT were taken to confirm that the terminal ileum was full.

Arm type	Experimental
Investigational medicinal product name	Lumentin® 44
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension in sachet
Routes of administration	Oral use

Dosage and administration details:

Lumentin 44 was provided to the clinical site as a powder for oral suspension. After dispersion of a sachet (dose unit) of powder in water, the dispersion was whipped to 0.9 L of a drinkable foam. Each subject required preparation of 1 or 2 sachets. The foam contained 44% of air, which was the radiological key ingredient that caused the agent's contrast properties.

Arm title	MRE – Movprep®
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Arm description:

Before MRE-examination, the subjects received Movprep (in accordance with clinical praxis) which should be taken orally within 1-1.5 hour. The final dose and time of administration depended on the time to fill the terminal ileum. The motility was monitored on MRI to confirm that the terminal ileum was full.

Arm type	Active comparator
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Investigational medicinal product name	Movprep®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Movprep® is distributed as two dose units, Unit A and Unit B. Before oral administration, the Movprep dose Units A and B were dissolved in 1000 mL of water.

Number of subjects in period 1	CTE – Lumentin® 44	MRE – Movprep®
Started	60	60
Completed	52	52
Not completed	8	8
Consent withdrawn by subject	1	1
Physician decision	1	1
Could not attend visit due to common cold	1	1
Lost to follow-up	1	1
Early withdrawal	1	1
Protocol deviation	3	3

Baseline characteristics

Reporting groups

Reporting group title	CTE – Lumentin® 44
Reporting group description: Before CTE-examination, subjects received Lumentin 44 in volumes of 1.3-1.8 L (sufficient volume of contrast agent to fill the terminal ileum and cecum), which should be taken orally within 1-1.5 hour prior to examination. The final dose and time of administration depended on the time to fill the terminal ileum. Low radiation scout views on CT were taken to confirm that the terminal ileum was full.	
Reporting group title	MRE – Movprep®
Reporting group description: Before MRE-examination, the subjects received Movprep (in accordance with clinical praxis) which should be taken orally within 1-1.5 hour. The final dose and time of administration depended on the time to fill the terminal ileum. The motility was monitored on MRI to confirm that the terminal ileum was full.	

Reporting group values	CTE – Lumentin® 44	MRE – Movprep®	Total
Number of subjects	60	60	60
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	51	51	51
From 65-84 years	9	9	9
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	28	28	28
Male	32	32	32

Subject analysis sets

Subject analysis set title	Safety Analysis Set (SAS)
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set was defined as all subjects who received at least some portion of Lumentin® 44.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) is defined as all correctly included and randomised subjects who received at least some portion of the investigational compound and for whom a CTE-scan has been performed.	
Subject analysis set title	Per Protocol Analysis Set (PPAS)
Subject analysis set type	Per protocol
Subject analysis set description: The per-protocol analysis set (PPAS) is defined as the subset of subjects in the full analysis set for whom	

both MRE images and CTE images are available, and no protocol deviation judged as having an impact on the primary efficacy analysis were identified.

Reporting group values	Safety Analysis Set (SAS)	Full Analysis Set (FAS)	Per Protocol Analysis Set (PPAS)
Number of subjects	55	54	49
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	47	46	42
From 65-84 years	8	8	7
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	28	27	22
Male	27	27	27

End points

End points reporting groups

Reporting group title	CTE – Lumentin® 44
Reporting group description: Before CTE-examination, subjects received Lumentin 44 in volumes of 1.3-1.8 L (sufficient volume of contrast agent to fill the terminal ileum and cecum), which should be taken orally within 1-1.5 hour prior to examination. The final dose and time of administration depended on the time to fill the terminal ileum. Low radiation scout views on CT were taken to confirm that the terminal ileum was full.	
Reporting group title	MRE – Movprep®
Reporting group description: Before MRE-examination, the subjects received Movprep (in accordance with clinical praxis) which should be taken orally within 1-1.5 hour. The final dose and time of administration depended on the time to fill the terminal ileum. The motility was monitored on MRI to confirm that the terminal ileum was full.	
Subject analysis set title	Safety Analysis Set (SAS)
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set was defined as all subjects who received at least some portion of Lumentin® 44.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) is defined as all correctly included and randomised subjects who received at least some portion of the investigational compound and for whom a CTE-scan has been performed.	
Subject analysis set title	Per Protocol Analysis Set (PPAS)
Subject analysis set type	Per protocol
Subject analysis set description: The per-protocol analysis set (PPAS) is defined as the subset of subjects in the full analysis set for whom both MRE images and CTE images are available, and no protocol deviation judged as having an impact on the primary efficacy analysis were identified.	

Primary: Matching percentages using RCDAS (CTE vs MRE)

End point title	Matching percentages using RCDAS (CTE vs MRE) ^[1]
End point description: Two investigators evaluated both CTE and MRE images from each patient. The evaluation was done using the RCDAS which includes 18 evaluations. For each investigator and patient, it was counted how many of these 18 evaluations were exactly the same (defined as “matches”) when evaluating the CTE image and the corresponding MRE image. The percentage of matches was calculated and could range between 0% (no matching at all) and 100% (perfect matching). The mean percentage of matches was calculated between both investigators and for all patients, and this mean value was defined as the primary endpoint. The null (H0) and alternative (H1) hypotheses were: H0: $\mu \leq 80\%$ H1: $\mu > 80\%$ where μ denotes the expected value for the percentages of matches. A Wilcoxon signed rank test (exact version) was used to test the H0 which assumed that there would be $\leq 80\%$ matches. The test was one-sided using a significance level of 2.5%. The results were not statistically significant ($p=0.0440$).	
End point type	Primary
End point timeframe: Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.	

Notes:

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

Justification: The reason for only reporting 1 group (and no statistics) is:

Each patient attended both a CTE and an MRE examination. The evaluation of both CTE and MRI images used RCDAS, including 18 evaluations. For each patient, it was counted how many of the 18 evaluations

were matches between CTE and MRE. The percentage of matches was calculated for each patient and could range between 0% and 100%.

The primary endpoint takes both CTE and MRE into account for each subject (so no group comparison).

End point values	Per Protocol Analysis Set (PPAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: percent				
arithmetic mean (standard deviation)	82.74 (\pm 11.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Gastroenterologist's qualitative assessment of the Radiologist's evaluation of the CTE in relation to MRE

End point title	Gastroenterologist's qualitative assessment of the Radiologist's evaluation of the CTE in relation to MRE
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End point description:

The endpoint was to evaluate if the radiologists' evaluation of the CTE-L enterography was at least as useful for the gastroenterologist in setting the patient's diagnosis, as the radiologists' evaluation of the patient's MRI-Enterography.

The reports from the CTE and MR assessments were denominated A and B, where A was the method first in order of time. The referring gastroenterologist answered the following question: "Is the information from report A better or worse than the information from report B, in terms of supporting or guiding clinical decision making?" The endpoint was the qualitative assessment of the CTE image in relation to the MRE image and was rated as follows: Much worse, Worse, Equal to, Better or Much better, where Equal = 0. The null and alternative hypotheses were:

H0: $\mu = 0$

H1: $\mu \neq 0$

The Radiologist's evaluation of the CTE-L was better than the evaluation of the MRE; statistically significant ($p < 0.0001$, Wilcoxon signed rank test (exact version)).

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

End point values	Per Protocol Analysis Set (PPAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: No. of assessments				
Much better	12			
Better	9			
Equal	22			
Worse	6			
Much worse	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Radiologist's assessment of CD activity in the small bowel according to the RCDAS

End point title	Radiologist's assessment of CD activity in the small bowel according to the RCDAS
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End point description:

Two investigators evaluated both CTE and MRE images of the small bowel from each patient. The evaluation was done using the RCDAS which for the small bowel includes 13 evaluations. The RCDAS score for the SB can range between 0-22 points. For each investigator and patient, it was counted how many of the 13 evaluations were exactly the same (defined as "matches") when evaluating the CTE image and the corresponding MRE image. The percentage of matches was calculated and could range between 0% (no matching at all) and 100% (perfect matching). The mean percentage of matches was calculated between both investigators and for all patients, and this mean value was defined as the primary endpoint.

The null hypothesis for this variable was that the percentage matches would be $\leq 80\%$. At a pre-defined significance level of 2.5%, the results were not statistically significant ($p=0.0375$, Wilcoxon signed rank test (exact version)).

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

End point values	Per Protocol Analysis Set (PPAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: percent				
arithmetic mean (standard deviation)	82.81 (\pm 11.70)			

Statistical analyses

No statistical analyses for this end point

Secondary: Radiologist's assessment of CD activity in the colon according to the RCDAS

End point title	Radiologist's assessment of CD activity in the colon according to the RCDAS
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End point description:

Two investigators evaluated both CTE and MRE images of the colon from each patient. The evaluation was done using the RCDAS which for the colon includes 5 evaluations. The RCDAS score for the colon

can range between 0-12 points. For each investigator and patient, it was counted how many of the 5 evaluations were exactly the same (defined as "matches") when evaluating the CTE image and the corresponding MRE image. The percentage of matches was calculated and could range between 0% (no matching at all) and 100% (perfect matching). The mean percentage of matches was calculated between both investigators and for all patients, and this mean value was defined as the primary endpoint.

The null hypothesis for this variable was that the percentage matches would be $\leq 80\%$. At a pre-defined significance level of 2.5%, the results were not statistically significant ($p=0.1456$, Wilcoxon signed rank test (exact version)).

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

End point values	Per Protocol Analysis Set (PPAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: percent				
arithmetic mean (standard deviation)	83.13 (\pm 15.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Non-inferiority of CTE RCDAS (alternative non-inferiority analysis)

End point title	Non-inferiority of CTE RCDAS (alternative non-inferiority analysis)
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End point description:

In an alternative non-inferiority analysis, a non-inferior RCDAS item score was defined as the RCDAS item score from the CTE examination which is equal to or higher than the item score from the MRE examination.

The null hypothesis for this variable was that the percentage of non-inferior item scores would be $\leq 80\%$ and at a pre-defined significance level of 2.5% (one-sided test), the results were statistically significant ($p<0.0001$, Wilcoxon signed rank test (exact version)).

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

End point values	Per Protocol Analysis Set (PPAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: percent				
arithmetic mean (standard deviation)	94.44 (± 6.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total RCDAS score

End point title	Total RCDAS score
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End point description:

The total RCDAS, consisting of 18 evaluations, based on the CTE assessment was compared with the same score based on the MRE assessment and the difference between the 2 scores was calculated. By definition, the total RCDAS score can range between 0-34 points. The difference between the 2 scores was the endpoint. The scores were calculated as the mean scores between the two assessing investigators. All non-missing assessments were used when calculating the total RCDAS score. In the per protocol set, there was a mean (SD) difference of 1.21 (2.28) points between the 2 scores. The difference between the scores was statistically significant ($p < 0.0003$, Wilcoxon signed rank test (exact version), two-sided using a significance level of 5%). Although the total RCDAS score was generally higher according to the CTE examination, there were also patients who had lower CTE-based RCDAS scores than MRE-based RCDAS scores as the difference between the scores ranged from -4.0 points to 8.0 points.

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

End point values	CTE – Lumentin® 44	MRE – Movprep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: Total RCDAS score				
arithmetic mean (standard deviation)	5.82 (± 4.44)	4.60 (± 4.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total supplementary MRE/CTE score

End point title	Total supplementary MRE/CTE score
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End point description:

The total score of all the bowel locations of the supplementary MRE/CTE evaluation based on the CTE assessment was compared to the corresponding score based on the MRE assessment. Per definition, the total supplementary MRE/CTE-L score can range between 2-266 points. The difference between the 2 scores was the endpoint. Unassessable parameters were given the value of 0 when the total score was

summarized.

In the per protocol set, there was a mean (SD) difference of 5.8 (10.3) points between the 2 scores. The difference between the scores was statistically significant ($p < 0.0002$, Wilcoxon signed rank test (exact version), 2-sided using a significance level of 5%). Although the total supplementary score was generally higher according to the CTE examination, there were also patients who had lower CTE-based supplementary scores than MRE-based supplementary scores as the difference between the scores ranged from -21 points to 30 points.

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

End point values	CTE – Lumentin® 44	MRE – Movprep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: Total supplementary score				
arithmetic mean (standard deviation)	15.9 (± 12.3)	10.1 (± 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall disease activity according to the CDMRIS scale

End point title	Overall disease activity according to the CDMRIS scale
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End point description:

The CTE and MRE images were assessed for inflammation by a radiologist and the CDMRIS score was calculated based on how many 20 cm-segments of the SB exhibited defined signs of inflammation. The CDMRIS score can range between 0-120 points. The total CDMRIS score for all segments based on the CTE assessment was compared to the total CDMRIS score for all segments based on the MRE assessment. The difference between the 2 scores was the endpoint.

The difference between the CDMRIS scores was calculated for 47 patients (per protocol set). There was a difference of 0.9 (2.9) points. The difference between the scores was statistically significant ($p = 0.0173$, Wilcoxon signed rank test (exact version, two-sided using a significance level of 5%).). Although the CDMRIS score was generally higher according to the CTE examination, there were also patients who had lower CTE-based CDMRIS scores than MRE-based CDMRIS scores as the difference between the scores ranged from -7 points to 8 points.

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

End point values	CTE – Lumentin® 44	MRE – Movprep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: CDMRIS score				
arithmetic mean (standard deviation)	3.2 (± 3.6)	2.4 (± 3.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal ileum disease activity according to the CDMRIS scale

End point title	Terminal ileum disease activity according to the CDMRIS scale
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End point description:

To assess disease activity specifically in the terminal ileum, the CDMRIS sub-score was calculated separately based on signs of inflammation in this segment using CTE and MRE images. Per definition, the CDMRIS sub-score for the terminal ileum can range between 0-6 points. The CDMRIS sub-score for the terminal ileum based on the CTE assessment was compared to the sub-score based on the MRE assessment. The difference between the 2 sub-scores was the endpoint.

The difference between the CDMRIS sub-scores was calculated for 47 patients (per protocol set). There was a difference of 0.2 (1.2) points. This was not statistically significant ($p=0.1648$, Wilcoxon signed rank test (exact version), two-sided using a significance level of 5%).

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

End point values	CTE – Lumentin® 44	MRE – Movprep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: CDMRIS score				
arithmetic mean (standard deviation)	1.7 (± 1.5)	1.5 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall tissue damage according to the Lémann Index

End point title	Overall tissue damage according to the Lémann Index
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End point description:

Overall tissue damage was evaluated by one radiologist according to the Lémann Index based on morphological signs of stricturing and penetrating lesions in different SB segments. The Lémann Index can range between 0-158 points. The Lémann Index based on the CTE images was compared to the Lémann Index based on the MRE images.

In the per protocol set, there was a difference between the Lémann Indexes of 2.4 (4.9). The difference was statistically significant ($p<0.0001$, Wilcoxon signed rank test (exact version), two-sided using a

significance level of 5%).

End point type	Secondary
End point timeframe:	
Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.	

End point values	CTE – Lumentin® 44	MRE – Movprep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: Lehmann Index				
arithmetic mean (standard deviation)	4.8 (± 5.2)	2.4 (± 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Capsule examination: Correlation between CTE RCDAS for SB and modified LS (disease severity) for SB

End point title	Capsule examination: Correlation between CTE RCDAS for SB and modified LS (disease severity) for SB
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End point description:

For the 9 patients in the subset who had the optional capsule examination performed, disease severity was assessed using the Lewis score (LS).

The Spearman's rank correlation was used to calculate the correlation between the CTE RCDAS for SB (0-22 points) and the LS (defined as the highest LS among the scores for the 3 segments proximal SB, middle SB, and distal SB; 0-8000 points).

For the 9 patients in the subset, the mean (SD) RCDAS for the SB was 2.94 (3.82). The mean (SD) LS was 517.4 (1085.0), where the LS was defined as the highest score of the LS for the 3 segments (i.e., proximal SB, middle SB and distal SB). The mean (SD) LS for the individual SB segments was 8.3 (25.0) for the proximal SB, 0.0 (0.0) for the middle SB, and 509.1 (1089.1) for the distal SB. The mean (SD) of the mean LS across all 3 SB segments (proximal, middle, and distal SB) was 172.5 (361.7); the mean (SD) of the median LS across the 3 SB segments was 0.0 (0.0).

End point type	Secondary
End point timeframe:	
Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. The optional capsule examination took place on Visit 6 (Day 42) in the trial. Visit windows were allowed.	

End point values	Per Protocol Analysis Set (PPAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Correlation				
number (not applicable)	0.55			

Statistical analyses

No statistical analyses for this end point

Secondary: Ultrasound examination: Correlation between the total CTE RCDAS score and the ultrasound composite score

End point title	Ultrasound examination: Correlation between the total CTE RCDAS score and the ultrasound composite score
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End point description:

For the 40 patients in the subset who had an ultrasound (US) examination performed, the adjusted US composite score (range 0-80) and the adjusted US composite score excluding the caecum (range 0-60) were calculated.

The Spearman's rank correlation was used to calculate the following 2 correlations:

1 Correlation between the total CTE-L RCDAS score (0-34 points) and the adjusted US composite score (calculated as the sum of the 4 non-missing segment scores for jejunum, ileum, terminal ileum and caecum; 0-80 points)

2 Correlation between the CTE-L RCDAS for SB (0-22 points) and the adjusted US composite score excluding the caecum (0-60 points)

For the 40 patients in the subset who had the US examination performed, the mean (SD) total CTE RCDAS was 5.9 (4.3), and the mean (SD) CTE RCDAS for the SB was 5.2 (3.9). The mean (SD) adjusted US composite score was 5.6 (3.7) and the mean (SD) adjusted US composite score excluding the caecum was 5.3 (3.8).

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. The optional ultrasound examination took place on the End of Study Visit (Visit 5 or 7, Day 49 or 63) in the trial.

Visit windows were allowed.

End point values	Per Protocol Analysis Set (PPAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: Correlation				
number (not applicable)				
total CTE RCDAS vs adj. US comp. score	0.67			
SB CTE RCDAS vs adj. US comp. score excl. caecum	0.68			

Statistical analyses

No statistical analyses for this end point

Secondary: Patients' assessment of contrast agent

End point title	Patients' assessment of contrast agent
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End point description:

The patients were asked to assess the contrast agents Lumentin 44 and Movprep in terms of smell, taste, consistency, ability to swallow and fullness. The assessments were evaluated and summarised using descriptive statistics in the full analysis set.

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

End point values	CTE – Lumentin® 44	MRE – Movprep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: Rating				
Smell: Very negative	1	0		
Smell: Negative	5	1		
Smell: Neutral	22	30		
Smell: Positive	17	16		
Smell: Very positive, good	9	5		
Smell: Missing	0	1		
Taste: Very negative	3	2		
Taste: Negative	15	9		
Taste: Neutral	22	19		
Taste: Positive	9	17		
Taste: Very positive, good	5	5		
Taste: Missing	0	1		
Consistency: Very negative	11	0		
Consistency: Negative	17	2		
Consistency: Netral	16	20		
Consistency: Positive	9	21		
Consistency: Very positive, good	1	9		
Consistency: Missing	0	1		
Ability to swallow: Very difficult	12	2		
Ability to swallow: Difficult	17	5		
Ability to swallow: Medium	19	16		
Ability to swallow: Easy	5	24		
Ability to swallow: Very easy	1	5		
Ability to swallow: Missing	0	1		
Fullness: Very full	21	3		
Fullness: Full	18	16		
Fullness: Medium full	12	26		
Fullness: Barely full	2	7		
Fullness: Not at all full	1	0		
Fullness: Missing	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Contrast agent volume and time to drink

End point title	Contrast agent volume and time to drink ^[2]
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End point description:

The volume of the contrast agent Lumentin 44, consumed at CTE examination, and the time it took to drink the contrast agent were summarised descriptively. In the per protocol set, the volume of Lumentin 44 foam consumed at CTE examination ranged from 460 mL to 1763 mL for individual patients, and the time to drink the foam ranged from 35 min to 105 min.

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial. Visit windows were allowed.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Contrast agent volume and time to drink was only investigated for Lumentin 44 as part of the characterisation of the new product's properties in patients with Crohn's disease. The rationale behind this approach is that transit times through the gastrointestinal channel varies not only inheritably from one individual to another, but is also influenced by bowel diseases and lesions, and by ongoing pharmaceutical treatments.

End point values	CTE – Lumentin® 44			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: unit as in category				
arithmetic mean (standard deviation)				
Volume of foam drunk (ml)	1094.8 (± 367.4)			
Time to drink (min)	53.5 (± 11.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bowel filling properties of Lumentin 44

End point title	Bowel filling properties of Lumentin 44 ^[3]
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End point description:

The CTE images of 47 patients (per protocol set) were assessed by a radiologist with respect to the bowel filling properties of Lumentin 44 in 5 sub-segments (duodenum, jejunum, proximal ileum, distal ileum, and terminal ileum) of the SB. Extension and distension scores (each ranging from 1 to 9) were calculated for the individual sub-segments and total extension and distension scores (each ranging from 5 to 45) were calculated.

The mean (SD) extension was in the duodenum 5.3 (2.3), in the jejunum 7.3 (1.8), in the proximal ileum 8.3 (1.2), in the distal ileum 8.0 (1.7), and in the terminal ileum 7.0 (3.0).

The mean (SD) distension was in the duodenum 4.6 (2.0), in the jejunum 5.7 (1.5), in the proximal ileum 7.2 (1.0), in the distal ileum 7.2 (1.4), and in the terminal ileum 6.3 (2.6).

End point type	Secondary
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End point timeframe:

Radiologic examinations (CTE and MRE) took place on Visit 2 (Day 14) and Visit 4 (Day 28) in the trial.

Visit windows were allowed.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Bowel filling properties was only investigated for Lumentin 44 as part of the characterisation of the new product's properties. CD affects primarily the distal parts of the small bowel. It is therefore important to guarantee that the various per-oral contrast agents used in MRE and CTE reach down to and fill the distal and terminal loops of ileum.

End point values	CTE – Lumentin® 44			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Total score				
arithmetic mean (standard deviation)				
Extension	35.8 (± 7.1)			
Distension	30.9 (± 6.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of intake of study medication and 14 days after each treatment or until the next investigational product was administered, whichever occurred first.

Adverse event reporting additional description:

Treatment emergent adverse events reported during the trial were to be summarized using the safety population (all subjects who received at least some portion of Lumentin 44).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	CTE – Lumentin® 44
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Reporting group description:

Before CTE-examination, subjects received Lumentin 44 in volumes of 1.3-1.8 L, which should be taken orally within 1-1.5 hour prior to examination. The final dose and time of administration depended on the time to fill the terminal ileum. Low radiation scout views on CT were taken to confirm that the terminal ileum was full.

Reporting group title	MRE – Movprep®
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Reporting group description:

Before MRE-examination, subjects received Movprep, which should be taken orally within 1-1.5 hour. The final dose and time of administration depended on the time to fill the terminal ileum. The motility was monitored on MRI to confirm that the terminal ileum was full.

Serious adverse events	CTE – Lumentin® 44	MRE – Movprep®	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 55 (3.64%)	0 / 54 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma	Additional description: A large liver mass with extrahepatic metastases was incidentally discovered during the CTE examination		
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction	Additional description: Recurrent intermittent mechanical bowel obstruction		
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CTE – Lumentin® 44	MRE – Movprep®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 55 (36.36%)	20 / 54 (37.04%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 55 (18.18%)	16 / 54 (29.63%)	
occurrences (all)	10	16	
Nausea			
subjects affected / exposed	3 / 55 (5.45%)	3 / 54 (5.56%)	
occurrences (all)	3	3	
Flatulence			
subjects affected / exposed	2 / 55 (3.64%)	2 / 54 (3.70%)	
occurrences (all)	2	2	
Abdominal pain upper			
subjects affected / exposed	1 / 55 (1.82%)	2 / 54 (3.70%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	1 / 55 (1.82%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Crohn's disease			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			

subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	1 / 54 (1.85%) 1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 55 (1.82%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2020	<p>Change of PI.</p> <p>Secondary objectives (CTP Section 6.2) updated: Addition of two secondary objectives:</p> <ul style="list-style-type: none">• To compare the RCDAS results from CT enterography performed with Lumentin 44 as a bowel filling contrast agent, with the PillCam examination from a subgroup of patients who have not displayed a significant change in disease activity, defined as a change of one or more incremental steps in the PGA.• To compare the RCDAS from CTE performed with Lumentin 44 as a bowel filling contrast agent, with the ultrasound examination results from a subgroup of patients who have not displayed a significant change in disease activity, defined as a change of one or more incremental steps in the PGA. <p>Reason: Endpoints added to include evaluation of the patients' disease activity in the context of capsule and ultrasound examination.</p> <p>Exploratory objectives (CTP Section 6.3) added: Evaluation of stress and anxiety.</p> <p>Sections updated: Procedures for evaluating CTE and MRE images (CTP Section 10.1.1)</p> <p>Gastroenterologist's qualitative assessment of the Radiologist Crohn's Disease Evaluation of the MRE and CTE examinations (CTP Section 10.1.2)</p> <p>Gastroenterologist's assessment of the capsule examinations (CTP Section 10.1.6)</p> <p>Reason: Clarification added that there should be at least one month between the assessment of an individual patient's CTE and MRE images by the same radiologist to avoid, that findings from the first assessment influence the second assessment.</p> <p>Other minor changes and clarifications.</p> <p>Adverse event (CTP Section 10.3.1):updated: Untoward medical occurrences occurring prior to the MRE and/or CTE examinations or in relationship with the capsule or ultrasound examinations will not be reported as an AE.</p> <p>Reason: Clarification added that only AEs occurring in relation to procedures for which Lumentin 44 is indicated should be reported. The capsule and ultrasound examinations are standard commonly used procedures and Lumentin is not used during any of these procedures.</p>
20 April 2020	<p>A temporary halt in recruitment due to the COVID-19 pandemic.</p> <p>The amendment was submitted on 20 April 2020. No approval was received (this is documented in the Trial Master File).</p>
13 September 2020	<p>Restart of recruitment.</p> <p>Risk-benefit assessment (CTP Section 5.4) updated: The increased risk, for patients participating in the trial, of contracting COVID-19 is considered low. Patients with CD are not considered a risk group for infection with SARS-CoV-2 or severe COVID-19 illness.</p> <p>All patient visits to the hospital will occur in facilities which are not used for patients with COVID-19. Recommended procedures to prevent COVID-19 infection, as recommended by the Swedish Public Health Agency, will be followed. The Follow-Up visit will be conducted as a telephone call for those patients that declines to perform the ultrasound examination.</p> <p>Reason: To account for possible risks associated with participation in the trial during the COVID-19 pandemic. Description of risk mitigation strategy.</p> <p>Adverse events (CTP Section 10.3.1) updated.</p> <p>Reason: Clarification of the AE recording period.</p>

05 February 2021	<p>Preparation in advance of CTE and MRE examination (CTP Section 9.6.1) updated: New routines with respect to bowel cleansing before MRE was implemented as of November 2020. Patients will only have to fast for 6 hours prior to the examination. Clear liquid is allowed. Rectal cleansing is no longer required. MRE is performed according to the hospital's procedure and the change in procedure is not expected to influence the quality of the MRE images. Reason: Updated to reflect current standard routines at the clinic.</p> <p>Procedures for evaluating CTE and MRE images (CTP Section 10.1.1) updated with new text: Supplementary Assessment of MRE/CTE, described as "All CTE and MRE images will be assessed by a radiologist according to a supplementary MRE/CTE evaluation. The supplementary MRE/CTE evaluation will be used together with the RCDAS in the gastroenterologist's qualitative assessment of the Radiologist Crohn's Disease evaluation of the MRE and CTE examinations." Specifications of parameters to be assessed included. Reason: To provide the gastroenterologist with more detailed clinically relevant information to be taken into account when performing the gastroenterologist's qualitative assessment and comparison of the MRE and CTE examinations. The following sections were updated with detailed instructions on how the different assessments should be performed: Gastroenterologist's qualitative assessment of the Radiologist Crohn's Disease Evaluation of the MRE and CTE examinations (CTP Section 10.1.2); Radiologist's assessment of MRE and CTE images with respect to overall disease damage according to the Lémann Index (CTP Section 10.1.5); Gastroenterologist's assessment of the capsule examinations (CTP Section 10.1.6); Gastroenterologist's assessment of the ultrasound examination (CTP Section 10.1.7); and Bowel filling properties (extension and distension) as evident from CTE in each of 5 selected sub-segments of the SB (CTP Section 10.1.8).</p>
23 October 2021	<p>Sections updated: Planned sample size and number of trial centres (CTP Section 8.4) and Determination of sample size (CTP Section 13.4): Number of patients planned to be randomised increased from 55 to 60 to account for a drop-out rate of 20% rather than 10%. Reason: Updated to account for a larger drop-out rate than initially expected.</p> <p>Sections updated: Administration (CTP Section 9.2), Preparation in advance of CTE and MRE examination (CTP Section 9.6.1), CTE examination (CTP Section 9.6.2), MRE examination (CTP Section 9.6.3): Clarifications added that CT and MRE examinations will not be performed if the respective contrast agent has not filled the terminal ileum. Reason: The terminal ileum needs to be filled with contrast agent to achieve good image quality.</p> <p>Substantial Amendment 6 – Amendment date: 21 February 2023 NOTE: This amendment could not be entered as a separate amendment as it was not accepted by the system due to the late amendment date (later than the global end of the trial date).</p> <p>Amendment description: Section updated: Adverse Events (CTP section 13.3.4) Clarification added that: All AEs will be summarised per investigational product i.e. during a 2-week period after each investigational product or until the next investigational product is administered, whichever occurs first. Reason: Clarification of Adverse Event summarisation in previous non-substantial amendment.</p> <p>Addition of previous non-substantial amendment.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported