# CLINICAL TRIAL PROTOCOL

An uncontrolled, single centre, healthy volunteer, Phase II proof-of-concept trial investigating MR-enterography image quality of Lumentin® 44, a new egg albumen based oral small bowel filling contrast agent.


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| Trial Drug Name: | Lumentin® 44 |
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# 1 PROTOCOL SYNOPSIS

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| **Title:** | An uncontrolled, single centre, healthy volunteer, Phase II proof-of-concept trial investigating MR-enterography (MRE) image quality of Lumentin® 44, a new egg albumen based oral small bowel filling contrast agent. |
| **Short title:** | Lumentin MR-enterography PoC trial in healthy volunteers |
| **EudraCT Code:** | 2022-002193-84 |
| **Phase of development** | Phase II |
| **Background & study rationale** | Lumentin® 44 is being developed as a novel oral contrast medium to be used in diagnostic examinations of the abdomen. Phase II studies have been performed using computed tomography (CT) assessment with encouraging results. If the same product can also be used in Magnetic Resonance-enterography (MRE) it could be an advantage for a radiological department to only handle a single oral contrast medium for both modalities, CT and MRI. In addition, administration of Lumentin® 44 has shown few side effects and may be a more tolerable alternative to the oral media used today in CT and MRI. The current study aims to explore if the signal characteristics of Lumentin® 44 is favourable in MRE.<br><br>This proof-of-concept (PoC) trial is performed in healthy volunteers (HVs) with the aim to show that Lumentin® 44 can be used as an oral small bowel filling contrast agent for MRE. |
| **Primary objective** | • To evaluate if Lumentin® 44 used as a bowel filling agent in MRE examination generates images with acceptable diagnostic quality. |
| **Secondary objectives** | • To evaluate plasma electrolytes including, potassium, sodium, phosphate, and calcium, as well as ionized calcium concentration levels during 24 hours after intake of Lumentin® 44.<br>• To evaluate bowel filling properties (extension and distension) of Lumentin® 44.<br>• To evaluate the safety and tolerability of Lumentin® 44 intake. |

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| **Primary outcome** | • Visual evaluation of the MRE images from each trial subject with respect to motility, artefacts, mucosal evaluation and overall diagnostic impression. |
| **Secondary outcomes** | • Concentration of plasma electrolytes including, potassium, sodium, phosphate, and calcium, as well as ionized calcium in blood samples taken at T0h, T1h, T2h, T4h, T6h, T8h, and T24h.<br>• Bowel filling properties (extension and distension) in each of 5 selected sub-segments of the small bowel.<br>• Any treatment emergent adverse events (TEAEs) and treatment emergent adverse drug reactions (TEADRs). |
| **Investigational product, formulation, dosage and mode of administration:** | Lumentin® 44 Powder for oral foam provided in labelled white sachets white sachets containing 17.4 g powder. Potable water (commercially available still water 0.5 L per bottle) for the preparation of the foam will be used.<br>Lumentin® 44 powder for oral foam will be delivered from APL to the clinical site, by order via the hospital pharmacy and stored temporarily at the site. The investigational product (Lumentin® 44 foam) is then prepared in-situ by adding 0.5 L potable water to Lumentin® 44 powder contained in one sachet, and the blend is then mixed to a stable foam in a dedicated preparation unit. The freshly prepared foam will be administered to the patient within 5 to 10 minutes. The in-situ preparation will follow a procedure attached to the clinical trial protocol. The staff responsible for the in-situ preparation will be trained using the procedure and their training documented in the Trial Master File. Two sachets (0.9 L foam per sachet) will be required per subject. |
| **Trial design** | This is an uncontrolled, single centre phase II trial. Enrolled HVs (n=10) will undergo gadolinium (Gd) based MRE after oral intake of Lumentin® 44.<br>Interested HVs will be identified primarily among medical students at the medical hospitals at Malmö and Lund. Posters will be placed at the departments and invitation letters will be handed out.<br>HVs interested in participating will be invited to attend a pre-screening visit where their suitability based on age and health status will be assessed. Fifteen HVs who fulfil the pre-screening criteria and are still interested in participating will be asked to attend a screening visit at the clinic and if |

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| | eligible for the trial they will then visit the clinic for MRE assessment within 1-2 weeks.<br><br>Only the first 10 of the eligible HVs will be asked to come for MRE examination and the remaining eligible subjects will be asked to stand by in case any of the 10 subjects are unable to come or cannot undergo the examination.<br><br>HVs will be asked to fast for 6 hours prior to the examination on the day of the MRE examination. Clear liquid in small volumes up to 2 decilitres is allowed. Prior to MRE, Lumentin® 44 will be provided to them in volumes of up to 1.5 L and at least 1.1 L of Lumentin® 44 must be drunk. The subjects will be asked to drink the solutions of oral contrast agent within 45 minutes to 1 hour.<br><br>Subjects not able to drink at least 1.1 L of Lumentin® 44 will be withdrawn from the trial.<br><br>Prior to the intake of Lumentin® 44, an intravenous (IV) antecubital cannula will be placed and used for blood sampling and administration of Gd contrast agent during the MRE assessment. |
| **Assessments** | **Screening assessments:** HVs fulfilling the eligibility criteria and who sign the consent to participate will undergo a physical examination, perform a pregnancy test (females only) and have a creatinine blood sample taken. Medical history, demographics, concomitant treatment and illnesses will also be recorded..<br><br>**MRE assessment:** MRE will start within 10 minutes after the contrast agent has been drunk and will last for approximately 40 minutes.<br><br>The HV will be brought to the MRE-scanner suite inside the magnet using the moving table and scanning will commence. All series will be taken as per standard clinical MRE protocol recognised by radiologists in Europe and North America. After dynamic series acquisition, a spasmolytic agent will be given and 3D gradient-echo series will be taken and will be repeated 40 seconds thereafter, following IV administration of Gd contrast agent at a dose of 0.1 mmol/kg per body weight. Subsequently, the remaining series will be taken according to protocol. |

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| | **Electrolyte assessment:** A blood (baseline) sample for electrolyte analysis will be collected just prior to the HV starting to drink Lumentin® 44. A second blood samples will be collected one hour after the baseline blood sample. No more Lumentin® 44 can be drunk after this blood sample has been collected. Additional blood samples will be collected at 2, 4, 6, 8, and 24 hours post baseline samples.<br><br>**Safety assessment:** The occurrence of adverse events and concomitant treatment will be recorded for the duration of the trial.<br><br>For safety reasons, subjects will be contacted within 2 to 4 days after the MRE examination by the investigator and asked about occurrence of any adverse event. No other follow-up is planned. |
| **Trial population** | HVs fulfilling the eligibility (in-/exclusion) criteria. |
| **Number of subjects** | A total of ten fully evaluable HVs will be included in the trial. |
| **Inclusion criteria** | 1. Healthy volunteers of either gender at least 18 years at the time of signing the informed consent.<br>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).<br>3. 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. |
| **Exclusion criteria** | 1. Glomerular Filtration rate (GFR) below 60 ml/min/1.73 sqm body surface. All subjects will have a plasma creatinine taken at screening for calculation of estimated GFR (eGFR).<br>2. History of drug related reaction to gadolinium contrast agents.<br>3. Have had gadolinium injection during the last 4 weeks.<br>4. Claustrophobia not coping with MRE examination.<br>5. Metal objects and medical devices in the body not judged by the investigator to be compatible with MRE.<br>6. Hypersensitivity to Buscopan® (Butylhyoscopin).<br>7. Having swallowing difficulties.<br>8. Known allergy to egg albumen. |

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| | 9. Known sensitivity to any of the components of the investigational product.<br>10. Clinical suspicion of ongoing disease by the investigator.<br>11. Being, in the opinion of the investigator, unlikely to comply with the clinical trial protocol.<br>12. Previously included in this trial.<br>13. Participating in or having participated in another clinical trial within the last 4 weeks. |
| **Statistical analyses** | All subjects who have completed the trial will be included in the statistical evaluation.<br>No statistical tests will be conducted. Confidence intervals may be constructed and will then be 2-sided and of 95% confidence.<br>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).<br>Unless otherwise stated, all analyses will be done on observed cases without any substitution of missing values. |

**Schedule of Assessments**

| Visit/Contact | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| | Pre-screening | Screening | MRE examination | Blood sampling | F-U [1] and early termination |
| Day | -21 to -1 | 0 | 14 | 15 | Visit 2 +2 days |
| Visit window (days) | | | +/- 7 days | - | + 2 |
| Subject information | X | X | | | |
| In/exclusion criteria | (X)[2] | X | | | |
| Informed consent | | X | | | |
| Physical examination | | X | | | |
| Pregnancy test [3] | | X | | | |
| Creatinine blood sample | | X | | | |
| Subject demographics (incl. height and weight) | | X | | | |
| Concomitant treatment | X | X | X | X | X |
| Concomitant illnesses | X | X | | | |
| Medical history | X | X | | | |
| Adverse event(s) recording | | | X [4] | X | X |
| Placement of IV antecubital cannula | | | X [5] | | |

| Visit/Contact | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| | Pre-screening | Screening | MRE examination | Blood sampling | F-U [1] and early termination |
| Day | -21 to -1 | 0 | 14 | 15 | Visit 2 +2 days |
| Visit window (days) | | | +/- 7 days | - | + 2 |
| MRE Scan | | | X | | |
| Dispensing of Lumentin® 44 | | | X | | |
| Administration of Gd contrast [6] | | | X | | |
| Administration of Buscopan® [6] | | | X | | |
| Evaluation of extension and distension of bowel filling agents | | | X | | |
| Blood sampling | | | X [5] (pre-, 1, 2, 4, 6, 8h) | X (24h) | |
| Compliance | | | X | | |

1) Subjects will be contacted by telephone two to four working days post MRE assessment.
2) Only some of the criteria will be checked including, inclusion criterion 1 and exclusion criteria 2, 3, 4, 5, 6, 7, 8, 12 and 13.
3) Urine pregnancy test of all females who are not surgically sterile (hysterectomy or tubal ligation) or postmenopausal (i.e., experienced 12 consecutive months without menstruation).
4) Telephone interviews will be conducted 2 days after MRE assessment to investigate if any AEs occurred during the first days after the imaging procedure
5) An IV antecubital cannula will be placed for pre-blood samples and used during the first 8h including administration of gadolinium during the MRE procedure. Thereafter it will be discarded. Blood sampling on the following day (24h time point) will be drawn without a cannula.
6) Gadolinium (Gd) and Buscopan® will only be administered as part of the MRE examination.

## 2 LIST OF TRIAL PERSONNEL

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# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| Abd-CT | Abdominal Computerised tomography |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| ASI | Additional Safety Information |
| b.w. | Body weight |
| CD | Crohn's Disease |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CT | Computerised Tomography |
| CTE | Computerised Tomography - enterography |
| CRO | Clinical Research Organization |
| DMF | Drug Master File |
| DRL | Drug Reference List |
| EC | European Community |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EU | European Union |
| EWP | Egg White Protein (also referred to as egg albumen) |
| FA | Full Analysis |
| GCP | Good Clinical Practice |
| Gd | Gd Gadolinium |
| (e)GFR | (estimated) Glomerular Filtration Rate |
| GI | Gastrointestinal |
| GRAS | Generally Recognized as Safe |
| HU | Hounsfield Units |
| HVs | Healthy Volunteers |
| IB | Investigator Brochure |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| IP | Investigational Product |

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|---|---|
| IV | Intravenous |
| MRE | Magnetic Resonance - enterography |
| MRI | Magnetic Resonance Imaging |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Ph. Eur. | European Pharmacopeia |
| PoC | Proof of Concept |
| RCDAS | Radiological Crohn's disease Activity Score |
| RCE | Relative Contrast Enhancement |
| RF | Radio Frequency |
| ROI | Region of Interest |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| STD | Standard Deviation |
| SDV | Source Data Verification |
| SUSAR | Serious Unexpected Suspected Adverse Reactions |
| TEAE | Treatment-Emergent Adverse Event |
| TEADR | Treatment-Emergent Adverse Drug Reaction |
| TMF | Trial Master File |
| V/V | Volume per volume |
| W/W | Weight per weight |
| WHO | World Health Organisation |

# 5 INTRODUCTION

## 5.1 Background and study rationale

Lumentin® 44 is being developed as a novel oral contrast medium to be used in diagnostic examinations of the abdomen. Initial clinical development has focused computerized tomography (CT) (Leander et al., 2022; Leander et al., 2022) while the present trial aims to explore if the signal characteristics of Lumentin® 44 is favourable in Magnetic resonance enterography (MRE), a specialized type of magnetic resonance imaging (MRI) performed with a contrast material to produce detailed images of the small intestine.

Oral contrast agents are used prior to abdominal CT (abd-CT) and CT of the small bowel (CT-enterography, CTE) to demarcate bowel loops from its surroundings and to create a difference in density between the bowel and other structures in the abdomen. Till now, the only contrast agents available and used for diagnosis in abd-CT are positive, with Hounsfield Units (HU) around +80, or neutral, i.e., with HU around and above zero. Both agent types provide CT-images with unsatisfactorily low contrast between the wall and lumen of the small intestine. Hence, there is a considerable need for a bowel filling contrast agent with true negative HU that would offer notably larger lumen-to-wall contrast, a prerequisite for improved mucosal lesion detectability.

A phase II study have been performed using Lumentin® 44 as a contrast agent for CT with encouraging results (Leander et al., 2022). If the same product can also be used in MRE assessment it would be an advantage for a radiological department to only handle a single oral small bowel filling contrast medium for both modalities CT and MRI. In addition, Lumentin® 44 has shown to have a favourable safety profile and may be a more tolerable alternative to the oral media used today in both CT and MRI. This proof-of-concept (PoC) trial is performed in healthy volunteers (HVs) with the aim to show that Lumentin® 44 can be used as an oral, small bowel filling contrast agent for MRE.

## 5.2 Lumentin® 44

Lumentin® 44 is a novel, HU-negative contrast agent which is formulated as a powder for oral foam. The powder product contains egg white protein (EWP) as foaming agent, xanthan gum as stabiliser, phosphate salts as buffering agents, and flavouring.

Prior to use, the powder is mixed with water and whipped to a stable foam, containing 44% v/v air and less than 4 % w/w dry matter, which is orally administered. The whipped, ready to use Lumentin® 44 foam is stable with suitable characteristics (air content, volume, bubble size, homogeneity, consistency, stability and palatability) for at least 2 hours.

The air trapped in the foam is the radiological key component 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, but mesenteric vessels bordering the bowel wall are radiologically better visualized when loops are filled with Lumentin® 44. The reason for this is fewer image artefacts compared to diluted Omnipaque® (Omnipaque) in the gastrointestinal tract (GI) tract.

### 5.3 Clinical development to date

A previous formulation of the agent, Lumentin® 60 (60% v/v air), has been tested in a pilot Investigator initiated trial, approved by the local ethics committee and local institute of radiation protection (ref 1). The results were validated by 4 external reviewers and showed that Lumentin® 60 in its bowel filling capacity was on par with contemporarily used bowel filling agents (Omnipaque and Movprep®, Movprep). Furthermore, it was superior in contrast between bowel lumen and wall and revealed a favourable profile of side effects with no or only mild symptoms such as burping and fullness with preserved bowel consistency. The promising results obtained with Lumentin® 60 encouraged improved formulation, leading to Lumentin® 44, and continued clinical development to further explore the clinical importance of the improved contrast between bowel lumen and bowel wall with Lumentin® 44. A second goal for the new formulation was to guarantee high patient acceptance.

Lumentin® 44 has been investigated in two phase II trials:

In the completed and reported LUM-001 trial (Leander et al., 2022), the relative mean difference in contrast density shown on abdominal CT-images when using the contrast agent Lumentin® 44, was compared with abdominal CT-images using diluted Omnipaque and with abdominal CT-images using Movprep in subjects referred to computerized tomographic X-ray examination of the abdomen or thoraco-abdominal CT-examination.

Evaluation of clinical safety data confirm the favourable safety profile shown with Lumentin® 44. The difference in contrast density between bowel lumen and bowel wall was significantly larger after intake of Lumentin® 44 as compared with the comparator contrast agents Movprep and Omnipaque. There was no statistical difference in bowel filling properties. Neither was there any difference in diagnostic ability between Lumentin® 44 and Movprep or Omnipaque in this patient population (which had neither bowel disease nor bowel symptoms). The subjects' assessments of taste, smell, consistency, ability to swallow, and fullness placed Lumentin® 44 between Omnipaque and Movprep.

In trial LUM-002, the Radiological Crohn's disease Activity Score (RCDAS) of a CTE performed with Lumentin® 44 as a bowel filling contrast agent was compared with the RCDAS of a routinely performed MRE in patients with small bowel Crohn's disease. Evaluation of clinical safety data confirms the favourable safety profile shown in trial LUM-001. This trial has been completed but efficacy evaluation is ongoing.

Further details are available in the Lumentin® 44 Investigator Brochure (IB).

### 5.4 Risk-Benefit Assessment

EWP is widely used as a food ingredient. All excipients in Lumentin® 44, are of pharmacopoeia quality (buffer and stabiliser). The flavour complies with regulations concerning flavouring in food and food additives.

The side effects reported by subjects drinking up to 1.2 L of the Lumentin® 44 formulation in previously conducted trials indicate that Lumentin® 44 was well tolerated with only mild to moderate AEs reported.

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 impact 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 4 hours before and until 1 hour after administration of Lumentin® 44.

Potential side effects associated with intravenous (IV) catheterization include insertion site pain, phlebitis, hematoma formation and infusate extravasation. Mechanical issues such catheter obstruction/occlusion and dislodgement may occur. The hospital sites staff is very familiar and alert to signs and symptoms of such complications, and preventive measures are in place, as well as intervention procedures for if/ when complications do occur. The IV catheter will remain in place for the duration of the visit 2 (day of MRE procedure), until collection of 8h blood sample.

The proposed Phase II study will enrol only HVs and as such no direct benefit is expected for the trial subjects.

**Risks associated with Covid-19**

Considering that the subjects in the trial will be HVs, the risk of contracting COVID-19, as part of the trial procedures is considered low.

All subject visits to the hospital will occur in facilities which are not used for patients with COVID-19. Procedures to prevent COVID-19 infection, as recommended by the Swedish "folkhälsomyndigheten", will be followed.

# 6 TRIAL OBJECTIVES

## 6.1 Primary Objective

To evaluate if Lumentin® 44 used as a small bowel filling agent in MRE examination generates images with acceptable diagnostic quality.

## 6.2 Secondary Objectives

- To evaluate plasma electrolytes including, potassium, sodium, phosphate, and calcium, as well as ionized calcium concentration levels during 24 hours after intake of Lumentin® 44.
- To evaluate bowel filling properties (extension and distension) of Lumentin® 44.
- To evaluate the safety and tolerability of Lumentin® 44 intake.

# 7 OVERALL DESIGN AND PLAN OF THE TRIAL

## 7.1 Trial Overview

This is an uncontrolled, single centre phase II trial. Enrolled HVs (n=10) will undergo Gd-enhanced MRE after oral intake of Lumentin® 44.

Interested HVs will be identified primarily among medical students at the medical hospitals at Malmö and Lund. Posters will be placed at the departments and invitation letters will be handed out.

The HVs interested in participating will be invited to attend a pre-screening visit where their suitability based on age and health status will be assessed. Fifteen HVs who fulfil the pre-screening criteria and are interested in participating will be asked to attend a screening visit at the clinic and if eligible for the trial they will then visit the clinic for the MRE assessment within 1-2 weeks.

Only the initial 10 of the eligible HVs will be asked to come for the MRE examination and the remaining eligible subjects will be asked to stand by in case any of the 10 subjects are unable to come or cannot undergo the examination.

HVs will be asked to fast for 6 hours prior to the examination on the day of the MRE examination. Small amount of clear liquid is allowed up to 2 decilitres. Prior to MRE, Lumentin® 44 will be provided to them in volumes of up to 1,500 mL and at least 1,100 mL of Lumentin® 44 must be drunk. The subjects will be asked to drink the solutions of oral contrast agent within 45 minutes to 1 hour.

Subjects not able to drink at least 1.1 L of Lumentin® 44 will be withdrawn from the trial.

Prior to the intake of Lumentin® 44, an IV antecubital cannula will be placed and used for blood sampling and administration of gadolinium (Gd) contrast agent during the MRE assessment.

## 7.2 Outcomes

### *7.2.1 Primary Outcome*

Visual evaluation of the MRE images from each trial subject with respect to motility, artefacts, mucosal evaluation and overall diagnostic impression.

### *7.2.2 Secondary Outcomes*

- Concentration of plasma electrolytes including, potassium, sodium, phosphate, and calcium, as well as ionized calcium in blood samples taken at T0h, T1h, T2h, T4h, T6h, T8h, and T24h.
- Bowel filling properties (extension and distension) in each of 5 selected sub-segments of the small bowel.
- Any treatment emergent adverse events (TEAEs) and treatment emergent adverse drug reactions (TEADRs).

## 7.3 Justification of the Trial Design

### *7.3.1 Justification for Design and Parameters*

Lumentin® 44 is currently being developed to be used as a small bowel filling contrast agent when CT examination is performed. Two clinical trials have so far been performed and a phase 3 trial is planned to start 2023.

Most radiology departments perform both CT and MRE examinations and it is advantageous and convenient for them to be able to provide the same oral contrast agent for both procedures. Lumentin® 44 is food based with Generally Recognized as Safe (GRAS) excipients and has in the previous clinical trial been accepted and tolerated well with only mild to moderate AEs reported. In the LUM-001 trial in subjects referred for abdominal CT-examination that evaluated the CT image quality and diagnostic feasibility of Lumentin® 44 in comparison with diluted Omnipaque and Movprep, the most common TEAEs in the Lumentin® 44 arm, were flatulence (4 subjects, 22%) and nausea (2 subjects, 11%). In the LUM-002 clinical trial in patients with small bowel Crohn's disease that evaluated Lumentin® 44 as contrast agent in CT-enterography as compared to MRE, the most common (occurring in ≥2 subjects) TEAEs, in the Lumentin® 44 arm, were diarrhoea (10 subjects, 18%), nausea (3 subjects, 5%), and flatulence (2 subjects, 4%).

To be able to use Lumentin® 44 in MRE, the diagnostic quality cannot be inferior to the standard oral regimen. Therefore, the trial selected pivotal parameters in reading MRE as primary endpoints.

As the air in Lumentin may degrade the image quality in MRI in the interface to soft tissue the most relevant parameters were chosen. In motility sequences the moving small intestine filled with air may aggravate the problem and the other parameters where the small intestine should remain still it is most relevant to scrutinize the structures, e.g., mucosal folds, in the interface between air and soft tissues.

It is important for the quality of the MRE images that the small bowel is adequately filled with the contrast agent. The clinical endpoint measuring filling properties is therefore included. Extension is the measurement of how far down in the small bowel the contrast agent has reached, and the distension parameter measures the how distended (widened) the small bowel is.

Palatability of the contrast agent is an important factor for the subject's acceptance and ability to drink it. The subjects are therefor asked to evaluate features describing how they experience drinking the Lumentin® 44 foam.

The choice of not including a comparator and expose the HV to another contrast agent have been made based on that the aim of the trial is to investigate the general quality of the MR images when using Lumentin® 44, and that both the investigational MRE examination and the drug Lumentin® 44 are safe to use. From a medical, empirical, perspective it is not considered necessary to include more than 10 subjects to generate data sufficient for showing PoC. The sample size is not determined on any mathematical grounds as this is a PoC trial.

HVs to be enrolled in the trial must be able to undergo an MRE examination and should not have any known egg allergy.

### *7.3.2 Justification for Route and Dosage*

A total of 73 subjects in previous clinical trials (LUM-001 and LUM-002) were asked to drink between 0.75 -1.5 L foam and the average amount drunk was 1026 mL of Lumentin® 44 foam. The amount of contrast agent that a subject can drink varies between subjects depending on e.g., age, weight, gender and medical condition. It is therefore necessary to define the recommended dose within a range.

This trial will recruit predominantly young HVs, and electrolyte levels will be investigated. The range is therefore narrower and the lower limit in the range is also higher than in previous trials. The lower limit in the dose range is set to 1.1 L. The recommended dose will be 1.2 L with the allowed upper range set to 1.5 L.

The route of administration is according to standard practice for an oral contrast agent.

# 8 TRIAL POPULATION

The trial population will consist of healthy volunteers.

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 the following criteria:

1. Healthy volunteers 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. 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. GFR below 60 ml/min/1.73 sqm body surface. All subjects will have a plasma creatinine taken at screening for calculation of eGFR.
2. History of drug related reaction to gadolinium contrast agents.
3. Have had gadolinium injection during the last 4 weeks.
4. Claustrophobia not coping with MRE examination.
5. Metal objects and medical devices in the body not judged by the investigator to be compatible with MRE.
6. Hypersensitivity to Buscopan® (Butylhyoscopin).
7. Having swallowing difficulties.
8. Known allergy to egg albumen.
9. Known sensitivity to any of the components of the investigational product.
10. Clinical suspicion of ongoing disease by the investigator.
11. Being, in the opinion of the investigator, unlikely to comply with the clinical trial protocol.
12. Previously randomized to participate in this trial.
13. Participating in or having participated in another clinical trial within the last 4 weeks.

## 8.3 Subject Withdrawal and Replacement

### *8.3.1 Withdrawal from Trial Therapy*

Subjects must be withdrawn if the intake of the contrast agent has to be stopped, please see section 9.2 Dosage and Administration.

### *8.3.2 Withdrawal from Study*

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
- Subjects who have not fasted (clear water allowed) for at least six hours prior to the intake of the contrast agent
- The subject is unable to drink at least 1.1 L of Lumentin® 44
- The subject is unable to complete the MRE examination, due to e.g., claustrophobia.
- Violation of eligibility criteria

Subjects withdrawn due to the above circumstances will be replaced by one of the five remaining eligible HV subjects on standby after screening.

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 10)
- At the discretion of the Investigator

In all cases, the reason(s) for withdrawal must be recorded on the Case Report Form (CRF). 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 **Fel! Hittar inte referenskälla.**).

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

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

HVs withdrawn prior or during the MRE examination (i.e., no evaluable MRE scan has been generated) will be replaced by a new HV. HVs withdrawn after the completion of MRE examination and NOT fulfilling the mandatory criteria for withdrawal listed above will not be replaced.

### 8.4 Definition of End of Study

The end of trial visit will be the last subject last visit which will occur at the follow up visit, two days after the MRE examination, or in case of an ongoing AE at the follow up visit, any additional visit required for AE follow-up.

### 8.5 Medical Care of Subjects after End of Study

The trial will only include healthy volunteers and there is therefore not need for medical care after the trial. However, in case the MRE examination reveals any relevant previously unknown medical condition, the subject will be informed and guided to contact appropriate medical expertise.

### 8.6 Planned Sample Size and Number of Trial Centres

It is planned to enrol 10 evaluable subjects in a single clinical site.

# 9 INVESTIGATIONAL PRODUCT AND PROCEDURES

## 9.1 Investigational product

Lumentin® 44 Powder for oral foam (Table 1) will be manufactured by Apotek Production & Laboratories AB, Prismavägen 2, SE-141 75 Kungens Kurva, Sweden and provided in labelled white sachets containing 17.4 g powder. Potable water (commercially available still water 0.5 L per bottle) for the preparation of the foam will be used.

**Table 1: Lumentin® 44 Powder for oral foam**

| Ingredients | Concentration (g/sachet) |
|---|---|
| Egg White Powder | 10.0 |
| Sodium dihydrogen phosphate dihydrate ($NaH_2PO_4 \cdot 2H_2O$) [1] | 1.0 |
| Dipotassium phosphate ($K_2HPO_4$) [1] | 3.4 |
| Xanthan gum [1] | 2.5 |
| Flavour [2] | 0.5 |

1) Ph. Eur.: European Pharmacopeia
2) The flavour complies with the regulations (EC) 1334/2008 and (EC) 178/2002 concerning flavouring in food and food additives.

Lumentin® 44 powder for oral foam will be delivered from APL to the clinical site, by order via the hospital pharmacy and stored temporarily at the site. The investigational product (Lumentin® 44 foam) is then prepared in-situ by adding 0.5 L potable water to Lumentin® 44 powder contained in one sachet, and the blend is then mixed to a stable foam in a dedicated preparation unit. The freshly prepared foam will be administered to the patient within 5 to 10 minutes as directed in the clinical trial protocol. The in-situ preparation will follow a procedure attached to the clinical trial protocol. The staff responsible for the in-situ preparation will be trained using the procedure and their training documented in the Trial Master File (TMF). Two sachets (0.9 L foam per sachet) will be required per subject.

For a detailed description of the preparation of Lumentin® 44 Foam (see Appendix 1 Lumentin® 44 : Lumentin 44 reconstitution protocol summary).

Lumentin® 44 Foam contains the same ingredients as Lumentin® 44 Powder for oral foam, see **Fel! Hittar inte referenskälla.**, except for water added during the preparation.

### 9.2 Dosage and Administration

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

A volume of 1.1 L to 1.5 L shall be consumed. A steady intake rate of the contrast agent is recommended to guarantee fullness of the gastrointestinal tract from stomach to terminal ileum of the small bowel.

The intake of the contrast agent will be stopped in case of an AE occurs or if the subject is unable to consume more than 1.1 L within 1 and ½ hour. The subject will be withdrawn in case the intake of the contrast agent has to be stopped.

The subject will be withdrawn from the trial if the maximum volume of the Investigational product taken by the subject is less than 1.1 L.

There is no risk of overdose.

### 9.3 Packaging, Labelling and Storage

Lumentin® 44 powder for oral foam will be supplied in white sachets labelled according to EU-GMP, Annex 13. Ten sachets will be placed in a secondary package consisting of white unprinted cardboard. Lumentin® 44 powder for oral foam should be stored at room temperature (below 25°C) in a restricted area, accessible to authorised personnel only.

### 9.4 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 CRF.

All unused investigational product (Lumentin® 44 powder for oral foam) will be returned to Lument AB at the end of the trial.

### 9.5 Lumentin® 44 Exposure and Compliance

All Lumentin® 44 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 CRF.

The exact volume of the Lumentin® 44 foam in the drinking container will be determined prior to dispensing it to the subjects but it will be at least 1.1 L. The weight of the contrast agent will be measured prior to dispensing and any remaining contrast agent will be weighed after intake. Volumes will be noted in the CRF Drug accountability will be carried out at regular intervals, as specified in the monitoring plan.

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 to obtain MRE scans with good diagnostic readability.

# 10 PROHIBITED PREVIOUS AND CONCOMITANT MEDICATION

## 10.1 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 CRF. The following information must be recorded in the CRF 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 treatment must be recorded in the CRF.

At visit 1, subjects will be asked what medications they have taken during the last 2 weeks before visit 1. Concomitant medications will be recorded at each visit and during telephone interviews, if applicable.

All subjects will receive:

1. An intravenous injection of Buscopan 40 mg. The dose given and batch number of Buscopan 40 mg will be noted in the CRF
2. An intravenous injection of the Gd contrast agent (Clariscan®, 0.5M) during the MRE-examination at a dose of 0.1 mmol/kg b.w. The volume given is typically 10 – 20 ml. The dose given and batch number of the Clariscan® 0.5M will be noted in the CRF.

## 10.2 Permitted/Prohibited Medicines

All use of medication taken by any route will be prohibited during 4 hours before taking the contrast agents and one hour post the intake. Thereafter only contraceptives and occasional painkillers are allowed.

## 10.3 Permitted/Prohibited Procedures

HVs shall not undergo more than normal physical living during the first 24h of the study, meaning that training and hard physical exercise are not allowed.

### 10.4 Precautions/overdose

Risks associated with intake of oral contrast agents include dysphagia with aspiration and secondary pneumonia. Although this trial intends to enrol only healthy volunteers and subjects 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 subjects, to those with swallowing disorders, or an acute abdomen problem.

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.

Intravenously administered Gd may cause allergic reaction of various severity from a mild rush to intensive care unit treatment. This is especially true for those with allergic reactions to a contrast agent earlier in life. Allergic reaction may be trigged in those with asthmatic bronchitis and treated with beta-blockers. 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. Neither Buscopan nor Gd should be administered to patients with severe kidney failure.

# 11 VISIT SCHEDULE AND ASSESSMENT DESCRIPTION

## 11.1 Visit schedule

### *11.1.1 Pre-screening visit (Visit 1: Day -21 to -1)*

Pre-screening assessments will include:

- Recording of subject information.
- Recording of past medical and surgical history.
- Recording of concurrent illness and treatments.
- Eligibility check with regards to inclusion criterion 1 and exclusion criteria 2, 3, 4, 5, 6, 7, 8, 12 and 13.

### *11.1.2 Screening visit (Visit 2: Day 0)*

Screening assessments will include:

- Obtaining of written informed consent prior to any study specific procedure (including screening procedures) being performed.
- Recording of subject information and demographics including, date of birth, sex, height and weight
- Recording of past medical and surgical history.
- Recording of concurrent illness and treatments.
- Inclusion/ exclusion criteria.
- Preforming a physical examination.
- Females will be asked to undertake a urine pregnancy test
- Obtaining a creatinine blood sample

### *11.1.3 MRE examination visit (Visit 3: Day 14)*

During this visit the MRE examination will be performed, including the following assessments:

- Recording of concomitant treatments
- Recording of AEs
- Placement of the IV antecubital cannula
- Dispensing of Lumentin® 44

- MRE examination
    - Administration of Gd contrast
    - Administration of Buscopan®
- Evaluation of extension and distension of bowel filling agents
- Blood sampling for electrolyte assessment (pre-, 1, 2, 4, 6, 8h)
- Recording of compliance

#### *11.1.4 Blood sampling visit (Visit 4: Day 15)*

During this visit the following assessment will be performed:

- Recording of concomitant treatments
- Recording of AEs
- Blood sampling for electrolyte assessment (24h)

#### *11.1.5 F-U and early termination visit (Visit5: Visit 2±2 days)*

During this visit the following assessment will be performed:

- Recording of concomitant treatments
- Recording of AEs

### 11.2 Assessment descriptions

#### *11.2.1 Subject Demography*

Subject demography consists of date of birth, sex, height and weight.

#### *11.2.2 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 CRF.

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.

#### *11.2.3 Pregnancy Test*

In women of childbearing potential, urine pregnancy test will be performed at screening.

### *11.2.4 Concomitant Medication*

Information on concomitant treatment will comprise all concomitant therapies at the MRE examination and until the end of treatment visit 2, blood sampling. Acceptable concomitant treatment options are described in Section 10.1.

### *11.2.5 Assessment of Safety*

AEs will be recorded from the time of informed consent (Day 0) until the follow-up visit or early termination visit.

For safety reasons, subjects will be contacted within 2 to 4 days after the MRE examination by the investigator and asked about occurrence of any adverse event. No other follow-up is planned.

Detailed instructions regarding AE handling, monitoring and reporting are provided in Section 0 (Adverse Events).

### *11.2.6 Electrolyte assessment*

Plasma potassium, sodium, phosphate, and calcium, as well as ionized calcium blood concentration levels will be monitored over 24 hours from just before (baseline) the subject starts drinking Lumentin® 44. Blood samples will be drawn at baseline (T0h), and then at 1 hour (T1h), 2 hours (T2h), 4 hours (T4h), 6 hours (T6h), 8 hours (T8h) and at 24 hours (T24h).

An IV antecubital cannula will be placed for pre-blood samples and used during the first 8h including administration of Gd during the MRE procedure. Thereafter it will be discarded. Blood sampling on the following day after (24h time point) will be drawn without a cannula.

Electrolyte blood samples will be taken, handled, and analysed according to standard procedures at the clinic. The laboratory will provide normal ranges.

### *11.2.7 MRE examination*

Preparation before MRE: Subjects will be fasting (2 decilitres of clear water is allowed) for at least six hours prior to the MRE procedure.

The MRE-examination will take approximately 40 minutes. The MR-examination will not be performed if the subject has not been able to drink at least 1.1 L of Lumentin® 44.

Broadly, MRE is a scanning technique for creating detailed images of parts of the human body, using a strong magnetic field and radio waves. It is based on the magnetisation properties of atomic nuclei. A powerful, uniform, external magnetic field is employed to align the protons that are normally randomly oriented within the water nuclei of the body part examined. This alignment (or magnetisation) is disrupted by introduction of an

external Radio Frequency (RF) wave energy. The nuclei return to their resting alignment through various relaxation processes and in doing so emit RF energy. Tissues are characterised by two different relaxation times, of which T1, the longitudinal relaxation time, determines the rate at which excited protons return to equilibrium. It is a measure of the time taken for spinning protons to realign with the external magnetic field. The contrast and brightness of the image are predominately determined by T1 properties of tissue.

During an MRE-examination, the subject will be asked to lie prone on a movable table that will slide into a doughnut-shaped, deep opening and centred for scanning the small bowel. As part of the procedure a strong magnetic field will be generated around the subject, and pulsating radio waves will be directed at the body. Because of loud thumping and tapping noises during the scan the subject will be given headphones to listen to music or earplugs to help block the sound. The subject will be able to communicate with the technician who gives instructions during the test. The contrast agent Clariscan® (0.1 mmol/kg) and the muscle relaxant Buscopan® (40 mg) (to reduce bowel motility) will be administered IV. Clariscan and Buscopan can be replaced with comparable product according to the standardised procedures at the clinic. The specific details of the MRE-system used will be noted in the CRF.

## 11.3 Outcome assessments

### *11.3.1 Primary outcomes*

All MRE images will be evaluated by one expert radiologist. Only one assessment of each MRE examination will be performed.

The primary endpoint is the visual evaluation of the MRE images according to the following parameters:

**Motility:** MRE examinations with Lumentin® 44 will be scored with respect to motility status based on a 5-graded scale, as follows:

1. No motility could be assessed
2. Motility is assessed to some degree but less good than conventional MRE
3. Motility is assessed to same degree as conventional MRE
4. Motility is assessed somewhat better than conventional MRE
5. Motility is assessed better than conventional MRE

Motility should be evaluated as a whole in the specific cine- sequences and resulting in one ordinal score 1-5.

**Artefacts:** MRE examinations with Lumentin® 44 will be scored with respect to artefacts based on a 5-graded scale, as follows:

1. Severe deteriorating artefacts in the interface between the lumen and wall
2. Disturbing artefacts in the interface between the lumen and wall less good compared to conventional MRE
3. Medium artefacts in the interface between the lumen and wall, same as for conventional MRE
4. Small artefacts that give minimal bright edges in the interface between the lumen and wall, somewhat better than conventional MRE
5. No artefacts and better than conventional MRE

Artefacts should be evaluated as a whole in all sequences and resulting in one ordinal score 1-5.

**Mucosal evaluation:** MRE examinations with Lumentin® 44 will be scored with respect to mucosal status based on a 5-graded scale, as follows:

1. No mucosal folds are seen
2. Some small mucosal folds can be discriminated
3. Mucosal folds can be discriminated, same as for conventional MRE
4. Small mucosal folds can be discriminated, somewhat better than for conventional MRE
5. Mucosal folds are seen in detail and better than conventional MRE

Mucosal evaluation a) coronal and b) axial T1 gradient-echo with Gd should be done and resulting in one ordinal score 1-5.

**Overall diagnostic impression:** MRE examinations with Lumentin® 44 will be graded for global quality of the information obtained with special reference to diagnostic purposes, as follows:

1. Poor diagnostic quality
2. Medium diagnostic quality, below conventional MRE
3. Good diagnostic quality, same as for conventional MRE
4. Very good diagnostic quality, somewhat better than conventional MRE
5. Excellent diagnostic quality, better than conventional MRE

The quality of the whole examination and what the impression is for using the examination for diagnostic purposes will be graded.

### *11.3.2 Secondary outcomes*

**Electrolyte changes:** Changes in electrolytes in the blood of each subject will be evaluated by comparing basel Plasma concentration was measured over 24h from before

administartion of Lumentin 44 (T0h) t0 24 hours post administration (T24h) ine (pre-Lumentin® 44 oral intake) and timepoints up to 24 hours post Lumentin® 44 oral intake.

**Bowel filling properties:** Extension and distension will be evaluated in each of five selected sub-segments of the small bowel. All images will be evaluated by the investigator with respect to how well the small bowel is filled from the bowel through to the terminal ileum (extension) and how well it is distended (distension) by Lumentin® 44. The small bowel will be divided in duodenum, jejunum, proximal ileum, distal ileum and terminal ileum. Both variables will be judged on a scale from 1 to 5, as follows:

- Extension: 1 is no filling and 5 is filled completely
- Distension of the segment of small bowel: 1 is no distension and 5 is optimal distension

**Safety outcomes:** All adverse events in this study will be collected and processed in accordance with ICH-GCP and national and local laws and regulations. In line with these, the Investigator is responsible for reporting Serious Adverse Events (SAEs) to Sponsor within the appropriate timelines. If required, the Investigator is also responsible for notifying the appropriate local ethics committee of SAEs per the guidelines of the Institution and in accordance with aforementioned laws and regulations. Detailed description on handling, monitoring and reporting AEs is provided in Section 0.

# 12 ADVERSE EVENTS

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. Untoward medical occurrences occurring prior to the MRI/ MRE assessment will not be reported as an adverse event. All AEs occurring throughout the trial will be recorded and followed.

*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 IMP, whether or not considered related to the IMP.

### *12.1.1 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.

### *12.1.2 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.

### *12.1.3 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.

## 12.2 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 of contrast agent until the follow-up visit. Also, telephone interviews will be made 2 days after MRE assessment to investigate if any AEs occurred during the first days after the examination. Any pregnancies occurring in the same trial period will be reported and followed.

Reported AEs will be followed up (see Section 12.5 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 CRF and should include the following information:

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

AEs will be coded with Medical Dictionary for Regulatory Activities (MedDRA), the version of which will be provided in the trial report.

### *12.2.1 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.

#### *12.2.2 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.

### 12.3 Follow-up of Subjects after Adverse Events

AEs that are serious or those that the investigator assesses as relevant to follow from a trial perspective will be followed until they are recovered, stabilised, or recovered with sequelae. The date and outcome will be recorded on the AE form in the CRF. Other ongoing AEs will not be followed within the trial after the date of the follow-up visit.

### 12.4 Abnormal Laboratory Values

Other than electrolytes, safety laboratory parameters will not be assessed in this trial.

### 12.5 Reporting of Serious Adverse Events

The Investigator is responsible for ensuring that all SAEs are reported to the Sponsor 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. All AEs that meet the criteria for SAE require the completion of a study specific SAE Form (or Additional Safety Information (ASI) Form).

This applies to all SAEs, whether they were considered to be related to the study treatment or not.

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

The Investigator must report all SAEs to Sponsor immediately, i.e., within 24 hours (via email or fax) of learning of its occurrence. For this reporting, an SAE Form (provided in the Investigator File) needs to be completed. Follow-up information about a previously reported SAE must also be reported to Sponsor within 24 hours of receiving the information. This follow-up data must be provided on an ASI Form.

If a SAE occurred after signing informed consent, but before study treatment and the subject continues on study, a SAE must also be entered on the relevant Medical History page of the CRF.

The SAE report should provide a detailed description of the AE and should include anonymised copies of hospital records and other relevant documents.

All SAEs will need to be followed actively until resolution or stabilisation. The above is also applicable to follow-up SAE information.

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 unexpected suspected adverse reactions [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.

The sponsor is required by law to report to the health authorities in a written safety report: 1) all fatal or life-threatening SUSARs within seven (7) calendar days of initial notification; and 2) all other SUSARs within fifteen (15) calendar days of initial notification.

### 12.6 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.

Intravenously administered Gd may cause allergic reaction of various severity from a mild rush to intensive care unit treatment. This is especially true for those with allergic reactions to a contrast agent earlier in life. Allergic reaction may be trigged in those with asthmatic bronchitis and treated with beta-blockers. 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. Neither iodine nor Gd should be administered to patients with severe kidney failure.

# 13 STATISTICAL METHODS

## 13.1 General statistical considerations

No statistical tests will be conducted. Confidence intervals may be constructed and will then be 2-sided and of 95% confidence.

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.

## 13.2 Sample Size

A total of 10 fully evaluable healthy volunteers will be included in the trial. The number of subjects is considered to be enough to draw clinical conclusions and is not based on any mathematical grounds.

## 13.3 Analyses Sets

All subjects who have fulfilled the trial will be included in the statistical evaluation.

## 13.4 Description of Statistical Analyses

A collected data will be summarised using descriptive statistics and confidence intervals. No statistical tests are planned to be conducted.

## 13.5 Data collection

The data in this trial will be recorded on paper CRFs, as per data management and quality assurance procedures described in Section 0. When the data on the CRFs has been verified (by the study monitor) against source data they will be sent for data entry. All CRFs will be signed by the principal investigator.

Data entry will be conducted using the verified CRFs as source. All data entry will be controlled using proof reading.

When data from all subject's CRFs are entered into the data base a clean file meeting will be held. At that meeting it will be decided if any of the subjects should be excluded from statistical analysis.

When it has been decided which subjects should be included in the data analyses, the trial database will be locked and a copy of the it will be sent for statistical analyses.

# 14 ETHICS

## 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 clinical study was designed and shall be implemented and reported in accordance with the protocol, ethical principles laid down in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP).

If any changes to the protocol are required, the protocol must be amended (see Section 16.2).

## 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 EU general data protection regulation 2016/679 (GDPR), 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 general data protection regulation 2016/679 (GDPR).

### 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

Our newly invented per oral agent for bowel filling prior to CT or MRE of the abdomen has revealed a good potential to improve imaging of the bowel wall in comparison to currently used contract imaging agents. In addition, being able to use the same agent for both these procedures will offer operational benefits to diagnostic clinics.

Potential benefits for future patients include first and foremost MRE images easier to interpret, thereby facilitating diagnostics of early and hitherto silent disease, and reducing the risk of misreading. Secondly, risks of adverse effects are likely to be notably low as our new agent is food-based with 44% v/v air in water, 2% egg white protein, less than 1% buffer agent, and less than 1% foam stabilizer and taste improving additives.

# 15 DATA MANAGEMENT AND 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 CRFs for this trial must, if applicable, 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 CRFs. The company has therefore assigned a CRO 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 attributable, legible, contemporaneous, original and accurate 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 CRF 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 CRFs 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 CRF 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, 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).

### 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. Documents are 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, 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).

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 CRFs by verifying data recorded in the CRF against data recorded in source documents to ensure such records are consistent.

To enable SDV, it is essential that source data/documents (see definition above) for the trial data to be collected in the CRF 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. The CRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified in the Origin of source data document at site.

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

- A statement that the subject participates in a clinical trial
- The identity of the trial e.g., Trial code
- Subject / number
- date of conducting informed consent process
- data for evaluation of eligibility criteria
- dispensation/administration of trial medication

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the CRFs. Data reported in the CRF that are derived from source documents should be consistent with the source documents or the

discrepancies should be explained. Completed sections of CRFs will be monitored on a regular basis.

### 15.5 Case Report Forms (CRFs)

Data collected in this trial will be by means of paper CRFs.

The CRFs 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 sign all sections of CRFs 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 CRF 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 CRFs for accuracy and completion and perform source data verification. For archiving purposes, each investigator will be supplied with a copy of the CRFs, for all patients enrolled at the site. Audit trail information will be included. CRFs 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 CRF by authorised site staff in a timely manner and not later than a week after the patients' visits. Data will be entered on the paper CRF by site staff

When a paper CRF is completed and signed by site staff it will be sent to StatCons for data entry. Personnel at StatCons will enter the data into an electronic data base. The data entry will be verified by proofreading by personnel at StatCons. When all data from all paper CRFs are entered into the electronic data base and proofread the data base will be locked and send to the sponsor for archiving. As well the statistical analyses/summaries will start based on data in the locked data base.

Any deviations, i.e., discrepancies and additions from the process defined in the Data Management Plan, will be described in the statistical report.

### 15.7 Archiving Trial Records

According to International Conference on Harmonisation (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: January 2023.
- Planned date of enrolment of last patient: February 2023.

## 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 amendments 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/favourable 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 duration of the trial for each subject from screening to the Follow-up (or early termination) visit will be up to 17 days, depending on the available time slots for MRE examination.

The trial will be closed when all enrolled subjects have completed the last subject last visit, as defined in section 8.4 Definition of End of Study.

## 16.5 Completion of Trial

### *16.5.1 Trial Completion Procedures*

The end of trial is defined as the date of the last subject last visit.

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

Trial enrolment will be stopped when the total requested number of evaluable subjects for the trial has been obtained i.e., 10 subjects.

Upon completion of the trial, Lument AB will undertake arrangements for collection and disposal of 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. In this case, 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 Lumentin® 44.

### 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/ her 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 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.

In the event of a publication, the names of the authors and their order of appearance will be in accordance with the agreement inter peers, viz. papers mainly dealing with medical and gastroenterological data will present the name of the principal gastroenterologist first (or last if wished for). Papers mainly dealing with radiologic issues will present the name of the principal radiologist first (or last if wished for). The second name will be the principal author of the other speciality. All other authors will primarily be presented in alphabetic order.

## 17 REFERENCE LIST

Leander P, Adnerhill I, Böök O, Casal-Dujat L, Stathis G, Fork T. A novel food-based foam as oral contrast agent with negative Hounsfield units for demarcation of small bowel loops on abdominal CT: tolerability and bowel distension in 25 volunteers. Acta Radiol. 2021 Dec;62(12):1559-1566.

Leander P, Stathis G, Casal-Dujat L, Boman K, Adnerhill I, Marsal J, Böök O, Fork T. A novel food-based negative oral contrast agent compared with two conventional oral contrast agents in abdominal CT: a three-arm parallel blinded randomised controlled single-centre trial. Eur Radiol Exp. 2022 Apr 5;6(1):15.

# 18 APPENDICES

## 18.1 Appendix 1: Lumentin 44 reconstitution protocol summary

SUMMARY OF CMPDU OPERATION

Gloves on

I. For the preparation for one trial subject, gather two L44 powder sachets, two glass jars, two 1.5-L PET jars and two 0.5-L bottles of water.

PREPARATION OF THE FIRST FOAM

2. Fill in the BEFORE FOAM PREPARATION section on the Whipping report_LUMRIS- 001 V3.0.

3. Open one L44 powder sachet and pour the entire sachet of powder into one of the glass jars outside the mixing chamber of the CMPDU.

4. Make sure the CMPDU is supplied with electricity and turn on power (button on the back side).

5. Open the mixing chamber door.

6. Install the mixing tool.

7. Put the jar into the mixing chamber.

8. CLOSE the mixing chamber door.

9. Open the water bottle.

10. Connect water bottle to the CMPDU.

11. Make sure the water bottle is tightened enough to the connector and the bottle is placed at the lower position, so water stays in the bottle.

12. Press the start button.

13. Flip the bottle to the top position.

14. Wait until the L44 foam reconstitution is finished, which is indicated by the complete lightened LED lights on the HMI.

15. Flip down the water bottle.

16. Open the mixing chamber door.

17. Take out the mixing tool with a piece of kitchen paper towel underneath to contain the excess foam from the blade; wash the mixing tool and dry it with kitchen paper towel. Install back the mixing tool to the CMPDU.

18. Take out the jar from the mixing chamber and close the door of the mixing chamber.

19. Fill in the AFTER FOAM PREPARATION section on the Whipping report_LUMRIS-001_V3.0.

20. GENTLY pour out L44 to a 1.5-L PET jar.

21. Take the 1.5-L PET jar with L44 foam and walk towards where the trial subject is sitting.

22. Give the trial subject the L44 foam in the 1.5-L PET jar and a small drinking cup.

23. Go back to prepare the second jar of L44 accordingly.

PREPARATION OF THE SECOND FOAM

24. Fill in the BEFORE FOAM PREPARATION section on the Whipping report_LUMRIS-001 V3.0.

25. Open one L44 powder sachet and pour the entire sachet of powder into one glass jar outside the mixing chamber of the CMPDU.

26. Make sure the power is on.

27. Open the mixing chamber door.

28. Install the mixing tool.

29. Put the jar into the mixing chamber.

30. CLOSE the mixing chamber door.

31. Open a new bottle of water bottle.

32. Replace the empty bottle of water with the new bottle; connect the new water bottle to CMPDU.

33. Make sure the water bottle is tightened enough to the connector and the bottle is placed at the lower position, so the water stays in the bottle.

34. Press the start button.

35. Flip the bottle to the top position.

36. Wait until L44 foam reconstitution is finished, which is indicated by the complete lightened LED lights on the HMI.

37. Flip down the water bottle.

38. Open the mixing chamber door.

39. Take out the mixing tool with a piece of kitchen paper towel underneath to contain the excess foam from the blade; wash the mixing tool quicky with tap water and dry it with kitchen paper towel. Install back the mixing tool to the CMPDU.

40. Take out the jar from the mixing chamber and close the door of the mixing chamber.

41. Fill in the AFTER FOAM PREPARATION section on the Whipping report_LUMRIS-001_V3.0.

42. GENTLY pour out L44 foam to the 1.5-L PET jar.

43. Take the 1.5-L PET jar with L44 foam and walk towards where the trial subject is sitting.

44. Give the trial subject the L44 foam in the 1.5-L PET jar and a small drinking cup.

45. Go back to the CMPDU.

46. Disconnect the empty water bottle if this is the last foam to prepare of the day; otherwise, leave the bottle connected before making a new foam with a new bottle of water.

47. Recycle the water tubing set back to Lument AB after the last foam of the day.

48. After the last foam of the day, hand wash the mixing tool with food-grade detergent and dry with kitchen tissue towel or wash the mixing tool in the dishwasher (foodstuff compatible is sufficient).

49. Wipe the mixing chamber if any visible L44 has dropped.

50. Power off the CMPDU at the end of the day (button on the back side of the CMPDU).

51. If there is any foam dropped onto the jar holder, press the cleaning mode button to let loose the jar holder.

52. Hand wash or wash in the dishwasher the jar holder.

53. Fix the jar holder back into the mixing chamber once it's cleaned.

# 19 SIGNATURE PAGES

**Declaration of Sponsor or Responsible Medical Officer**

**Title:** An uncontrolled, single centre, healthy volunteer, Phase II proof-of-concept trial investigating MR-enterography image quality of Lumentin® 44, a new egg albumen based oral small bowel filling contrast agent.

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).

_____ _____

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**Declaration of the Investigator**

**Title:** An uncontrolled, single centre, healthy volunteer, Phase II proof-of-concept trial investigating MR-enterography image quality of Lumentin® 44, a new egg albumen based oral small bowel filling contrast agent.

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).

_____ _____

Signature Date

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