CLINICAL TRIAL PROTOCOL

An open, randomized, controlled, single centre trial to evaluate CT image quality and diagnostic feasibility of Lumentin® 44, a new egg albumen based oral bowel filling agent, in comparison with diluted Omnipaque® and Movprep®, two commonly used agents in subjects referred for abdominal CT-examination.

Sponsor:	Lument AB Olof Böök Scheelevägen 22 Box 719 SE-220 07 Lund Sweden
Clinical Research Organization:	Q Clinical Research Consulting AB Johan Quensel Lärarvägen 12 SE-247 45 Torna Hällestad Sweden
Investigator	Dr. Peter Leander Verksamhetsområde Bild och funktion Skånes Universitetssjukhus Inga Marie Nilssons gata 49 SE-205 02 Malmö Sweden
Sponsor Protocol No.:	LUM-001
Protocol Version	4.0
EudraCT No.:	2017-002368-42
Trial Drug Name:	Lumentin® 44
Development Phase:	II
Date of Protocol:	05 July 2018
Date of Previous Protocol:	11 December 2017

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: An open, randomized, controlled, single centre trial to evaluate CT image quality and diagnostic feasibility of Lumentin® 44, a new egg albumen based oral bowel filling agent, in comparison with diluted Omnipaque® and Movprep®, two commonly used agents in subjects referred for abdominal CT-examination.

This trial protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, revised 2013, and the guidelines on Good Clinical Practice (GCP).

6/7/2018

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05 JUL 2018

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Date

Declaration of the Investigator

Title: An open, randomized, controlled, single centre trial to evaluate CT image quality and diagnostic feasibility of Lumentin® 44, a new egg albumen based oral bowel filling agent, in comparison with diluted Omnipaque® and Movprep®, two commonly used agents in subjects referred for abdominal CT-examination.

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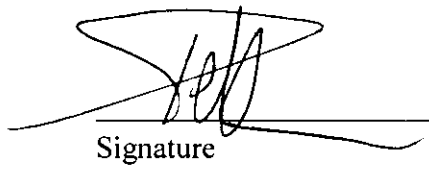

Signature

2018-07-05

Date

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Declaration of the Sub-Investigator

Title: An open, randomized, controlled, single centre trial to evaluate CT image quality and diagnostic feasibility of Lumentin® 44, a new egg albumen based oral bowel filling agent, in comparison with diluted Omnipaque® and Movprep®, two commonly used agents in subjects referred for abdominal CT-examination.

All documentation for this trial that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this trial protocol, Investigator's Brochure, Case Report Forms (CRFs), and other scientific data.

The trial will not be commenced without the prior written approval of a properly constituted Independent Ethics Committee (IEC). No changes will be made to the trial protocol without the prior written approval of the Sponsor and the IEC, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Sub-Investigator of the local trial centre

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

1 PROTOCOL SYNOPSIS

Title:	An open, randomized, controlled, single centre trial to evaluate CT image quality and diagnostic feasibility of Lumentin® 44, a new egg albumen based oral bowel filling agent, in comparison with diluted Omnipaque® and Movprep®, two commonly used agents in subjects referred for abdominal CT-examination.
Indication:	Subjects referred to computed tomographic X-ray examination of the abdomen or thoraco-abdominal CT-examination
Phase of development:	II
Primary objective	To compare the mean difference in contrast density shown on abdominal CT-images when using the contrast agent Lumentin® 44, with abdominal CT-images using diluted Omnipaque® and with abdominal CT-images using Movprep®
Secondary objectives	– To describe and compare the ability of Lumentin® 44 to fill the bowel as compared to Movprep® and diluted Omnipaque®. – To describe and assess how Lumentin® 44 influences reading of the abdominal CT-examination as compared to Movprep® and diluted Omnipaque® with respect to: o Diagnostics with particular regard to parenchymal organs, lymphatic system and tissue compartments beyond the gastrointestinal tract – To investigate signs of degradation of Lumentin® 44 in terms of o Coalesence o Syneresis or drainage – Describe and compare the ability to eat/drink for each of three contrast agents with respect to: o Taste o Smell o Consistency o Ability to swallow o Fullness – Validity and repeatability of the primary endpoint – To evaluate safety and tolerability after oral administration of each of three contrast agents

Assessments	**Mean difference in contrast density** The contrast will be assessed by both the investigator and the sub-investigator, independently of each other, in the small bowel and expressed in Hounsfield Units (HU). The difference in contrast density between lumen and wall (mucosal lining) will be measured in 9 locations of the small bowel as described below. The small bowel is divided in 6 sub-segments and defined as follows: – Duodenum is defined as the first part of small bowel down to ligament of Treitz; – Jejunum identified by its typical feathery mucosal pattern on Abd-CT – The small bowel between the jejunum and terminal ileum is visually divided into three parts: ○ Proximal ileum is approximately defined as 30 cm / 4 loops of small bowel following jejunum ○ Distal ileum is approximately 30 cm / 4 loops proximal to terminal ileum – Terminal ileum is defined as the last 15 cm of ileum mounding into the ileo-cecal valve The difference in contrast density is measured in two sites of each of 4 of the defined sub-segments: duodenum, jejunum, proximal ileum, and distal ileum, and in the terminal ileum where (due to its shortness in length) only one site is selected. Two regions of interest (ROI) measuring 6 mm in diameter will be selected by the investigator in the lumen of each segment except in the terminal ileum where only one region is selected. The ROIs will be placed where the lumen is best shown in the CT-image. The CT-scan software will provide a mean HU measurement of each of the selected ROIs and the values will be recorded by the investigator. The HU of the wall will be set to +80HU as a standard for all measurements. It is not possible to discriminate between the lumen and the wall when Movprep® and Diluted Omnipaque® is used as contrast agents as they have a contrast similar to the wall contrast. In each segment, the difference in contrast density between bowel lumen and wall will be calculated by subtracting the pin point HU value(s) of the wall (set to +80HU) from the mean ROI HU value(s) of the lumen. Two differences in contrast density values will thus be generated for each segment except in the terminal ileum where only one value is generated.

	The mean difference in contrast density in the small bowel is the sum of the differences in contrast density values (9 calculated values based on the observation of the investigator and 9 based on the sub-investigator observations, ie. In all 18 observations) divided by 18. All segments to which the contrast agent has not reached and thus, the contrast cannot be measured will not be included in the mean difference. The sum of the differences will in this case be divided by the number of measurable observations. The ability to fill the bowel will be investigated as a secondary objective, see below section 10.1.2 **Evaluation of ability to fill the bowel** The bowel filling agent will be distributed along the length of small bowel, i.e. the **extension**, but also cause a local widening of the bowel loop, **distension**. The filling of each of the 5 selected sub-segments of the small bowel in terms of extension and distension will be examined on the CT-scan both the investigator and the sub-investigator, independently of each other, and graded using Likert scales between 1 and 9. **Extension scale:** 1. no sign of contrast agent; 2. trace of contrast agent filling 3. segment filled to ca. 25% 4. segment filled to >25% but <50% 5. filled to segment filled to 50% 6. segment filled > 50% but <75% 7. segment filled to ca. 75% 8. segment filled to >75% but <100% 9. segment filled to 100% The Extension score will be the sum of the grades both assessors and in each sub-segment and hence range from 10 to 90. **Distension scale:** 1. no identifiable contrast agent 2. a minimal amount of contrast agent is identified 3. small amount of contrast agent, insufficient for placing a ROI of 6 mm 4. amount of contrast agent just allowing for a ROI of 6 mm 5. medium filled bowel loop 6. slightly better than grade 5 7. good filling

	8. optimal filling 9. excellent or almost overdistended The Distension score will be the sum of the grades both assessors and in each sub-segment and range from 10 to 90. **Diagnostic ability when examining Abd-CT** Diagnostic ability when examining Abd-CT will be assessed on the CT-scan by both the investigator and the sub-investigator, independently of each other. The following features will be assessed: – Small bowl appearance – parenchymal organs, i.e. pancreas, ovaries, urinary bladder – mesenterium and oment using a Likert scales of 1-9 ranging, where: 1. impossible to observe details 5. medium 9. excellent resolution The Diagnostic ability score will be the sum of the scores from both assessors and range from 6 to 54. **Degradation of contrast agents** Degradation of Lumentin® 44 is founded on the two characteristics Coalesence and syneresis or drainage. **Coalesence:** 0. No bubbles visually detectable at the CT-scan 1. Bubbles visually detectable at the CT-scan **Syneresis or drainage:** 0. No syneresis or drainage, i.e. separation of air and liquid phases, observed 1. Syneresis or drainage observed Sign of degradation will be assessed on the CT-scan, by both the investigator and the sub-investigator, independently of each other, in each of the 5 selected sub-segments of the small bowel. Degradation of contrast agents score will be the sum of the scores from both assessors and in each sub-segment and range from 0 to 20.

	Ability to eat/drink the contrast agents Subjects will assess taste, smell, consistency, ability to swallow and fullness on a five degree-scale: 1. Very negative/Very difficult/very full 2. Negative/difficult/ full 3. Neutral/medium/medium full 4. Positive/easy/barely full 5. Very positive, good/very easy/not at all full. Subjects will be handed an assessment form, see appendix 2, to be filled out during the period when the contrast agents are consumed.
Primary efficacy variable	The mean difference in contrast density in HU, expressed as the mean of 9 measurements of contrast density differences between bowel lumen and wall (mucosal lining) performed in the 5 selected sub-segments of the small bowel.
Secondary efficacy variables	• Bowel filling properties (extension and distension) on Abd-CT in each of 5 selected sub-segments of the small bowel • Degradation (presence of bubbles and signs of sedimentation) on Abd-CT in each of 5 sub-segments of the small bowel • Diagnostic ability on Abd-CT of the parenchyma, lymphatic system and tissue compartments beyond the gastrointestinal tract. • Subject assessments of taste, smell, consistency, ability to swallow and fullness after swallowing the contrast agent
Safety variables	• Especially solicited adverse events (AEs), i.e. stomach ache, burping, letting go of wind, Nausea and sensation of fullness • Any treatment emerging adverse events • Any treatment emerging adverse drug reactions (ADR) • Safety laboratory evaluations (clinical chemistry) • The reasons for withdrawal from the trial
Investigational product, formulation, dosage and mode of administration:	Lumentin® 44 The final formulation of the foam will be prepared at the clinic within one hour prior to use. A volume of 1000 ml ± 200 ml will be taken orally during a period of 45 minutes - 1 hour.

Comparator products, formulation, dosage and mode of administration:	Diluted Omnipaque® 30 mg Omnipaque 240 mg I/mL dissolved with water to the final volume of 1 000 ml Approximately 1 000 ml, taken orally during a period of 30 minutes to 1 hour Movprep® Movprep® is distributed as two dose units, Unit A and Unit B. Dose Unit A and B is dissolved in 1000 ml water. Approximately 1 000 ml, taken orally during a period of 1/2 hour The final preparation of the investigational product, Movprep® and Diluted Omnipaque® will be performed at the clinic.

Trial design	An open, randomized, controlled, single centre phase 2 trial. The open trial design is a consequence of each individual contrast agent being easy to recognize by subjects through taste and consistency and by the reading radiologists because of the unique image grey-scale caused by each individual agent. Subjects referred for -abdominal CT-examination will be invited by letter to participate in the study. This invitation is added to the referral letter that informs them on day and time for the CT-examination. Referral letters are routinely sent out within 4 weeks prior to the examination. All subjects who has received an invitation letter will be contacted by phone by a study nurse. Those subjects who are interested in participating will be forwarded a full patient information sheet. Patients at the oncology departments at the hospital of Lund and Malmö will also be informed about the trial. Posters will be placed at the departments and invitation letters will be handed out to those interested. Subjects interested in participating in the trial will, upon arrival to the clinic at the day of CT examination, be fully informed about the trial by the investigator. Eligible subjects will sign the consent to participate prior to randomisation and any treatment related procedures. Subject demography, medical history and concomitant medication is recorded and a clinical chemistry blood sample is taken just prior to drinking the oral contrast agent. Lumentin® 44 is given in volumes of 0.8 to 1.2 L and Omnipaque® and Movprep® is given according to the general praxis of care at the department "Verksamhetsområde Bild och funktion Skånes Universitetssjukhus". At least 750 mL of Lumentin® 44 must be drunk. At least the recommended, according to the general praxis of care, volume of Omnipaque® and Movprep® must be drunk. The subjects will be asked to drink the solutions of oral contrast agents within one hour. During the time the contrast agent is drunk, the subjects will be asked to complete a questionnaire assessing taste, smell, consistency, fullness and ability to swallow the contrast agent. The CT-examination will be started within 10 minutes after the contrast agent has been drunk. The CT-examination lasts in average eight minutes. Just prior to the CT examination a standard dose of iodine contrast (Omnipaque® 350 mg I/mL) will be intravenously administered.

	A post- examination clinical chemistry blood sample is taken prior to the subject is leaving the clinic and occurrence of any adverse events is recorded. The subjects are free to leave the clinic after 30 minutes post CT-examination. For safety reasons, subjects will be contacted, within 12 to 48 hours after the examination, by the investigator and asked about occurrence of any adverse event. No other follow-up is planned.
Trial population	The trial population will consist of subjects who are referred to CT-examination of the abdomen. The subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.
Number of subjects	The target is to randomise 88 subjects with the goal to reach 80 evaluable subjects. However, due to the duration of the trial is only one day for the subject, randomisation will stop when 80 evaluable subjects have completed the trial. Randomisation will be skewed so that 40 subjects will be allocated to the Lumentin arm and 20 each to the Omnipaque and Movprep arms.
Main inclusion criteria	Subjects will be entered into this trial only if they meet all of the following criteria: 1. Subjects of either gender at least 18 years at the time of signing the informed consent. 2. Females must either present a negative pregnancy test or be surgically sterile (hysterectomy or tubal ligation) or postmenopausal (i.e. experienced 12 consecutive months without menstruation) 3. Having a clinical indication for CT-examination of the abdomen 4. Having fasted (drinking allowed) for at least four hours prior to the intake of the contrast agent 5. Patients participating in concurrent oncology trial must either participate in the follow up phase of the clinical trial and currently receive no trial drug treatment since at least 6 weeks, or receive a reduced maintenance dose of the trial treatment 6. Following verbal and written information about the trial, the subject must provide signed and dated informed consent before any trial related activity is carried out.

Main exclusion criteria	Subjects will not be enrolled if they meet any of the following criteria: 1. IV administration of iodine is contraindicated 2. Clinical suspicion, according to medical record, of fistula formation and/or leakage 3. Having swallowing disorders preventing intake of the contrast agents 4. Referral indication of small bowel disease(s) 5. Known allergy to egg albumen. 6. Known sensitivity to any of the components of the investigational product or comparators 7. Having known manifest thyrotoxicosis 8. Having known phenylketonuria 9. Having known Glucose-6-phosphatase deficiency 10. Has taken any medication, absorbed through the small bowel, less than four hours before intake of the investigational product or comparators 11. Being, in the opinion of the investigator, unlikely to comply with the clinical trial protocol 12. Previously randomised to participate in this trial 13. Participating in, or having participated in another, non-oncology clinical trial where the final trial treatment was given within the last 6 weeks 14. Participating in an oncology clinical trial where the final full (i.e. non-maintenance) trial treatment was given within the last 6 weeks

Statistical analyses	The sample size estimation is based on a similar variable as the primary variable in this trial, i.e. the difference in contrast density in HU between bowel lumen and wall (mucosal lining), expressed as the mean of 9 measurement performed in the 5 selected sub-segments of the small bowel. At each measurement site, the equipment gives a mean value (given by the software of the X-ray equipment in Hounsfield Units) and a standard deviation (for the pixels in the Region of Interest, ROI). This mean value is from now on called "mean contrast density". In order to reach a 78 % probability (power) to detect (i.e. get a two-sided p-value less than 5 %) assuming a difference of 1.50 between the groups for the mean difference in contrast density and a standard deviation of 2.00 (assumptions based on an earlier trial, [1]) a total of 40 fully evaluable is needed in the Lumentin group and 20 in each of the comparator groups, i.e. a total of 80 fully evaluable subjects The randomisation will be stratified by gender as the drinking capacity on average differs between males and females. Descriptive statistics will be used to describe the results. When testing the hypotheses of equality between the groups p-values (two-sided) will be calculated by means of the Wilcoxon rank sum test or Fisher's exact test depending on the distribution of the variable of interest.

1.1 Schedule of Events:

Visit/Contact	0 Screening [a)]	1 CT-scan	2 Telephone interview and early termination [b)]
Day	**-28 to -1**	**0**	**1-2**
Visit window			**12-48 hours**
Subject information	X	X	
In/exclusion criteria		X	
Informed consent		X	
Pregnancy test [c)]		X	
Randomisation		X	
Subject demographics (incl. height and weight)		X	
Concomitant treatment		X	X
Concomitant illnesses		X	
Medical history		X	
Blood sample (clinical chemistry) [d)]		X	
Adverse event(s)		X	X
Dispensing of contrast agent		X	
Administration of Iodine contrast		X	
CT Scan		X	
Evaluation of contrast difference		X	
Evaluation of extension and distension composite score		X	
Evaluation of diagnostic ability		X	
Evaluation of contrast agent degradation		X	
Subject assessment of taste, smell, consistency etc.		X	
Compliance		X	

a) No formal screening will be performed in the trial. However, since only one visit to the clinic is planned in this trial, all subjects will receive information regarding the trial prior to the clinic visit. Subjects will thus have time to consider participation and prepare questions, if needed.

b) Also in case a subject is withdrawn after intake of the contrast agent the Early Termination form should be completed.

c) Urine pregnancy test of all fertile females

d) Blood sample (2 mL) will include Na, K, Ca, P in serum and will be taken prior to intake of contrast agents and post CT-scan.

2 LIST OF TRIAL PERSONNEL

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Coordinating Investigator	Dr. Peter Leander Verksamhetsområde Bild och funktion Skånes Universitetssjukhus Inga Marie Nilssons gata 49 SE-205 02 Malmö Sweden Phone: +46 40 338910 Mobile phone: +46 768 871069 E-Mail: peter.leander@skane.se
Contract Research Organization 1 Responsible for monitoring	Q Clinical Research Consulting AB Lärarvägen 12 SE-247 45 Torna Hällestad Sweden Phone: +46 760 46 97 44 E-Mail: jq@qcrc.se
Monitor	Johan Quensel

Contract Research Organization 2 Responsible for Serious Adverse Event (SAE) Management and Data Management	A+ Science AB Luntmakargatan 22 SE-111 37 Stockholm Phone: +46 (735 24 04 26 E-Mail: info@a-plusscience.com
Safety Medical Monitor	Dr Janet Post +46 735 24 03 98
Adverse Event Reporting	Email: safety@a-plusscience.com (preferred) Fax: +46 8 28 41 22

3 TABLE OF CONTENT

Appendices

Tables in Text

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abd-CT	Abdominal-CT
ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
eCRF	electronic Case report form
CT	Computed tomography
DMF	Drug Master File
DRL	Drug Reference List
EWP	Egg white protein (also referred to as egg albumen)
FA	Full analysis
GCP	Good Clinical Practice
HU	Hounsfield units
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
ITT	Intention-to-treat
IV	Intra Venous
MRI	Magnetic Resonance Imaging
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
Ph. Eur.	European Pharmacopeia
PP	Per protocol
ROI	Region of Interest
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SUSAR	Serious unexpected suspected adverse reactions
TEAE	Treatment-emergent adverse event
V/V	Volume per volume
W/W	Weight per weight
WHO	World Health Organization

5 BACKGROUND

5.1 Introduction

Subjects referred for examination with computed tomography, CT, of the abdomen are, according to clinical practice, prepared with an oral liquid contrast for demarcating loops of small bowel from surrounding tissues and abdominal and pelvic organ. Most often these oral contrast-agents are based on iodine, so-called positive contrast agent, which results in a bright bowel content, i.e. an intraluminal appearance with positive Hounsfield units, HU. Other options include iso-osmotic solutions based on either polyethylene glycol or Sorbitol / Mannitol, creating luminal densities near that of water, i.e. around 10-20 HU, hence by rights denominated as neutral oral contrast agents. The rationale behind administering a neutral solution is to establish a boosted attenuation difference between the small bowel wall and its lumen, further increased by an intravenously administered iodine contrast. The amplified difference between small bowel wall and lumen might theoretically result in augmented conspicuity of the interface itself, thereby improving diagnostics of the mucosal lining and of lesions in the bowel wall and its proximity. This knowledge is implemented in CT protocols aiming at pancreatic cancer, where neutral contrast is recommended, especially in the papillary part of duodenum, in order to increase the probability of detection of small tumours. A high attenuation difference between small bowel lumen and mucosal lining is also a prerequisite for virtual 3D-presentation of the small bowel, similar to CT-colonoscopy.

An intensified small bowel wall is currently depicted on images acquired with magnetic resonance imaging, MRI, technique [2]. On a special MRI-sequence the small bowel lumen appears dark. After IV. gadolinium contrast administration, the small bowel wall with its mucosa stand out with increased signal intensity (bright), particularly in a case with inflammatory bowel disease. The induced contrast enhancement facilitates and improves diagnostics. Unfortunately, the availability of MRI equipment is limited compared to that of CT, and is therefore mostly reserved for young subjects with inflammatory bowel disease, for those who need repeated imaging, and for those with complicated diseases of the small bowel. Thus, most subjects with abdominal problems needing imaging are referred for abdominal-CT (Abd-CT). It would therefore be desirable to present CT-images with a dark small bowel lumen, as seen on certain MRI sequences. In order to allow for the odd and clinically silent small bowel lesion to be unveiled, a “black” bowel lumen would be advantageous in all subjects for Abd-CT. Scientists have been eager to pursue this idea since the 1980s. Furthermore, radiologists have for decades expressed a wish for a negative bowel contrast in order to improve diagnostics and tested several agents based on fat and bubbles. So far none has been clinically successful [3-12] while a number of side-effects were reported in association with oil-based contrasts such as abdominal cramps, diarrhoea and oily taste. Furthermore, many of these bowel filling agents have been denominated as being negative although they were assigned higher mean scores than water in each segment of the bowel, i.e. with positive HU. Still, the use of a neutral oral contrasts, with HU of around that of water, have been established in clinical routine due to improved CT-diagnostics.

5.2 Rationale

Lument AB have been successful in developing a food-based oral product, characterized by being a true negative CT-contrast agent by providing a density contrast down to minus 600 HU. Necessary demands included in the research work were palatability (taste, smell and consistency), stability during its passage through the upper gastro-intestinal tract, and acceptable side effect profile. After approval from the local Ethical Committee (Dnr. 2015/912) and Institute of Radiation Protection (Dnr. SSF02015-048) we successfully accomplished our first pilot clinical study [1] of abdominal CT examinations on healthy volunteers using a slightly different formulation containing 60% air as compared to the current formulation containing 44% air. The results showed that the foam provided true negative, black bowel lumen, from pylorus to cecum; good acceptance of the foam by the volunteers with only mild adverse events reported, and that the diagnostic reading of the CT-examination as a whole, with "black" loops of small bowel, was easily accepted by the radiologist.

Lumentin® 44

Lumentin® 44 is a novel, HU-negative contrast agent which is formulated as an aqueous dispersion containing less than 4% dry matter. The product consists of a continuous aqueous phase that contains egg white protein (EWP) as foaming agent, xanthan gum as stabilizer, phosphate salts as buffering agents, and flavouring.

Prior to use, the product is whipped to a stable foam, containing 44% air, which is orally administered. The whipped, ready to use, Lumentin® 44 foam formulation is stable with suitable characteristics (air content, volume, bubble size, homogeneity, consistency, stability and palatability). A typical dose for an Abd-CT examination is 1000 ml ± 200 ml taken orally over a period of 45 to 60 minutes.

The air trapped in the foam is the radiological key ingredient that causes improved bowel lumen-to-wall contrast, with the interface at the surface of the mucosal lining of the bowel wall. The external demarcation of the small bowel from surrounding organs is on par with standard filling agents used in Abd-CT examinations of today.

5.3 Risk-Benefit Assessment

All excipients in Lumentin® 44, expect EWP, are of pharmacopoeia quality (buffer and stabilizer) or belongs to a product range (flavor) registered under a Drug Master File (DMF) in the US, and widely used in pharmaceuticals. The EWP is widely used as a food ingredient.

The side effects reported in the pilot trial, by volunteers drinking up to 1.4 L of the preliminary formulation (containing 60% air) were mild and hence it is considered that L60 were well tolerated. Most common side effects observed were eructation, abdominal distension, and mild nausea.

Allergic reactions towards egg protein cannot be excluded and patients with a known sensitivity towards egg should not be exposed to Lumentin® 44.

Ingestion of a large volume of foam in a short time may have an effect on the resorption pattern of concomitant medications. Intake of other medications, which are absorbed in

the small bowel, and having a narrow therapeutic window, should be avoided within a period of four hours before and until one hour after administration of Lumentin® 44. The patients in the planned trial are all referred for routine abdominal CT examination. No direct benefit is expected for patients receiving Lumentin® 44 in this trial compared to those receiving Omnipaque® or Movprep®.

6 TRIAL OBJECTIVES

6.1 Primary Objective

To compare the mean difference in contrast density shown on abdominal CT-images when using the contrast agent Lumentin® 44, with abdominal CT-images using diluted Omnipaque® and with abdominal CT-images using Movprep®

6.2 Secondary Objectives

- To describe and compare the ability of Lumentin® 44 to fill the bowel as compared to Movprep® and diluted Omnipaque®.
- To describe and assess how Lumentin® 44 influences reading of the abdominal CT-examination as compared to Movprep® and diluted Omnipaque® with respect to:
    - Diagnostics with particular regard to parenchymal organs, lymphatic system and tissue compartments beyond the gastrointestinal tract
- To investigate signs of degradation of Lumentin® 44 in terms of
    - Coalesence
    - Syneresis or drainage
- Describe and compare the ability to eat/drink for each of three contrast agents with respect to:
    - Taste
    - Smell
    - Consistency
    - Ability to swallow
    - Fullness
- Validity and repeatability of the primary endpoint
- To evaluate safety and tolerability after oral administration of each of three contrast agents

7 OVERALL DESIGN AND PLAN OF THE TRIAL

7.1 Overview

An open, randomized, controlled, single centre phase 2 trial.

Blinding of the trial is not possible due to the clear differences in the features and properties of the contrast agents. Thus, subjects will be able to identify the contrast agent through taste and consistency and the investigators will be able to identify which contrast agent the subject has been given through its unique image grey-scale

Subjects referred for abdominal or thoracoabdominal CT-examination will be invited by letter to participate in the study. This invitation is added to the referral letter that informs them on day and time for the CT-examination. Referral letters are routinely sent out within 4 weeks prior to the examination. All subjects who has received an invitation letter will be contacted by phone by a study nurse. Those subjects who are interested in participating will be forwarded a full subject information about the trial and they will be asked to read it prior to the CT-examination visit.

Patients at the oncology departments at the hospital of Lund and Malmö will also be informed about the trial. Posters will be placed at the departments and invitation letters will be handed out to those interested.

Subjects still interested in participating in the trial will, upon arrival to the clinic at the day of CT examination, be fully informed about the trial by the investigator and given opportunity to ask questions. Eligible subjects will sign the consent to participate form prior to randomisation and any treatment related procedures.

Subject demography, medical history and concomitant medication will be recorded, and a clinical chemistry blood sample (2 mL) will be taken just prior to drinking the oral contrast agent.

Lumentin® 44 is given in volumes of 750 mL to 1 200 mL and Omnipaque® and Movprep® is given according to the general praxis of care at the department "Verksamhetsområde Bild och funktion Skånes Universitetssjukhus". At least 750 mL of Lumentin® 44 must be drunk. At least the recommended, according to the general praxis of care, volume of Omnipaque® and Movprep® must be drunk.
The subjects will be asked to drink the solutions of oral contrast agents within one hour.

Subjects not able to drink at least 750 mL of Lumentin® 44 or, at least the recommended dose of Omnipaque® and Movprep®; will be classified as major protocol violators and the subject will be excluded from all efficacy evaluations.

During the time the subjects drink the contrast agent, the subjects will be asked to complete a questionnaire assessing taste, smell, consistency, fullness and ability to swallow the contrast agent.

The CT-examination will be started within 10 minutes after the contrast agent has been drunk and the CT-examination lasts in average eight minutes.

The CT-equipment comes with a moving table and a fixed gantry in which the X-ray tube is rotating with 2 revs per sec. The subject will be placed in supine on the table with hands-over-head, and prone for dedicated examination of the bowels. The table is then moved into the gantry for exposure of the abdomen. Before the examinations starts, an intravenous injection of an iodine based contrast medium (Omnipaque® 350 mg I/mL) is given in order to enhance any existing lesion or disease. The dose is adjusted to body weight and kidney function and is usually given in the range of 60 to 115 mL of Omnipaque® 350 mg I/mL. The dose and batch number of iodine will be noted in the eCRF.
At contrast peak in the aorta, and an extra fixed delay of 50 seconds, altogether approximately one minute, exposure starts and the table moves ahead while the body part is continuously irradiated from the rotating X-ray tube. The whole procedure is finished within 10 seconds and images presented within 30 seconds. After a quality check of the

CT-examination and affirmation of the subject's well-being, the subject is free to leave the CT-scanner.
The subject shall remain at the clinic for at least 30 minutes post the intravenous injection of the iodine based contrast medium in case of the occurrence of sensitivity reaction.

A post- examination clinical chemistry blood sample (2 mL) will be taken prior to the subject will be leaving the clinic and occurrence of any adverse events will be recorded.

The subjects will thereafter be free to leave the clinic.

For safety reasons, subjects will be contacted, within 12 to 48 hours after the examination by the investigator and asked about occurrence of any adverse event. No other follow-up is planned.

7.2 Parameters

7.2.1 Primary Efficacy Variable

The mean difference in contrast density in HU, expressed as the mean of 11 measurements of contrast density differences between bowel lumen and wall (mucosal lining) performed in the selected 5 sub-segments of the small bowel.

7.2.2 Secondary Efficacy Variables

- Bowel filling properties (extension and distension) on Abd-CT in each of 5 selected sub-segments of the small bowel
- Degradation (presence of bubbles and signs of sedimentation) on Abd-CT in each of 5 sub-segments of the small bowel
- Diagnostic ability on Abd-CT of the parenchyma, lymphatic system and tissue compartments beyond the gastrointestinal tract.
- Subject assessments of taste, smell, consistency, ability to swallow and fullness after swallowing the contrast agent

7.2.3 Safety Variables

The safety parameters consist of:

- Especially solicited adverse events (AEs), i.e. stomach ache, burping, letting go of wind, Nausea and sensation of fullness

- Any treatment emerging adverse events
- Any treatment emerging adverse drug reactions (ADR)
- Safety laboratory evaluations (clinical chemistry)
- The reasons for withdrawal from the trial

7.3 Justification of the Trial Design

7.3.1 Justification for Design and Parameters

This trial is designed to document the efficacy of Lumentin® 44 to show contrast difference between the small bowel lumen and the small bowel wall (mucosal lining) as compared to the comparators and to investigate safety. A parallel groups design has been

chosen as a cross-over design is considered both unethical, for reason of irradiation, and logistically impossible.

Data from an explorative trial [1] clearly indicates that the foam provided bowel loops with a black lumen and a large difference in contrast density between the lumen and surrounding small bowel wall (mucosal lining). The diagnostic readability of CT-examinations was highly accepted by the radiologists. The foam was also able to fill the small bowel from pylorus to cecum on par with routinely used contrast agents and was well accepted by the subject with no serious adverse events. The observed adverse events were all mild with no need to intervene.

The primary efficacy variable has been defined to be able to observe the contrast difference between the small bowel lumen and the small bowel wall (mucosal lining) in the whole length of the small bowel. The ability of the contrast agent to fill the small bowel is therefore reflected in the primary efficacy variable.

Secondary objectives have been chosen to investigate the safety profile, the filling property of the contrast agent, the stability of Lumentin® 44 after administration, the diagnostic potential and how the patients experience the contrast agents properties with respect to taste, smell etc.

The trial is not designed to investigate Lumentin® 44 with respect to diseases of the small bowel. No patients eligible for this trial have a clinical suspicion of a bowel disorder, viz. the bowel contrast agents are only used for demarcating the small bowel on the CT-scans. The use of Lumentin® 44 in this trial will thus not influence any diagnostic performance of bowel diseases. Future trial with Lumentin® 44 will be designed to investigate the diagnostic potential for small bowel disorder with Abd-CT.

7.3.2 Justification for Drug, Route, Dosage and Treatment Duration

Comparators used in the trial are both standard care treatment used for patients referred to abdominal CT-scan examinations.
Subjects in a previous explorative trial [1] were given 0.9 -1.5 L foam to take orally and 23 out of the 25 subjects could consume more than 0.9 L of the foam. The small bowel filling properties of the foam was on par with the normally used contrast agents, diluted Omnipaque® and Movprep®. A dose of 1 000 ml $\pm$ 200 ml was therefore selected.
Both route and treatment duration are according to standard praxis.

8 TRIAL POPULATION

The trial population will consist of subjects who are referred to CT-examination of the abdomen. The subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.

8.1 Inclusion Criteria

Subjects will be entered into this trial only if they meet all of the following criteria:

1. Subjects of either gender at least 18 years at the time of signing the informed consent.
2. Females must either present a negative pregnancy test or be surgically sterile (hysterectomy or tubal ligation) or postmenopausal (i.e. experienced 12 consecutive months without menstruation)

3. Having a clinical indication for CT-examination of the abdomen
4. Having fasted (drinking allowed) for at least four hours prior to the intake of the contrast agent
5. Patients participating in concurrent oncology trial must either participate in the follow up phase of the clinical trial and currently receive no trial drug treatment since at least 6 weeks, or receive a reduced maintenance dose of the trial treatment
6. Following verbal and written information about the trial, the subject must provide signed and dated informed consent before any trial related activity is carried out.

8.2 Exclusion Criteria

Subjects will not be enrolled if they meet any of the following criteria:

1. IV administration of iodine is contraindicated
2. Clinical suspicion, according to medical record, of fistula formation and/or leakage
3. Having swallowing disorders preventing intake of the contrast agents
4. Referral indication of small bowel disease(s)
5. Known allergy to egg albumen
6. Known sensitivity to any of the components of the investigational product or comparators
7. Having known manifest thyrotoxicosis
8. Having known phenylketonuria
9. Having known Glucose-6-phosphatase deficiency
10. Has taken any medication, absorbed through the small bowel, less than four hours before intake of the investigational product or comparators
11. Being, in the opinion of the investigator, unlikely to comply with the clinical trial protocol
12. Previously randomised to participate in this trial
13. Participating in, or having participated in another, non-oncology clinical trial where the final trial treatment was given within the last 6 weeks
14. Participating in an oncology clinical trial where the final full (i.e. non-maintenance) trial treatment was given within the last 6 weeks

8.3 Subject Withdrawal and Replacement

Subjects may withdraw from the trial at any time and for any reason without prejudice to his or her future medical care.

Subjects must be withdrawn under the following circumstances:

- The subject withdraws consent,
- The subject is unable to drink at least 750 mL of Lumentin® 44 or at least the lowest recommended dose, according to the general praxis of care at the department of "Verksamhetsområde Bild och funktion Skånes Universitetssjukhus", of Omnipaque® and Movprep®
- Violation of eligibility criteria

Subjects may be required to withdraw after discussion with the Sponsor and/or Investigator for the following reasons:

- AEs,
- Use of prohibited medication (see Section 9.7),
- At the discretion of the Investigator,
- Violation of eligibility criteria,

In all cases, the reason(s) for withdrawal must be recorded on the eCRF. If a subject is prematurely withdrawn from the trial for any reason, the Investigator must make every effort to perform the evaluations described for the Early Termination Visit (see Section 12).

If a subject has withdrawn informed consent and still agrees to attend the Early Termination Visit, this will be documented on the eCRF.

For subjects who are withdrawn after they receive the trial drug, the Early Termination page will be completed in the eCRF.

Subjects who are withdrawn from the trial will be provided care according to the judgement of the investigator. Normal praxis at the clinic is to perform the CT-scan even if the subject cannot consume the recommended volume of the contrast agent.

Subjects who withdraw after randomisation will not be replaced.

8.4 Planned Sample Size and Number of Trial Centres

It is planned to randomise 40 evaluable subjects to the Lumentin arm and 20 subjects to each of the Omnipaque and Movprep arms. To cover for a 10% drop out rate a total of 93 subjects will be randomised.

Randomisation will be terminated when 40:20:20 evaluable subjects are reached in respective arm. See Section 13.6 for a discussion of sample size.

8.5 Subject Identification and Randomisation

Subjects referred to CT examination of the abdomen will receive an invitation to the CT examination by letter. An advertisement letter informing about the trial will be included in this referral letter.

All referrals for abdominal CT are read and prioritized by the investigator/sub-investigator. Those subjects, irrespective from which medical clinic, who the radiologist think are possible candidates for the trial, will have the advertisement letter added to the referral letter sent home to them with date and time for their CT-examination.

An invitation log will be kept with names of those receiving the advertisement letter. Subjects will subsequently be contacted by and asked if they are interested in participation. Those interested will be sent the subject information leaflet.

All subjects receiving the patient information leaflet will receive a screening number consisting of S followed by three digits: S-XXX starting with S-101.

The Investigator will allocate the screening numbers in ascending order.

Enrolled subjects who drop out of the trial before randomisation will retain their screening number.

Randomisation will occur at the clinic on the day of examination when all screening procedures have been performed and eligibility for the trial confirmed. Each randomised subject will receive a unique randomisation number consisting of R followed by three digits: R-XXX stating with R-101. Randomisation numbers will be allocated in strict ascending order according to a randomisation list

Randomised subjects who terminate their trial participation for any reason, regardless of whether trial drug was taken or not, will retain their randomisation number.

Subjects will be randomised on a 1:1:1 basis to Lumentin® 44, diluted Omnipaque® or Movprep®. The randomisation will be in blocks and stratified by gender as the drinking capacity differs between males and females.

9 INVESTIGATIONAL PRODUCTS

9.1 Investigational products

9.1.1 Lumentin® 44

Lumentin® 44 Dispersion will be manufactured and released by Bioglan AB, Borrgatan 31, 202 13 Malmö, Sweden.

Table 1: Lumentin® 44 Dispersion

Ingredients	Lumentin® 44 Dispersion
	Concentration (g/100g)
Egg White Powder	1.93
Sodium dihydrogen phosphate dihydrate ($NaH_2PO_4 \cdot 2H_2O$) [1]	0.19
Dibasic potassium phosphate (K_2HPO_4) [1]	0.63
Xanthan gum [1]	0.48
Flavour [2]	0.24
Water, purified [1]	96.53

1) *Ph. Eur.: European Pharmacopeia*
2) *The flavour mixture contains vanillin, Propylene Glycol (E1520) and water and belongs to a product range registered under a DMF in the US.*

Lumentin® 44 Foam

The final preparation of the investigational product, Lumentin® 44, will be performed at the clinic, see appendix 1, Lumentin® 44 dispersion whipping protocol
Lumentin® 44 contains the exact same ingredients as Lumentin® 44 Dispersion, see table 1, except for added air due to the whipping process.

9.1.2 Diluted Omnipaque®

Omnipaque® 240 mg I/mL is manufactured by GE Healthcare AS, Nycoveien 1-2, P.O. Box 4220 Nydalen, N-0401 Oslo, Norge.

Table 2: Omnipaque® 240 mg I/mL

Ingredients	Concentration (mg/mL)
Iohexol	518
Iodine equivalent	*240*
Tromethamine	1.21
Edetate calcium disodium	0.1
Hydrochloric acid	[1]
Sodium hydroxide	[1]

[1] For pH adjustment only

Diluted Omnipaque®
30 ml of Omnipaque® 240 mg I/mL will be mixed with 970 ml water.
The final preparation of the investigational product, diluted Omnipaque®, will be performed at the clinic.

9.1.3 Movprep®

Movprep® is distributed by Norgine BV, Hogehilweg 7, 1101CA, Amsterdam ZO, The Netherlands.
Movprep® is distributed as two dose units, Unit A and Unit B.

Table 3: Movprep®

Ingredients	Content (g)
Unit A	-
- Macrogol 3550	100
- Sodium Sulphate, waterfree	7.500
- Sodium Chloride	2.691
- Potassium Chloride	1.015
Unit B	-
- Ascorbic Acid	4.700
- Sodium Ascorbate	5.900

Preparation of Movprep®

Dose Units A and B are dissolved in 1000 ml water.
The final preparation of the investigational product, Movprep® will be performed at the clinic.

9.2 Administration

The Investigational products will be taken orally by the subject during a period of 30 minutes - 1 hour.

Lumentin® 44

A volume of 1000 ml ± 200 ml shall be consumed. A steady intake rate of the contrast agent is recommended and the time period of intake should be 45 minutes - 1 hour.

The subject will be withdrawn from the trial if the maximum volume of the Investigational product taken by the subject is less than 750 mL.

There is no risk of overdose.

Diluted Omnipaque® and Movprep®

The volume of **Omnipaque® and Movprep®** consumed will be according to the standard of care praxis at the department of "Verksamhetsområde Bild och funktion Skånes Universitetssjukhus". A steady intake rate of the contrast agent is recommended, and the time period of intake should be 30 minutes – 1 hour.

The subject will be withdrawn from the trial if the maximum volume of the Investigational product taken by the subject is below the recommended dose.

9.3 Packaging, Labelling and Storage

The Lumentin® 44 dispersion will be filled in 1.5L PET jars with white plastic screw-caps at Bioglan AB. The head-space above the dispersion will be filled with Argon gas, which is an inert gas that acts as preservative due to its antioxidant and antimicrobial properties.

The jars will be packed in aluminium laminated plastic bags which will be filled with argon and immediately sealed. The containers in their outer bags will be placed in a cardboard box to protect them during transport and storage.

All Lumentin® 44 dispersion supplies must be stored and transported under 2-8°C. Lumentin® 44 dispersion will be transported to the site upon request. Until final preparation and dispensing to the subjects, the Lumentin® 44 dispersion will be stored in a refrigerator, accessible to authorised personnel only.

Omnipaque® 240 mg I/mL and Movprep® will be stored in room temperature in a restricted area, accessible to authorised personnel only.

Packaging and labelling of the contrast agents will be performed by Bioglan AB in accordance with applicable regulatory requirements.

9.4 Blinding and Breaking the Blind

Not Applicable. The trial is an open label trial.

9.5 Drug Accountability

The Investigator is responsible for maintaining accurate investigational product accountability records throughout the trial.

Each dispensing of investigational product will be documented in the drug accountability log and the eCRF.

The height of the Lumentin® 44 foam in the PET jar will be measured prior to dispensing it to the subjects. The weight of all three contrast agents will be measured prior to dispensing as well as after intake. Height and weights will be and noted in the eCRF Drug accountability will be carried out at regular intervals, as specified in the monitoring plan.

All unused investigational product (Lumentin® 44 dispersion) will be returned to Bioglan AB for destruction at the end of the trial. The Sponsor will be provided with the documentation of destruction of unused investigational product.

9.6 Drug Exposure and Compliance

All containers will be weighed before they are dispensed to the subject and again when returned by the subject and these weights (in gram) will be recorded in the eCRF.

Drug exposure will be estimated based on the weight of ingested contrast agent and the weight of the subject.

Data from this trial will be used to the extent possible for providing future advice as of how much Lumentin® 44 should be used in order to obtain CT-scan with good diagnostic readability.

The subject may be withdrawn from the trial if his/her wellbeing is jeopardised during intake of the contrast agent. The subject must be withdrawn if less than 750 mL of Lumentin® 44, or less than the, according to the general praxis of care, recommended dose of Omnipaque® and Movprep® can be consumed.

Details and procedures in case of subject withdrawal are described in Section 8.3.

9.7 Concomitant Medications

Concomitant Medication

Any medication the subject takes other than the investigational product (prescribed and over-the-counter-drugs) is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At visit 1, CT-scan, subjects will be asked what medications they have taken during the last 2 weeks before visit 1, CT-scan.

At the contact 2, telephone interview, subjects will be asked what concomitant medications they are currently taking or have taken since they left the clinic.

All subjects will receive an intravenous injection of an iodine based contrast medium (Omnipaque® 350 mg I/mL) during the CT-scan examination. This is a standard of care procedure for all subjects undergoing a CT-scan at the clinic and is as such not part of the trial protocol defined procedures. The dose will be adjusted to body weight and kidney function and is usually given in the range of 60 to 115 ml of Omnipaque® 350 mg I/mL. The dose given and batch number of the Omnipaque® 350 mg I/mL will be noted in the eCRF.

Prohibited Previous and Concomitant Medication

All use of medication taken by oral route will be prohibited during 4 hours before taking the contrast agents and one hour post the intake.

All other medication taken by other routes are allowed.

10 PARAMETERS AND METHODS OF ASSESSMENT

10.1 Assessments of efficacy Parameters

10.1.1 Mean difference in contrast density

The contrast will be assessed by both the investigator and the sub-investigator, independently of each other, in the small bowel and expressed in Hounsfield Units (HU). The difference in contrast density between lumen and wall (mucosal lining) will be measured in 9 locations of the small bowel as described below.
The small bowel is divided in 5 sub-segments and defined as follows:

- Duodenum is defined as the first part of small bowel down to ligament of Treitz;
- Jejunum identified by its typical feathery mucosal pattern on Abd-CT
- The small bowel between the jejunum and terminal ileum is visually divided into two parts:
    - Proximal ileum is approximately defined as 30 cm / 4 loops of small bowel following jejunum
    - Distal ileum is approximately 30 cm / 4 loops proximal to terminal ileum
- Terminal ileum is defined as the last 15 cm of ileum mounding into the ileo-cecal valve

The difference in contrast density is measured in two sites in each of 4 of the defined sub-segments: duodenum, jejunum, proximal ileum, and distal ileum, and in the terminal ileum where (due to its shortness in length) only one site is selected.

Two regions of interest (ROI) measuring 6 mm in diameter will be selected by the investigator in the lumen of each segment except in the terminal ileum where only one region is selected. The ROIs will be placed where the lumen is best shown in the CT-image. The CT-scan software will provide a mean HU measurement of each of the selected ROIs and the values will be recorded by the investigator.

The HU of the wall will be set to +80HU as a standard for all measurements. It is not possible to discriminate between the lumen and the wall when Movprep® and Diluted Omnipaque® is used as contrast agents as they have a contrast similar to the wall contrast.

In each segment, the difference in contrast density between bowel lumen and wall will be calculated by subtracting the pin point HU value(s) of the wall (set to +80HU) from the mean ROI HU value(s) of the lumen. Two differences in contrast density values will thus be generated for each segment except in the terminal ileum where only one value is generated.

Each examination produced in the CT-scanner consist of more than 1 000 images which are stored in the patient's medical record. The investigator and the sub-investigator will independently select the best images on which contrast differences are calculated. Screen-shots of all selected images will clearly identify sites of ROIs in the images, and an electronic footprint of storage time will be included in images when saved. Each image will also be uniquely identified by the CT-scanner's software. The images unique code and the time point they are saved will be entered in the eCRF, in order to document that the investigators are assessing the images independently. The investigators will also be given unique access codes to the eCRF so that they cannot access each other's assessment data.

The mean difference in contrast density in the small bowel is the sum of the differences in contrast density values (9 calculated values based on the observation of the investigator and 9 based on the sub-investigator observations, ie. in all 18 observations) divided by 18. All segments to which the contrast agent has not reached and thus, the contrast cannot be measured will not be included in the mean difference. The sum of the differences will in this case be divided by the number of measurable observations. The ability to fill the bowel will be investigated as a secondary objective, see below section 10.1.2.

10.1.2 Evaluation of ability to fill the bowel

The bowel filling agent will be distributed along the length of small bowel, i.e. the **extension**, but also cause a local widening of the bowel loop, **distension**. The filling of each of the 5 selected sub-segments of the small bowel in terms of extension and distension will be examined on the CT-scan by both the investigator and the sub-investigator, independently of each other, and graded using Likert scales between 1 and 9.

Subjects will be asked to fast for at least 4 hours prior to the intake of the contrast. The probability of the contrast agent to reach the terminal ileus is improved if the subject arrives fasted. Subject will be allowed to drink during the 4 hours.

The time point of assessment will be noted in the eCRF for both the investigator and the sub-investigator to document that the assessment has been done independently.

Extension scale:

1. no sign of contrast agent;
2. trace of contrast agent filling
3. segment filled to ca. 25%
4. segment filled to >25% but <50%
5. filled to segment filled to 50%
6. segment filled > 50% but <75%
7. segment filled to ca. 75%
8. segment filled to >75% but <100%
9. segment filled to 100%

The Extension score will be the sum of the grades both assessors and in each sub-segment and hence range from 10 to 90.

Distension scale:

1. no identifiable contrast agent
2. a minimal amount of contrast agent is identified
3. small amount of contrast agent, insufficient for placing a ROI of 6 mm
4. amount of contrast agent just allowing for a ROI of 6 mm
5. medium filled bowel loop
6. slightly better than grade 5
7. good filling
8. optimal filling
9. excellent or almost overdistended

The Distension score will be the sum of the grades both assessors and in each sub-segment and range from 10 to 90.

10.1.3 Diagnostic ability when examining Abd-CT

Diagnostic ability when examining Abd-CT will be assessed on the CT-scan by both the investigator and the sub-investigator, independently of each other.

The following features will be assessed:

- Small bowl appearance
- parenchymal organs, i.e. pancreas, ovaries, urinary bladder
- mesenterium and oment

using a Likert scales of 1-9 ranging, where:

1. impossible to observe details
5. medium
9. excellent resolution

The Diagnostic ability score will be the sum of the scores from both assessors and range from 6 to 54.
The time point of assessment will be noted in the eCRF for both the investigator and the sub-investigator to document that the assessment has been done independently.

10.1.4 Degradation of contrast agents

Degradation of Lumentin® 44 is founded on the two characteristics Coalesence and syneresis or drainage.

Coalesence:

0. No bubbles visually detectable at the CT-scan
1. Bubbles visually detectable at the CT-scan

Syneresis or drainage:

0. No syneresis or drainage, i.e. separation of air and liquid phases, observed
1. Syneresis or drainage observed

Sign of degradation will be assessed on the CT-scan, by both the investigator and the sub-investigator, independently of each other, in each of the 5 selected sub-segments of the small bowel.
Degradation of contrast agents score will be the sum of the scores from both assessors and in each sub-segment and range from 0 to 20.
The time point of assessment will be noted in the eCRF for both the investigator and the sub-investigator to document that the assessment has been done independently.

10.1.5 Ability to eat/drink the contrast agents

Subjects will assess taste, smell, consistency, ability to swallow and fullness on a five degree-scale:

6. Very negative/Very difficult/very full
7. Negative/difficult/ full
8. Neutral/medium/medium full
9. Positive/easy/barely full
10. Very positive, good/very easy/not at all full.

Subjects will be handed an assessment form, see appendix 2, to be filled out during the period when the contrast agents are consumed.

10.1.6 CT-scan examination

The CT-examination will be started within 10 minutes after the contrast agent has been consumed and the CT-examination as a whole lasts in average eight minutes.

The CT-equipment comes with a moving table and a fixed gantry in which the X-ray tube is rotating with 2 revs per sec. The subject will be positioned in supine on the table with hands-over-head, and prone for dedicated examination of the bowels. The table is then moved into the gantry for exposure of the abdomen. Before the examinations starts, an intravenous injection of an iodine based contrast medium (Omnipaque 350 mg I/mL) is given in order to enhance any existing lesion or disease. The dose is adjusted to body weight and kidney function and is usually given in the range of 60 to 115 ml of Omnipaque 350 mg I/mL. The dose and batch number of iodine will be noted in the eCRF.

At contrast peak in the aorta, and an extra fixed delay of 50 seconds, altogether approximately one minute, exposure starts and the table moves ahead while the body part is continuously irradiated from the rotating X-ray tube. The whole procedure is finished within 10 seconds and images presented within 30 seconds.

A quality check of the CT-examination images is performed (in rare cases at the discretion of the X-ray nurse a second exposure is performed if the quality is poor) and affirmation of the subject's well-being, the subject is free to leave the CT-scanner.

10.2 Safety Parameters

10.2.1 Adverse Event

Any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

10.2.2 Adverse Reaction

All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Comment: All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

10.2.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorised IP or summary of product characteristics for an authorised product).

Comment: When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

10.2.4 Serious Adverse Event

Any untoward medicinal occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Comments: Life-threatening in the definition of an SAE or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgement should be exercised in deciding whether an AE/reaction is serious in other situations. Important AEs/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

10.3 Reporting of Adverse Events

All trial subjects will be carefully monitored for the occurrence of AEs during the trial period, from start of intake of the first dose until the contact 2, telephone interview 12 – 48 hours after the CT-examination. Reported AEs will be followed up (see 10.4 below). The Investigator will collect AEs with a non-leading question such as “have you experienced any new health problems or worsening of existing conditions” as well as reporting events directly observed or spontaneously volunteered by subjects.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the subject, or reported in answer to an open question by the Investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the eCRF and should include the following information:

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding trial treatment
- Opinion on causality

- Seriousness
- Outcome

10.3.1 Severity

Severity describes the intensity of an event, and will be assessed as:

Mild: The AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.

Moderate: The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe: The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the subject.

If an AE changes in severity, the worst severity should be reported.

10.3.2 Causality

Causality will be assessed as:

Probable: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

10.4 Follow-up of Subjects after Adverse Events

AEs that are serious or those that the investigator assesse as relevant to follow from a trial perspective will be followed until they are recovered, stabilized or recovered with sequelae. The date and outcome will be recorded on the AE form in the eCRF. Other ongoing AEs will not be followed within the trial after the date of the contact 2, telephone interview.

10.5 Abnormal Laboratory Values

The reporting of abnormalities as both laboratory findings and AEs should be avoided.

An asymptomatic abnormal laboratory finding should only be reported as an AE if it is clinically significant.

Clinically significant abnormal findings noted before treatment start at Visit 1 will be recorded on the medical history page in the eCRF. New or worsening clinically significant abnormal findings will be recorded on the AE page in the eCRF.

If an abnormal laboratory value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result should be considered additional information.

10.6 Reporting of Serious Adverse Events

The Investigator is responsible for ensuring that all SAEs are reported to the Sponsor or the sponsor's designee immediately, by e-mail (preferred) or fax, but in any event no later than 24 hours of any site staff becoming aware of the event. Initial notification should be followed as soon as possible by detailed written reports. The initial and follow-up reports should identify subjects by unique code numbers assigned in the trial and not by the subjects' names, personal identification numbers, and/or addresses. The following information is **mandatory** for the initial report:

- Subject trial identification data (ID)
- Trial treatment
- Start date (time, if relevant) of the trial treatment
- Brief description of the event (diagnosis)
- Start date (time, if relevant) of the event
- Seriousness criteria
- Causality assessment

For reported deaths, the Investigator should supply the Sponsor with any additional requested information (e.g. autopsy reports and terminal medical reports).

SAE REPORTING CONTACT DETAILS

A+ Science AB

Dr Janet Post Medical Director

E-mail: safety@a-plusscience.com (preferred)

Fax : +46 8 28 41 22

Phone: +46 735 24 03 98

The Sponsor is responsible for informing the Competent Authorities, the European Medicines Agency (EMA) and Ethics Committees of any individual case reports of SAEs that are determined to be reportable by the sponsor (i.e. adverse events considered as serious, related and unexpected [SUSARs]). SUSARs will be distributed by the Sponsor's

pharmacovigilance team within 7/15 working days to the EMA (EudraVigilance) and concerned Competent Authorities and Ethics Committees, according to local regulations. The investigator will be notified of safety issues/SUSARs according to current legislation.

10.7 Precautions/Overdose

Risks associated with intake of oral contrast agents include dysphagia with aspiration and secondary pneumonia. Although patients with acute problems are excluded, a pre-emergency small bowel status might be aggravated to an established ileus by ingesting a large volume. Oral contrast agents should not be given to subconscious patients, to those with swallowing disorders, or an acute abdomen.
Known sensitivity or allergy to contrast agent ingredients are exclusion criteria in clinical studies. However, unknown sensitivities or allergies might cause reactions that may need to be medically treated.
Iodine may be absorbed and causes disturbance of functional test of the thyroid gland for weeks.

Intravenously administered iodine may cause allergic reaction of various severity from a mild rush to intensive care unit treatment. Routines for handling these cases are well known to the staff which is regularly trained in dealing with emergency cases. Equipment for emergency care treatment is available at the clinic and the clinic is located in close proximity to the hospital emergency care department.

11 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and Baseline Characteristics consist of those parameters that are assessed only at screening/baseline.

11.1.1 Subject Demography

Subject demography consists of:

- Date of birth,
- Height,
- Weight,
- Sex

The body weight will be measured with standard scales, and the subject will be asked about height, at Visit 1, CT-scan.

11.1.2 Medical History

For the documentation of the medical history, any previous and concomitant diseases within the last 2 years before screening will be documented in the eCRF.

The medical history will be obtained by asking the subject and by inspecting his/her medical records if available.

For statistical analysis, all previous and concomitant diseases will be coded with Medical Dictionary for Regulatory Activities (MedDRA), the version of which will be provided in the trial report.

12 TRIAL CONDUCT

Table 4 Schedule of Events

Visit/Contact	0 Screening [a)]	1 CT-scan	2 Telephone interview and early termination [b)]
Day	**-28 to -1**	**0**	**1-2**
Visit window			**12-48 hours**
Subject information	X	X	
In/exclusion criteria		X	
Informed consent		X	
Pregnancy test [c)]			
Randomisation		X	
Subject demographics (incl. height and weight)		X	
Concomitant treatment		X	X
Concomitant illnesses		X	
Medical history		X	
Blood sample (clinical chemistry) [d)]		X	
Adverse event(s)		X	X
Dispensing of contrast agent		X	
Administration of Iodine contrast		X	
CT Scan		X	
Evaluation of contrast difference		X	
Evaluation of extension and distension composite score		X	
Evaluation of diagnostic ability		X	
Evaluation of contrast agent degradation		X	
Subject assessment of taste, smell, consistency etc.		X	
Compliance		X	

a) No formal screening will be performed in the trial. However, since only one visit to the clinic is planned in this trial, all subjects will receive information regarding the trial prior to the clinic visit. Subjects will thus have time to consider participation and prepare questions, if needed.

b) Also in case a subject is withdrawn after intake of the contrast agent the Early Termination form should be completed.

c) Urine pregnancy test of all fertile females

d) Blood sample (2 mL) will include Na, K, Ca, P in serum and will be taken prior to intake of contrast agents and post CT-scan.

12.1 Procedures by Visit

Visits should occur within the time windows specified in the schedule of events, Table 4. All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

12.1.1 Contact 0 (Screening, Day -28 to Day -1)

Contact 0 (Screening) will take place up to 28 days before Visit 1.

Subjects referred for abdominal- or thoraco-abdominal CT-examination will be invited by letter to participate in the study. Referral letters that informs them on day and time for the CT-examination are routinely sent out within 4 weeks prior to the examination. The invitation is added to the referral letter together with the full subject information about the trial. Subjects that are interested in participating in the trial will be asked to contact the investigator. If the subject has not contacted the clinic a week before the examination the investigator will contact the subject to confirm if the subject is willing to participate or not.

During the screening period, the Investigator will:

- Provide the subject with an invitational letter providing information about the trial
- Document subjects interest of participation in the trial by entering interested subjects to the screening log,
- Provide interested subjects with full subject information by sending out subject information leaflet,
- Answer any questions the subject might have regarding the trial

12.1.2 Visit 1 (CT-scan, Day 1)

Subjects still interested in participating in the trial will, upon arrival to the clinic at the day of CT examination, be fully informed about the trial by the investigator and given opportunity to ask questions. Eligible subjects will sign the consent to participate form prior to randomisation and any treatment related procedures.

During Visit 1 the Investigator will:

- Provide the subjects with full subject information and answer any question the subject might have
- Obtain informed consent
- Check in-/exclusion criteria
- Randomise the subject
- Record demography parameters
- Record concomitant medication and illness
- Record medical history
- Take blood sample (2 mL) before and after contrast agent administration
- Dispense the contrast agent
- Record the subject’s assessment of taste, smell, consistency etc.
- Check and record compliance
- Note adverse events
- Perform the CT-scan including providing iodine contrast agent
- Assess efficacy

12.1.3 Contact 2, Telephone interview

The subject will be contacted by telephone by the investigator 12 to 48 hours after the CT-scan visit and interviewed about any possible adverse events that has occurred during the period after the CT-scan. The interview will include a set of predefined questions (see appendix XX) and also an open question, e.g. "have you experienced any untoward events or side effects since you left the clinic". Concomitant medication and any change in concomitant medication will also be checked.

During telephone interview, the Investigator will:

- Check any occurrence or change in adverse events
- Check of use or change in concomitant medication

SAE and other AEs that the investigator assesses as relevant to follow from a trial perspective will be followed up, see section 10.4

13 STATISTICAL METHODS

Before disclosure of randomisation codes, a separate statistical analysis plan (SAP) may be finalised, providing detailed methods for the analyses outlined below.

In general, data summaries will be stratified by the randomised treatment group (Lumentin® 44, diluted Omnipaque® and Movprep®). The randomisation is stratified by gender and this will be taken into consideration in the statistical analyses

Any deviations from the planned analyses will be described and justified in the final integrated trial report.

13.1 Trial Subjects

13.1.1 Disposition of Subjects

The number and percentage of subjects will be presented, stratified by treatment and overall, with sub-stratification by randomisation stratification factors.

Reasons for withdrawal will also be summarised.

13.1.2 Protocol Deviations

Deviations to the trial protocol will be documented in a Protocol Deviation Log.

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as "minor" or "major" on a case-by-case basis in cooperation with the Sponsor. This assessment will take place during a data review meeting. Major deviations from the protocol will lead to the exclusion of a subject from the per protocol analysis set.

Unless decided otherwise during the data review meeting, the following will be major protocol deviations:

- Deviations of inclusion/exclusion criteria,
- Subjects not able to drink at least 750 mL Lumentin® 44
- Subjects not able to drink at least the, according to the general praxis of care, recommended dose of diluted Omnipaque®
- Subjects not able to drink at least the, according to the general praxis of care, recommended dose of Movprep®

13.1.3 Analysis Populations

Safety set:	All subjects who received at least some portion of the contrast agents (Lumentin® 44, diluted Omnipaque® and Movprep®). Subjects will be included in the analysis according to the treatment actually received.
Full analysis (FA) set:	All correctly included and randomised subjects who received at least some portion of the contrast agents (Lumentin® 44, diluted Omnipaque® and Movprep®) and for whom a CT-scan has been performed. All subjects will be included in the group according to the intention based on the randomisation.
Per protocol (PP) set:	All subjects of the FA set who are compliant with the trial protocol, i.e., who do not experience any major protocol deviations.

All efficacy analyses will be performed for both the FA set and the PP set. The analysis of the primary efficacy parameter based on the PP set will be regarded as the primary analysis. The analyses on the FA set will be considered as sensitivity analyses.

All safety analyses will be based upon the Safety Set.

13.2 General Considerations

All statistical tests will be 2-sided and significance-values less than 5 % will be considered statistically significant even though adjustment for multiplicity will not be performed, unless otherwise stated. Confidence intervals will be two-sided at the 95% confidence level.

Continuous data will be summarised using descriptive statistics (N, mean, median, standard deviation, minimum and maximum). Categorical data will be summarised by frequency tables (numbers and percentages).

Unless otherwise stated, all analyses will be done on observed cases without any substitution of missing values.

13.3 Demographics, Baseline Characteristics and Concomitant Medications

Demographic data, baseline characteristics and concomitant medication will be summarised by means of descriptive statistics, stratified by treatment and randomisation stratification factors. Tables will be provided for the FA set and the PP set.

Concomitant medication will be presented by ATC classification.

13.4 Efficacy Analyses

The primary efficacy objective will be analysed using data from patients in both the FA set and the PP set considering the results from the PP set as the primary results.

13.4.1 Primary Efficacy Analysis

There are two primary objectives

- to compare the primary efficacy variable between patients randomised to Lumentin® 44 and patients randomised to diluted Omnipaque®
- to compare the primary efficacy variable between patients randomised to Lumentin® 44 and patients randomised to Movprep

The null-hypothesis that the primary efficacy variable is equal in the groups will be tested by means of the Wilcoxon rank sum test. In each of these analyses a two-sided p-value less than 5 % is considered statistically significant. A successful result is that both these tests are statistically significant and hence there is no need for multiplicity adjustment. The randomisation is stratified by gender but the statistical analysis of the primary objective will not be stratified.

13.4.2 Secondary Efficacy Analysis

The secondary efficacy objectives will be analysed using the same principles and methods as the primary efficacy objectives.

13.4.3 Drug Exposure

Extent of exposure will be assessed using the amount contrast agent taken and body weight. The total exposure and exposure divided by the subject´s body mass index will be summarised by treatment group using descriptive statistics.

13.4.4 Validity and repeatability of the primary endpoint

The primary endpoint (i.e. the contrast) will be assessed by both the investigator and the sub-investigator, independently of each other. As an exploratory analysis, the relationship between the contrast measurements done by the investigator and the sub-investigator will be analysed. The relationship will be investigated by calculating the Spearman rank correlation coefficient. As an analysis of a systematic difference between the operators the hypothesis that the contrast level is equal for the investigator and the sub-investigator will be tested using the Wilcoxon signed rank test.

13.4.5 Adverse Events

AEs will be coded using the latest available version of the MedDRA, the version of which will be provided in the clinical trial report.

Pre-treatment AEs are AEs with onset prior to the intake of the contrast agent (Visit 1) that either stop prior to first administration of trial drug or are ongoing but do not deteriorate with respect to severity and/or relationship to trial drug after start of trial treatment. Pre-treatment AEs will be listed separately and will not be included in the AE tabulations. All other AEs will be considered as treatment-emergent AEs (TEAEs) and will be summarised per treatment group for the whole trial period.

An overall summary table will be provided showing the number and percentage of subjects with any:

- AE
- TEAE
- Severe TEAE

- Serious TEAE
- AEs leading to withdrawal
- Drug-related TEAE
- Drug-related severe TEAE
- Drug-related serious TEAE
- TEAE leading to withdrawal
- TEAE with outcome death

The two-sided p-values of Fisher's exact test for the 3 comparisons "Lumentin® 44 versus diluted Omnipaque®", "Lumentin® 44 versus p Movprep®" and "diluted Omnipaque® versus Movprep®" with regard to the percentages of subjects affected will be given in the overall summary table. The number of reported AEs will also be shown in this summary table.

The above summary table may be repeated, stratified by randomisation stratification factors.

13.5 Interim Analyses

An interim analysis is not planned.

13.6 Determination of Sample Size

13.6.1 Sample size (per group)

The standard deviation of the primary variable (i.e. the difference in contrast density in HU between bowel lumen and wall (mucosal lining), expressed as the mean of 9 measurements performed in the 5 selected sub-segments of the small bowel) is estimated from the first pilot clinical study of abdominal CT examinations on healthy volunteers using a slightly different formulation (L60). Based on data from that study [1] it is assumed that the standard deviation will be around 2.00 and the difference between Lumentin® 44 and Omnipaque® as well as the difference between Lumentin® 44 Movprep will be 1.50. Then 40 fully evaluable patients in the Lumentin group and 20 patients in each of the comparator groups are needed to get 78 % power for each of the two primary objectives (no adjustment for multiplicity). This means that the total probability in the trial to get a p-value less than 5 % in the test of both the primary objectives is 0.78×0.78=0.61.

13.6.2 Sample Size Formula

The following formula has been used to calculate the number of patients needed [13] per group ($N_{\text{per group}}$):

$$N_{\text{per group}} = \frac{2 \times \sigma^2 \times \left(\lambda_\alpha + \lambda_\beta\right)^2}{\Delta^2}$$

In the formula above σ is the standard deviation, Δ is the difference to detect between the groups, λ_α is the $1-\alpha$ percentile of the standardized normal distribution and λ_β is the $1-\beta$ percentile of the standardized normal distribution. If the test is two-sided and the

significance level should be 0.0500 then $\lambda_\alpha = 1.9600$. If the power is 80% then $\lambda_\beta = 0.8416$ and if the power is 90% then $\lambda_\beta = 1.2816$.

14 ETHICAL

14.1 Independent Ethics Committee (IEC)

The clinical trial must be approved by/receive favourable opinion from relevant Independent Ethics Committees (IECs) prior to enrolment of subjects.

Any amendments to the approved clinical trial must likewise, as required, be approved by/receive favourable opinion from relevant IECs prior to implementation.

The appropriate regulatory authority(ies) must be notified of/approve the clinical trial, as required.

14.2 Ethical Conduct of the Trial

This trial will be conducted to conform to the principles set out in the Declaration of Helsinki, revised 2013.

This trial will be conducted in accordance with the principles of the Good Clinical Practice (GCP), relevant legislation including (Clinical Trial) Directive 2001/20/EC and guidelines of the ICH.

This trial will be conducted in strict adherence to this protocol. If any changes to the protocol is required the protocol has to be amended, see section 16.2 Protocol Amendments.

14.3 Subject Information and Consent

All subjects will receive written and verbal information regarding the trial before any trial-related procedures are performed. This information will emphasise that participation in the trial is voluntary and that the subject may withdraw from the trial at any time and for any reason. All subjects will be given the opportunity to ask questions about the trial and will be given sufficient time to decide whether to participate in the trial.

The patient's signed and dated informed consent to participate in the trial will be obtained **prior** to any trial related procedure is being carried out. The consent form must also be signed by the person who conducted the informed consent discussion

The consent includes information that data will be recorded, collected, processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union (EU) Data Protection Directive (95/46/EC), the data will not identify any persons taking part in the trial.

A copy of the subject information including the signed informed consent form will be provided to the subject, for their records.

14.4 Subject Data Protection

All information containing personal data will be handled in accordance with Swedish data protection legislation and with the EU Data Protection Directive (95/46/EC).

14.5 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties: Regulatory Authorities, Investigators and IECs.

A significant safety issue is one that has a significant impact on the course of the clinical trial or program (including the potential for suspension of the trial program or amendments to protocols) or warrants immediate update of informed consent.

14.6 Ethical Consideration statement

The justification of this CT-trial is founded on the observation that the small bowel wall and its mucosal lining is so much better depicted on MRI images of the small bowel, especially on T1-weighted images after iv. Gadolinium, viz. with black bowel content and a contrast enhanced bowel wall. An equivalent image has hitherto not been possible to create with CT of the abdomen. As the availability world-wide of CT-equipment is plentiful and patient through-put is so much greater with CT than with MRI, most patients are referred for CT of the abdomen and for dedicated CT of the small bowel, even when a MRI-examination would be the preferred one, and in spite of the irradiation that comes with any CT-examination. Our newly invented per oral agent for bowel filling prior to CT of the abdomen has the potential to improve the CT-image of the bowel wall to the same quality as the T1 Gadolinium enhanced MRI image. This has been shown in a series of healthy, adult volunteers [1].
Allegedly benefits for future patients includes first and foremost CT-images easier to interpret, thereby facilitating diagnostics of early disease and reducing the risk of misreading's. Secondly, risks of adverse effects are supposed to be reduced to a minimum as our new agent is food-based with 44% air in water, 2% egg white protein and less than 1% stabilizing components and taste improving additives
No extra treatment to the patient having the new perusal agent is foreseen."

15 DATA QUALITY ASSURANCE

15.1 Quality Assurance

The Sponsor or designee will conduct a site visit to verify the qualifications of the Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the trial for each trial participant. All information recorded on the eCRFs for this trial must be consistent with the subjects' source documentation (i.e., medical records).

Trial sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit by Lument AB or inspection by competent authorities.

Any aspect of the trial may be subject to audit by Lument AB and/or inspection by regulatory authorities or IEC. Such audits/inspections may take place at the sponsor's site(s) or at any trial site including laboratories, pharmacies etc.

The monitor will, in case of audit, announce this in advance to the investigator and be present at the particular trial site during the audit.

The site staff should assist in all aspects of audit/inspection.

15.2 Trial Monitoring

Lument AB, as sponsor of this clinical trial, is responsible to the regulatory authorities for assuring the proper conduct of the clinical trial with regard to protocol adherence and validity of the data recorded in the eCRFs. The company has therefore assigned persons to monitor this trial. Their duties are to serve as the principal link between investigators and Lument AB and advise the investigator on the collection and maintenance of accurate, complete, legible, well organised, and easily retrievable data for the trial. In addition, they will explain to the investigators any aspect of the (conduct of the) trial, including interpretation of the protocol, the purpose of collecting the specified data and reporting responsibilities.

The monitor will visit the trial sites before, during and after the trial to ensure that the trial is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements and any trial specific documents such as eCRF completion guidelines.

Monitoring visits will be conducted to confirm that e.g.:

- The rights and well-being of human subjects are protected
- The investigational team is adhering to the trial protocol
- Informed consent has been obtained from all participants
- AEs have been reported as required
- Data are being accurately recorded in the eCRFs and are in accordance with source data
- IP is being stored correctly and drug accountability is being performed on an on-going basis
- IP is given to correct subject
- Facilities are, and remain, acceptable throughout the trial
- The Investigator and the site are receiving sufficient information and support throughout the trial

The eCRF data will be monitored on at regular intervals. The monitoring will include source data verification (SDV) according to the SDV list and verification of data consistency over time. The Investigator and other relevant trial personnel should be available during the monitoring visits.

In order to perform their role effectively, monitors and persons involved in quality assurance and inspections (see above) will need direct access to primary subject data, e.g., medical records, laboratory reports, appointment books, etc. The review of medical records will be performed in a manner to ensure that subject confidentiality is

maintained. Because this affects the subject's confidentiality, this fact is included on the Subject Information Sheet and Informed Consent Form. The Investigator assures the Sponsor of the necessary support at all times.

This trial is organised by Lument AB and all enquiries should be made to a member of Lument AB staff (see Section 2, Company Personnel).

15.3 Confidentiality

All trial findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on CRFs by their subject number. On the SAE reports and all other source documents, the subject will be identified via subject number, second letters of the subject's names and birth date. Documents not to be submitted to the Sponsor that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

15.4 Source Data

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)*. (ICH E6, 1.51).

Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

Source Data Verification (SDV) is a key function in assuring the sponsor that clinical trial information is recorded and handled in a way that allows its accurate reporting, interpretation and verification. Monitors will, during the conduct of the clinical trial, perform SDV to confirm the accuracy and completeness of eCRFs by verifying data recorded in the eCRF against data recorded in source documents to ensure such records are consistent.

To enable SDV it is essential, that what constitutes source data/documents (see definition above) for the trial data to be collected in the eCRF as well as where such data can be found at the trial site is established and agreed with the investigator at each trial site and documented, prior to initiation of the clinical trial.

Source data cannot be entered directly into the eCRF. Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data may be entered on a worksheet only if the clinical trial requires capture of data, which are normally not part of the subject's medical record.

For this trial, since data are entered into eCRF, all parameters collected in the eCRF should be verifiable from source documents available on site. These parameters include, but are not limited to:

- A statement that the subject is in a clinical trial
- The identity of the trial e.g. Trial code
- Subject screening number and/or subject number
- date of conducting informed consent process
- date of study visits and date leaving study
- relevant medical history and diagnosis
- data for evaluation of eligibility criteria
- dispensation/administration of trial medication
- concomitant medication (including changes) and diagnoses
- subject demographics; sex and date of birth
- laboratory data
- adverse events, (nature, dates)
- Date of trial termination

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Completed sections of eCRFs will be monitored on a regular basis.

15.5 Case Report Forms (CRFs)

Data collected in this trial will be by means of Remote Data Capture. The investigator or staff authorised by the investigator will enter patient data into electronic CRFs.

A separate, numbered eCRF will be used for each patient enrolled. Data recorded in the eCRFs will be accessible to site staff through a secure internet connection immediately after entry. The eCRFs must be maintained in an up-to-date condition at all times by the investigator. The investigator, or sub-investigator(s) authorised by the investigator, will electronically sign all sections of eCRFs used. This signature information (incl. date of signature) will be kept in the audit trail and is unalterable. Only appropriately medically-qualified (sub)investigators can sign data on clinical assessments/safety. Any correction(s) made by the investigator, or authorised site staff, to the eCRF after original entry will be documented in the audit trail. Changes to data already approved, requires the re-signature of investigator or authorised staff. The audit trail will identify the person making the change and the date, time and reason for the change.

The trial monitor will check the eCRFs for accuracy and completion and perform source data verification. For archiving purposes, each investigator will be supplied with a copy of the eCRFs, for all patients enrolled at the site, via an electronic medium at completion of the trial. Audit trail information will be included. cCRFs will be available for

inspection by authorised representatives from Lument AB, from Regulatory Authorities and/or IEC.

15.6 Data Management

Patient data should be entered into the electronic eCRF by authorised site staff in a timely manner and not later than a week after the patients visits. Data will be entered by site staff and systematic data validation will be performed through the discrepancy management system within the data collection software. Queries for discrepant data may be generated automatically by the system upon entry or generated manually by the monitor or the study data manager. All queries, whether generated by the system or by a user, will be in an electronic format. This systematic validation will provide a clean and consistent database prior to the statistical analysis.

Before database closure a reconciliation will be performed between the SAEs entered in the safety database and the trial database.

Any deviations, i.e. discrepancies and additions from the process defined in the Data Management Plan, will be described in a trial specific Data Management Report.

15.7 Archiving Trial Records

According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

16 TRIAL MANAGEMENT

16.1 Time Schedule

Planned date of enrolment of first patient: November 2017.
Planned date of enrolment of last patient: December 2018.
Planned date of completion of last patient: December 2018.

16.2 Protocol Amendments

Neither the investigator(s) nor Lument AB will change the Clinical Study Protocol without written agreement between Lument AB and the Investigator. Any modification considered substantial requires approval/favourable opinion by the appropriate regulatory authority and IEC/IRB.

Non-substantial changes (e.g. Changes not affecting the subject benefit/risk ratio) may be made without the need for a formal IEC/Competent Authority approval. All non-substantial amendment will be logged on a non-substantial amendment list. All non-substantial amendments will be distributed to all protocol recipients, with appropriate instructions.

Protocol amendments are issued as Consolidated Clinical Study Protocols comprising all current amendments. Consolidated Clinical Study Protocols become effective when written approval has been provided by the Investigator, the Sponsor, and approval/favorable opinion from regulatory authorities and/or IEC has been obtained, as required.

16.3 Agreements

Before the initiation of a clinical trial at a trial site, all financial arrangements with the investigator/institution and all other relevant parties (such as laboratories) must be confirmed in writing in formal agreement(s).

16.4 Duration of the Trial

The maximum duration of the trial for each subject will be up to 3 days (including telephone contact).

The trial will be closed when all subjects have completed contact 2, telephone interview or resolution of ongoing AEs, whichever occurs last.

16.5 Completion of Trial

16.5.1 Trial Completion Procedures

The end of trial is defined as the date of the last patient's last visit.

The Investigator will be informed when patient recruitment is to cease.

Trial enrolment will be stopped when the total requested number of evaluable subjects for the trial has been obtained, or when a total of 88 subjects have been randomized, whichever comes first.

Upon completion of the trial, Lument AB will undertake arrangements for collection and disposal any unused trial material that the investigator is not required to keep in his/her files.

The trial may stop prematurely If the Investigator or the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects if the trial continues, the trial may be terminated after appropriate consultation between the relevant parties. The trial may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the trial,
- Failure to enrol subjects at an acceptable rate,
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

16.6 Liability and Insurance

Lument AB will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this trial are governed by the applicable law.

Lument AB will arrange for Liability Insurance if subjects should be injured due to the participation in the trial and provided that sponsor is legally liable for that.

Excluded from the insurance cover are injuries to health and deteriorations of illnesses already in existence which would have occurred or continued to exist even if the subject had not taken part in the clinical trial.

The insurance cover is jeopardised if the subject fails to report immediately to the Investigator or responsible physician any injury to health, which might have resulted from participation in the clinical trial, or if he/she undergoes any other medical treatment without their consent before the clinical trial has been completely finished insofar as the individual subject is concerned.

Any injury to health, which might have occurred as a result of participation in the clinical trial, must be reported by the subject to the Investigator without delay. The Investigator is obliged to make such a report in any case.

16.7 Use of information

All unpublished information relating to this clinical trial and/or to the investigational product(s), is considered confidential by Lument AB and shall remain the sole property of Lument AB. The investigator should understand and agree that Lument AB may use the information from this clinical trial in connection with the development of the product, and therefore, may disclose it as required to other investigators, to regulatory authorities and commercial partners.

16.8 Publication Policy

By signing the trial protocol, the Investigator agrees with the use of results of the trial for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

An integrated clinical trial report will be prepared by the Sponsor and reviewed by Investigator. A summary of the clinical trial report (according to CPMP/ICH137/95) should be sent to the Regulatory Authorities and IEC according to the relevant guidelines.

No data from the clinical trial may be published, presented or communicated, except to regulatory authorities, prior to the release of the internal clinical trial report, unless approved by the Sponsor in writing.

The Sponsor and/or the investigators are obliged to publish the results of the trial. A publication will be prepared in a peer-reviewed indexed journal irrespective of the

outcome. Considerations should be made regarding potential patents or other clinical trial data. Should a publication not be available within 200 days from the end of the analysis, the investigators are free to prepare such a publication on condition of notifying the Sponsor and giving the Sponsor 60 days to comment any manuscript.

In the event of a publication, the names of the authors and their order of appearance will be as follows: The Investigator, the Sub-investigator, and representatives of Lument AB.

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18 APPENDICES

Appendix 1

LUMENTIN® 44 whipping protocol

This document give the protocol to follow to whip the pre-formulated dispersion to obtain Lumentin® 44 per-oral negative contrast agent.

The container with the pre-formulated dispersion must be taken from the fridge 30 minutes before whipping and must be left on the bench at room temperature. The material needed for the procedure is: immersion blender Bamix Gastro 350 with whipping-lid, pre-cut silicone tubing (supplied in pre-cut lengths ready to use), gloves, tape, scissors, timer, ruler, Pasteur pipette, whipping protocol and whipping report.

It is important to read the whole document before whipping, and to use gloves during the whole procedure (the foam is significantly sensitive to the fat skin naturally present in our hands).

1. General information

1.1. Aluminium bag with container

The aluminium bag with the container is taken from the fridge 30 minutes before the whipping process. It must be checked the conditions of the bag. The container must be discarded if any hole/perforation is detected on the aluminium bag. Once the bag looks good, it is opened and the container is left on the bench.

After 30 minutes on the bench at room temperature, the dispersion is ready to be whipped.

1.2. Dispersion

The dispersion must look a homogenous yellow liquid with vanilla aroma.

1.3. Material

The material that will be needed for the whipping procedure should be ready to use and reachable on the bench. Thus, immersion blender Bamix Gastro 350 with whipping-lid, pre-cut silicone tubing (supplied in pre-cut lengths ready to use), gloves, tape, scissors, timer, ruler, Pasteur pipette, whipping protocol and whipping report, must be all on the bench.

1.4. Container

The container has a label with a band at the upper part that corresponds to the range of height (or volume) that must be reached by the foam during whipping. The bottom and the top limit of the band (10.6 and 12.0 cm) corresponds to the minimum and maximum height or volume that must be reached, not lower than the minimum (10.6 cm) and not higher than the maximum (12.0 cm). The silicon stoppers incorporated on the leg of the blender will control the final height, so no special check or task must be performed during whipping to obtained the aimed foam height or volume.

1.5. Blender

The blender must be clean and dry. The leg of the blender cannot be separated from the motor (it is one piece leg-motor).The head of the blender should not be tried to be removed.

The **flat disc blade** must be put in the head of the blender by pushing, pressing and making the spike coincide with the slot in the disc flat blade. Make sure that is well-connected, **Figure 1** shows how it looks when it is NOT correctly put and when it is correctly connected.

Figure 1. Head of the blender with spike where the blade is connected by pressing. Head of blender with no blade (left), head of the blender with the blade on but NOT correctly put (middle), head of the blender with the blade correctly put since the spike is completely at the end of the hole in the blade (right).

Silicon stoppers must be put on the bottom and the middle part of the leg of the blender as shown in **Figure 2**. The stoppers must be of one use, clean and dry. The stoppers must be put in their correct positions:

- Bottom stopper must be put at the lowest part of the leg of the blender. The down border corresponds to the upper limit of the head of the blender.
- Top stopper must be put between the marks on the middle of the leg of the blender.

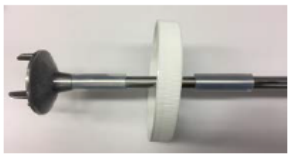

Figure 2. Leg of the blender with the whipping-lid and the stoppers placed on their corresponding positions on the blender leg for height control. Stopper between the head of the blender and the lid corresponds to the bottom stopper (left side in the picture), while the stopper between the lid and the white (motor) part of the blender corresponds to the top stopper (right side in the picture).

The pre-cut silicone tubing are of one use only, they are placed on the leg of the blender before whipping and disposed of after each whipping process.

The stoppers, together with the whipping-lid, help to control the aimed final foam volume and to avoid hitting the plastic bottom of the container.

Whipping-lid is a lid that is entrapped between the stoppers placed on the leg of the blender. In contrary to the stoppers that are removed and thrown away after every whipping process, the whipping-lid remains entrapped between the motor and the head of the blender. The whipping-lid, together with the stoppers, helps to control the aimed final foam volume and to avoid hitting the plastic bottom of the container.

2. Whipping method

2.1. Preparation

Place the container with the dispersion on the bench and close to the edge, at a position that will make the whipping process comfortable for 5 minutes (if the container stays too apart from the edge of the bench, the whipping process can become too tiring for the person who whips).
Fix the container to the bench with four long pieces of tape in cross positions as shown in **Figure 3**.

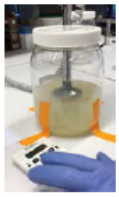

Figure 3. Container with dispersion fixed to the bench and ready to be whipped. Container is fixed to the bench with tape pieces, the container has the whipping-lid tightly closed, the blade at the surface of the dispersion and the timer reachable.

Open the container and keep its lid aside, to use it after the whipping process. Put the blender with the whipping-lid in the container, keep the blade at the surface of the dispersion as shown in **Figure 3**, do not deepen it to the bottom. Close the whipping-lid tightly to avoid displacement of the lid (if the lid is free and moves, the height of the foam will not be controlled).

2.2. Whipping procedure

The whipping procedure is divided in "upwards" and "downwards" steps and movements which always are in vertical direction, and as perpendicular as possible to the lid or the bench.

The dispersion is whipped with the Bamix Gastro 350 at minimum speed (18 000 rpm), whose button is the one at the lowest position on the blender (button with 1 spot, see **Figure 4**).

Figure 4. Buttons of two different speeds in the Bamix Gastro 350. Upper button with one spot (right side in picture) corresponds to 18 000 rpm, and the lower button (left side in picture) with 2 spots corresponds to 23 000 rpm.

The procedure is summarized in **Table 1** and explained in more detailed below.

Table 1. Whipping procedure steps.

Step	Time[a] [s]	Total time
Upwards 1	17	20 sec
Keep blender at the top	3	
Downwards 1	17	40 sec
Keep blender at the bottom	3	
Upwards 2	17	1 min
Keep blender at the top	3	
Downwards 2	17	1 m 20 s
Keep blender at the bottom	3	
Upwards 3	17	1 m 40 s
Keep blender at the top	3	
Downwards 3	17	2 min
Keep blender at the bottom	3	
Upwards 4	17	2 m 20 s
Keep blender at the top	3	
Downwards 4	17	2 m 40 s
Keep blender at the bottom	3	
Upwards 5	17	3 min
Keep blender at the top	3	
Downwards 5	17	3 m 20 s
Keep blender at the bottom	3	
Upwards 6	17	3 m 40 s
Keep blender at the top	3	
Downwards 6	17	4 min
Keep blender at the bottom	3	
Upwards 7	17	4 m 20 s
Keep blender at the top	3	
Downwards 7	17	4 m 40 s
Keep blender at the bottom	3	
Upwards 8	17	5 m
Keep blender at the top	3	

[a] The time that the blender is moved upwards or backwards may vary in 1-2 seconds (due to difficulty in accuracy during the displacement). Thus, the time that the blender is kept at the top (blocked by the stopper) and at the bottom (blocked by the stopper) it can turn to be 2-4 seconds.

Upwards 1 and top

Hold the blender with the head of the blender deepened in at the top of the dispersion (not at the bottom) making sure that the four teeth of the head of the blender are immersed in the dispersion as shown in **Figure 3**. To have the head of the blender immersed at the top of the dispersion allows incorporating air in the dispersion as soon as the whipping process is started.

Press start on the timer (chronometer from 00:00) and start whipping at low speed (18 000 rpm, 1 spot on the button). The blender is very slowly moved upwards to incorporate air between the surface of the dispersion and the empty space in the container. The blender is moved upwards until the silicone tubing at the bottom of the leg blocks a further upward displacement of the blender. The displacement should take 17 seconds, and the blender is kept at the top (limit to the bottom stopper) for 3 seconds. The time that the blender is moved upwards may vary in 1-2 seconds (due to difficulty in accuracy during the displacement). Thus, the time that the blender is kept at the top (blocked by the stopper) it can turn to be 2-4 seconds.

The total time that takes the upwards/top step is 20 seconds, 20 seconds is read on the timer.

It is important to displace the blender very slowly, so all the foam is homogeneously prepared and whipped. Otherwise the top would be whipped for longer time than different positions in the foam.

Downwards 1 and bottom

Once 20 seconds could be read in the timer, move very slowly the blender downwards until the stopper blocks further downwards displacement. The displacement should take 17 seconds, and the blender is kept at the bottom (limit to the top stopper) for 3 seconds. The time that the blender is moved downwards may vary in 1-2 seconds (due to difficulty in accuracy during the displacement). Thus, the time that the blender is kept at the bottom (blocked by the stopper) it can turn to be 2-4 seconds.

The total time that takes the downwards/bottom step is 20 seconds, 40 seconds is read on the timer.

It is important to displace the blender very slowly, so all the foam is homogeneously prepared and whipped. Otherwise the bottom would be whipped for longer time than different positions in the foam.

Upwards 2 and top

Once 40 seconds are read on the timer, the blender is very slowly moved upwards until the stopper at the bottom of the leg blocks a further upward displacement of the blender. The displacement should take 17 seconds, and the blender is kept at the top (limit to the bottom stopper) for 3 seconds. The time that the blender is moved upwards may vary in 1-2 seconds (due to difficulty in accuracy during the displacement). Thus, the time that the blender is kept at the top (blocked by the stopper) it can turn to be 2-4 seconds.

The total time that takes the upwards/top step is 20 seconds, 1 minute is read on the timer.

It is important to displace the blender very slowly, so all the foam is homogeneously prepared and whipped. Otherwise the top would be whipped for longer time than different positions in the foam.

The whipping process continues by repetitions of the previous steps until 8 repetitions in total for upwards and 7 repetitions for downwards displacements are completed, and a total time of 5 minutes can be read on the timer (see **Table 1**).

2.3. Remove blender

Once the whipping process is completed, the blender is stopped at the top and the whipping-lid is opened with one hand while the other is holding the blender. Once the whipping-lid is opened, the blender is slowly moved upwards and taken out from the foam. Do not take the blender to high, keep the head of the blender tilted and very close to the foam surface, so rest of foam that remains in the head of the blender drops on the foam without creating big bubbles. Once most of the remaining foam has dropped on the foam, take the blender out of the container with one of yours hands below the head of the blender to avoid that any foam drops on the bulk of foam creating big bubbles.

It is crucial that the final foam looks homogenous and absent of isolated and visible bubbles among the microbubbles that the foam is made up of. If the foam contains visible bubbles, they would create interferences in the X-ray images and make the foam lose its properties as negative contrast agent.

In case any or some isolated visible and big bubbles are detected at the surface of the foam, they can be removed with the Pasteur pipette. The foam can be slightly tilted and manually stirred by holding the container and moving the container in circles to check the presence/absence of visible bubbles that should be removed with the Pasteur pipette. If too many bubbles are observed, the foam must be discarded and another dispersion must be taken to prepare another foam. **Figures 5-8** show foam that can be acceptable or not acceptable depending on the bubbles detected at the end of the whipping process.

Figure 5 shows an example of a totally non-acceptable foam. It's very inhomogeneous and must be discarded. **Figure 6** shows a better foam but still not acceptable one. A lot of small bubbles are visible. And **Figure 7** shows an acceptable foam because there are only a few visible bubbles, and **Figure 8** shows a very good foam with absolutely no visible bubbles, or only few big bubbles (right) that can be very easily removed with a Pasteur pipette.

Figure 5. Totally non-acceptable foams that must be discarded. New dispersion must be used to prepare a new foam.

Figure 6. Non-acceptable foams that must be discarded. New dispersion must be used to prepare a new foam.

Figure 7. Acceptable foam with only few (from 1 to 5) small visible bubbles.

Figure 8. Very good foams with no small visible bubbles (left), or only few big bubbles (right) that can be very easily removed with a Pasteur pipette.

Once the foam looks good, the container is closed with its lid that was put aside before whipping. Then, the Whipping Report must be filled in before sending the foam to the Radiology Department.

3. Fill in the form "whipping report"

Fill in the whipping report.

To measure the **foam height**, place the container at the edge of the bench and the ruler at the edge of the bench and touching all the wall of the container. The height of the foam is measured by setting the 0 cm at the surface of the bench, and looking at the foam as horizontal as possible to the surface of the foam to avoid optical effect of higher or lower volume. In case the height of this foam is not within the acceptable range between 10.6 and 12 cm, the foam must be discarded and a new foam must be prepared.

If the foam looks good and the foam height is within the acceptable range. The foam is ready to be used, and the container with the foam can be sent to the Radiology Department.

4. Washing procedure

Keep your gloves on to was as well. The material should be free of any substance/contamination.

- The **Pasteur pipettes**, in case they have been used, can be disposed of.
- The **blender** is unplugged.
- The **stoppers** are removed from the leg of the blender and disposed of.
- The **flat disc blade** is removed by pulling out, washed with detergent in a sponge, thoroughly rinsed with water, and let it dry out.
- The **leg of the blender with** the **whipping-lid** are washed with detergent in a sponge, thoroughly rinsed with water, and let it dry out.

Keep all the material in their corresponding storing boxes.
Avoid any contact of the material with any other material or substance.

Appendix 2

Protocol: LUM-001, Version: 1.0 → → ¶

¶

Protokoll för bedömning av kontrastdryckens egenskaper¶

¶

Nedan finner ni en tabell som vi önskar att ni fyller i för att beskriva hur ni uppfattar kontrastdryckens egenskaper med avseende på smak, lukt, konsistens, drickbarhet och mättnadskänsla.¶

¶

Smak, lukt och konsistens kan ni med fördel bedöma medan ni intar drycken. Vi ber er dock att vänta med er bedömning av drickbarhet och mättnadskänsla tills det att ni skall gå till röntgen.¶

¶

Fyll i er bedömning genom att sätta ett kryss i respektive ruta i tabellen nedan.¶
Har ni några frågor så hjälper studiesjuksköterskan er mer än gärna.¶

¶

Tack på förhand för ett ni hjälper oss med att utvärdera kontrastdrycken!¶

¶

Kontrastdryckens egenskaper:¶

¤	Mycket negativ¤	Negativ¤	Neutral¤	Positiv¤	Mycket positiv¤
Smak¤	¤	¤	¤	¤	¤
Lukt¤	¤	¤	¤	¤	¤
Konsistens¤	¤	¤	¤	¤	¤
¤	Mycket svårt¤	Svårt¤	Medium¤	Lätt¤	Mycket lätt¤
Drickbarhet¤	¤	¤	¤	¤	¤
¤	Mycket mätt¤	Mätt¤	Lagom mätt¤	Omätt¤	Mycket omätt¤
Mättnadskänsla¤	¤	¤	¤	¤	¤

¶

¶

Ifylles av studiepersonal¶

¶

Patientnummer: ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤

¶

Patient Id: ¤ ¤ ¤ ¤ ¤ ¤

¶

Datum: ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤

Å¤ Å¤ M¤ M¤ D¤ D¤

Studiesjuk. Signatur: ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤

¶

2017-08-15 → → Sida 1 av 1¶

Appendix 3

Protocol: LUM-001, Version: 1.0 → →

Rapporteringsformulär inför uppföljningssamtal 12 - 48 timmar efter CT-undersökning

Patientnummer: ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤ ¤

Patient Id: ¤ ¤ ¤ ¤ ¤

Vid uppföljningssamtalet följes nedan angivna beskrivning. Det är av vikt att alla patienter utfrågas på ett likvärdigt sätt för att få en så objektiv bedömning av eventuella biverkningar och användande av läkemedel.

Börja intervjun med att fråga om patienten tagit några läkemedel sedan sist eller ändrat sin dosering av redan rapporterad pågående läkemedelsbehandling. För pågående läkemedelsbehandling, var god se patientens journal.

Använd en öppen fråga, t.ex har ni tagit något läkemedel sedan ni lämnade kliniken efter er CT-undersökning eller ändrat eller slutat ta eventuell behandling ni har haft?".

Har patienten tagit något nytt läkemedel eller ändrat pågående medicinering? ¤	Ja¤	Nej¤
	¤	¤

Om patienten har tagit nytt läkemedel eller ändrat sin medicinering fylles patientjournalens "concomitant medication form" i.

Fråga därefter ut patienten om eventuella biverkningar. Använd en öppen fråga, t.ex har ni haft några besvär eller obehag sedan ni lämnat kliniken efter er CT-undersökning?".

Har patienten rapporterat någon biverkan? ¤	Ja¤	Nej¤
	¤	¤

Om patienten svarar jag på denna fråga så fylles patientjournalens "AE form" i. Använd en AE form för varje enskild biverkan.

..... Sidbrytning .....

Om patienten har rapporterat någon biverkning under tiden på kliniken och denna fortfarande var pågående när patienten lämnade kliniken, så frågas patienten ut om det skett några förändringar.

	Ja	Nej
Har patienten rapporterat förändring på pågående biverkan?		

Notera eventuella förändringar i patientjournalens "AE form". Använd en AE form för varje enskild biverkan.

Därefter frågas patienten ut om han/hon haft problem med:

- Magknip
- Mättnad
- Rapningar
- Vädersläpp
- Illamående

	Ja	Nej
Har patienten rapporterat någon av ovan biverkningar?		

Om patienten svarar jag på denna fråga så fylles patientjournalens "AE form" i. Använd en AE form för varje enskild biverkan.

OBS!
Alla biverkningar som anses vara allvarliga eller utifrån prövarens åsikt behöver följas upp skall följas upp i enlighet med protokollet. Om någon av de biverkningar som rapporterats vid uppföljningssamtalet faller inom någon av dessa kategorier skall patienten informeras om att han/hon kommer att bli kontaktad igen av prövaren.

Datum: Å Å M M D D **Tidpunkt:** T T M M

Intervjuares signatur: