CLINICAL STUDY PROTOCOL

Document Date: Version 1.2, November 18, 2021

NCT #: NCT04893239

Exploratory study to assess delivery of LMN-201 components via enteric capsules in the gut of individuals with ileostomies

Protocol Study Number CDI01

Investigational Product: LMN-201

LMN-201 is a cocktail consisting of a bacteriophage lysin specific for C. difficile organism and three VHH-derived proteins that bind and inhibit C. difficile toxin B, delivered in whole, spray-dried spirulina biomass

Version 1.2

November 18, 2021

Principal Investigator: Carl Mason, MD Senior Medical Director Lumen Bioscience, Inc. 1441 N. 34th Street, Suite 300 Seattle, WA 98103, USA cmason@lumen.bio Lead Site Principal Investigator: James Daveson, MD Director Coral Sea Clinical Research Institute Suite 7, 76 Willetts Road North Mackay QLD 4740 james@coralseaclinical.com	Company Sponsor: Lumen Bioscience, Inc. 1441 N. 34th Street, Suite 300 Seattle, WA 98103, USA (206) 899-1904 www.lumen.bio Local Sponsor: Avance Clinical Level 1, 2 Ann Nelson Drive, Thebarton South Australia 5031 Phone: +61 8 8249 4788 www.avancecro.com

PRINCIPAL INVESTIGATOR'S AGREEMENT

An exploratory study to assess delivery of LMN-201 components via enteric capsules in the gut of individuals with ileostomies

I have received and read the Investigators' Brochure for LMN-201. I have read this clinical protocol and agree to conduct the study as outlined in this protocol and according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, The Nuremberg Code, The Belmont Report, The Declaration of Helsinki 2000, US 21 CFR Part 50--Protection of Human Subjects, 32 CFR 219 (The Common Rule), and all regulations pertinent to the Department of Defense, and relevant regional and/or national laws. Confidentiality of all information received or developed in connection with this protocol will be maintained by me, as well as all other personnel involved in the clinical trial who are employed or contracted by me or my organization.

_____ _____

Site Principal Investigator Date

SPONSOR SIGNATURE

Carl Mason, MD
Senior Medical Director

Date

CONTACT INFORMATION

Table 1: Contact Information

Role in Study	Name	Address and Telephone
Site Principal Investigator (PI)	Dr. James Daveson	Coral Sea Clinical Research Institute Suite 7, 76 Willetts Road North Mackay QLD 4740 Phone: +61 7 4910 9532 Email: james@coralseaclinical.com
Data Management/ Safety Reporting Contract Research Organization	Florin Bercu	Avance Clinical Level 1, 2 Ann Nelson Drive, Thebarton South Australia 5031 www.avancecro.com Phone: +61 8 8249 4788 Email: Florin.Bercu@avancecro.com
Sponsor Medical Monitor/ 24-Hour Emergency Contact	Dr. Carl Mason	Lumen Bioscience, Inc. 1441 N. 34th Street, Suite 300 Seattle, WA 98103, USA Phone: +1(206) 899-1904 Mobile: +1(805) 455-8593 Email: cmason@lumen.bio

Table of changes, version 1.1	Location	Reason	Date
Edited to use the term 'ileostomy' rather than 'ostomy'	All	HREC request	27MAY21
Clarified enrollment criteria for second cohort	Synopsis	HREC request	27MAY21
Clarified that first cohort participants will receive only one of the VHH proteins, administered in 3 capsules	Synopsis	HREC request	27MAY21
Modified exploratory objectives and endpoints	Synopsis, Section 4	Sponsor-initiated change	27MAY21
Removed statements that "no AEs were observed" in preclinical studies	Sections 3.1 and 3.2	HREC request	27MAY21
Clarified that no GLP or toxicology studies have been conducted with LMN-201	Section 3.2	HREC request	27MAY21
Clarified that immediate release capsules may be used in the second cohort	Section 5.1	HREC request	27MAY21
Added descriptions of Vcaps Enteric and Vcaps Plus capsules	Section 9.4	HREC request	27MAY21
Removed label design as not needed in the protocol	Section 9.7	Sponsor-initiated change	27MAY21
Edited to use the term 'ileostomy' rather than 'ostomy' throughout the PICF	PICF	HREC request	27MAY21
The following statements were added to p. 4, point 6: "The size of each capsule is about 20 mm. If you would like to see what the capsule looks like, the study staff can show you an empty capsule at the screening visit."	PICF, p. 4	HREC request	27MAY21
"Therapeutic Goods of Australia [TGA]" was changed to "Australian Therapeutic Goods Administration [TGA]."	PICF, p. 2	HREC request	27MAY21
An explanation of LMN-201 was added to the section What is the purpose of this research? (p. 2): "To be effective, the capsules must deliver LMN-201, undamaged, to the end of the small intestine. This is where the LMN-201 components will be effective in treating *C. difficile* bacterial infection by specifically destroying the *C. difficile* bacteria and binding to the toxins produced by the *C. difficile* bacteria. This study will give the researchers information about if the LMN-201 components are still present at the end of the small intestine."	PICF, p. 2	HREC request	27MAY21
The following statement was added to point 4 on p. 3 and p. 4: "Women who are pregnant, planning to become pregnant, or are breastfeeding, cannot participate in this study"	PICF, p. 3 and 4	HREC request	27MAY21
The following statement was added to the Study Visit section: "You may start eating again 2 hours after administration of the study drug. You will be provided snacks and up to two meals during the study visit."	PICF, p. 3	HREC request	27MAY21
The following statement has been added above the text in bold in the "Pregnancies, Breastfeeding, and Birth Control Information" section: "It is highly recommended that you inform your partner of your participation in this study and	PICF, p. 7	HREC request	27MAY21

that highly effective methods of contraception (as detailed above) are strongly recommended."			
Opioid test was mistakenly included in the procedures done at the study visit. This was removed Study Visit Section. Opioid test will only be done at the screening visit	PICF, p. 4 and 5	Sponsor-initiated change	27MAY21

Table of Contents

1. PROTOCOL SUMMARY

1.1 Synopsis

Study Title: Exploratory study to assess delivery of LMN-201 components via enteric capsules in the gut of individuals with ileostomies	
Study Number: CDI01	
Phase of development: Phase 1	
Investigational Product: Components of LMN-201 *(a cocktail consisting of a bacteriophage lysin specific for C.* difficile *organism and three VHH-derived proteins that bind and inhibit* C. difficile *toxin B, delivered in whole, spray-dried spirulina* (*Arthrospira platensis*) *biomass*	
Sponsor: Lumen Bioscience, Inc.	
Principal Investigator (PI): James Daveson, MD	
Study Center: Coral Sea Clinical Research Institute	
Study Objectives (Primary):	• To determine if enteric capsules are sufficient to deliver LMN-201 therapeutic proteins (VHH proteins and lysin) to the terminal ileum.
Study Objectives (Exploratory):	• To document the presence of LMN-201 therapeutic proteins at the terminal ileum • To determine variability between individuals in the quantity of LMN-201 therapeutic proteins at the terminal ileum
Subject Population	Adults aged 19 and above with mature ileostomy
Study Design	This is a Phase 1, multi-site, open label, exploratory study of LMN-201 to evaluate the function of enteric capsules on drug release. Eligible volunteers with mature ileostomies will be enrolled and sequentially assigned to treatment. After documentation of informed consent, subjects will be asked to swallow 4 enteric capsules of LMN-201 components, 1 enteric capsule containing ring-shaped transit markers, and 1 immediate release capsule containing tube-shaped transit markers. Every hour following ingestion, ileostomy fluid will be collected, weighed, filtered, and analyzed. The procedure will be repeated for 4 hours after capsules and/or transit markers are observed in the collected ileostomy fluid, or 12 hours after ingestion, whichever time is shorter. In the first cohort, participants will receive only one of the LMN-201 VHH proteins administered in 3 enteric capsules as well as 1 enteric capsule containing lysin, 1 enteric capsule containing ring-shaped transit markers, and 1 immediate release capsule containing tube-shaped transit markers. In the second cohort, participants will receive 1 enteric capsule of each of the LMN-201 VHH proteins as well as 1 enteric capsule containing lysin, 1 enteric

	capsule containing ring-shaped transit markers, and 1 immediate release capsule containing tube-shaped transit markers.
	
	The trial will be adapted between the first and the second cohort in the following manner:
	
	• If intact enteric capsules are observed in the ileostomy fluid of more than one participant
	  ○ And the transit time is less than 4 hours, then a fluid restriction to less than 150 ml per hour will be implemented for the second cohort.
	  ○ And the transit time is greater than 4 hours, then immediate release capsules will be utilized for the second cohort.
	• If the number of enteric capsules that remain encapsulated in the ileostomy fluid is less than 20%
	  ○ Then the number of subjects in the second cohort will decrease from six to three.

Number of Subjects	Enrollment is planned for 2 cohorts of up to 6 subjects per cohort
Study Duration	Estimated time from when study opens to enrollment until completion of data analysis is 1-2 months.
Participant Duration	Each participant will complete the study in a single calendar day. The screening visit, to be completed up to 15 days prior to study visit, will take 1-2 hours.
Inclusion Criteria	• Adult (19 years of age or older) • Stable ileostomy (no revisions in the last 6 months) • Medically stable, but may be on medications for chronic conditions • Willing to participate in the clinical trial
Exclusion Criteria	• Individuals unable or unwilling to provide adequate informed consent • Non-English-speaking individuals • Clinically significant disease • Pregnancy, anticipated pregnancy, or breastfeeding • Use of anti-diarrheal medicine • Gastroparesis • Opioid use
Study Endpoints (Primary)	• Presence or absence of capsules and/or transit markers in ileostomy fluid by visual observation
Study Endpoints (Exploratory)	• Detect presence of LMN-201 therapeutic proteins (VHHs and lysin) in collected ileostomy fluid by EIA • Quantitate LMN-201 therapeutic proteins (VHHs and lysin) in collected ileostomy fluid by EIA

Safety and Tolerability Parameters	All dosed subjects will be evaluated for any safety and/or tolerability concerns

1.2 Schedule of Activities (SoA)

	Screening Visit	Study Visit		End of Study
		Dose	Follow up	
	Day -15 to 0	Hour 0	Hourly for 4 hours following observation of any transit markers or capsules, or for 12 hours, whichever time is shorter	
Study Procedures				
Consent	X			
Inclusion/exclusion criteria	X	X		
Medical History	X			
Physical Exam	X	X		
Vitals signs	X	X	X	
Urine Sample	X	X		
Study investigational product (IP) administered		X		
Collect ileostomy fluid for analysis[1]		X	X	
Record AEs			X	
Ship ileostomy fluid [1]				X

[1] See Manual of Procedures (MOP) for complete descriptions.

2. LIST OF ABBREVIATONS AND TERMS

ADME	Absorption, Distribution, Metabolism, and Elimination
AE	Adverse event
CDI	*C. difficile* infection
CRF	Case report form
eCRF	Electronic case report form
EIA	Enzyme Immunoassay
GI	Gastrointestinal tract
cGMP	Current Good Manufacturing Practices
GRAS	Generally Regarded as Safe
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
MOP	Manual of Procedures
PI	Principal Investigator
SAE	Serious adverse event
US FDA	United States Food and Drug Administration
VHH	Binding domain fragment of a single-domain camelid antibody

3. INTRODUCTION

3.1 Background and Rationale

Targeted delivery of any therapeutic agent is the key consideration of efficacy. Typically, therapeutic agents are delivered by oral or injection pathways and are then subjected to Absorption, Distribution, Metabolism, and Elimination (ADME) effects. Each of these effects reduces the amount of active product able to be delivered to the site of action, thus reducing efficacy.

Lumen's solution to treat and prevent enteric diseases is to provide the drug directly to the site of action, bypassing ADME effects. Delivering the therapeutic biomolecule within a safe food product, for example, spirulina (*Arthrospira platensis*) biomass, that is not absorbed by the intestinal tract removes any loss of the active agent by gastric digestion.

Distribution concerns are thus fully eliminated as the product is delivered directly to the site of disease. With protein-based biomolecules, digestion of the therapeutic is the functional equivalent to metabolism within the gastrointestinal (GI) tract and remains the most significant challenge. Elimination, through the function of the GI tract, is linear and predictable. Most importantly, it does not reduce the amount of active agent at the site of action. Transit time, however, can affect the duration of action.

Severe *C. difficile* colitis is associated with significant morbidity and mortality worldwide (Balsells et al., 2019). It causes an inflammatory colitis that can lead to diarrhea, abdominal pain, fever, and malaise. The biomolecules Lumen Bioscience has developed to treat and prevent *C. difficile* infection (CDI) need to be delivered, undigested, and in a fully functional form to the distal small bowel and large intestine to be effective. LMN-201 in its final form will be a 'cocktail' of several prophylactic proteins of two distinct classes: a bacteriophage lysin, and several engineered binding domain fragments of a single-domain camelid antibody (VHHs) delivered orally within whole, spray-dried spirulina biomass. The spirulina-bioencapsulated therapeutic proteins are delivered in vegetable-based, enteric delivery capsules of 500 mg total spirulina biomass. Such capsules are designed to release the drug product at or before the terminal ileum, the earliest point in the GI tract where conditions, including CDI, become established in most patients. These capsules are commonly used and procured from an industry provider (Vcaps Enteric, Capsugel, a Lonza company) and are covered by an active Drug Master File with the United States Food and Drug Administration (US FDA).

The first class of LMN-201 contains a single representative: a bacteriophage-derived lytic enzyme that is highly specific for degrading the *C. difficile* cell wall resulting in rapid hypotonic death (Wang, et al., 2015). These lytic enzymes, also called 'endolysins' or simply 'lysins', are a class of cell wall hydrolases with a narrow spectrum of activity. Research by the Fischetti Lab at Rockefeller University has shown that these enzymes efficiently kill all clinical isolate *C. difficile* strains tested to date, while leaving commensal bacteria undisturbed.

The second class consists of several VHHs that neutralize *C. difficile* exotoxins. Prior research has shown toxin B to be the primary driver of the disease pathology (Carter et al., 2015). Lumen Bioscience has developed three distinct VHHs that target different epitopes of toxin B.

As discussed further in the Investigator's Brochure, the safety and efficacy of LMN-201's therapeutic proteins were evaluated in a series of *in vitro* and *in vivo* studies. I*n silico* assessments of target epitope homology to human and commensal bacterial proteomes showed a low risk of cross-reactivity. The

efficacy of LMN-201 was successfully demonstrated in both mouse and hamster challenge models of CDI. These data strongly support the evaluation of LMN-201 in human subjects.

This is a preliminary study to determine if enteric capsules containing constituents of LMN-201 are sufficient to deliver therapeutic proteins to the terminal ileum.

3.2 Risk/Benefit Assessment

Spirulina has a well-established and documented safety profile, leading the US FDA to conclude that spirulina is Generally Regarded as Safe (GRAS) and requires no further toxicity studies. Possible non-serious adverse events (SAEs) have been reported with spirulina intended as a nutritional supplement. The US FDA MedWatch from January 2001 to July 2009 identified the most common non-SAEs from spirulina as: nausea; diarrhea; vomiting; fatigue; headache; dizziness; itching; rash, and abdominal cramps. These reports lacked information on the quantity, duration, individual history, or quality of spirulina used and were based on non-GMP spirulina (Marles et al*.,* 2011).

VHH antibodies are too large for systemic absorption through the gut lining and are directed with high specificity at pathogen target epitopes, unlike anything in the human body. As a result, the risk of off-target toxicity in humans is close to zero. Lumen Bioscience completed a successful Phase 1 clinical trial in Australia in March 2020 with its initial VHH candidate, LMN-101. Systemic absorption of the engineered prophylactic protein was not detected, and there were no significant AEs.

Lytic enzymes have an excellent profile for an orally dosed anti-microbial targeted to organisms in the GI tract. Similar to VHHs, they are too large to be systemically absorbed, greatly reducing concerns of immunogenicity. Bacteriophages produce lytic enzymes that are ubiquitous in the human GI tract. At any given time, as many as 10^{12} bacteriophage are present in the human gut (Shkoporov et al., 2019). Humans are continuously exposed to lytic enzymes during normal microbiome activity with no known ill effects. An intravenous (IV)-infused *Staphylococcus aureus* specific lytic enzyme, CF-301, has been shown to be safe and effective in Phase 2 clinical trials (Fowler et al., 2020), further demonstrating the safety of this class of enzymes. Lysozyme, the canonical member of this enzyme family, is a broad spectrum bacteriolytic enzyme. It is approved for use in several countries, including Japan (Hashida, et al., 2002), and possesses various applications for oral administration as contemplated by Lumen Bioscience. The US FDA has concluded that lysins are also GRAS and has required no further toxicity studies from other companies producing oral lysin-containing products.

These safety records are consistent with the results generated by Lumen in a non-GLP safety study involving administration of LMN-201 to mice. No GLP studies or formal toxicology studies have been conducted with this product.

While participation may not offer direct medical benefit to subjects, an effective CDI preventative would offer a societal benefit. Considering the overall burden of the disease, the Sponsor considers the potential benefits of participation to exceed the risks.

4. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To determine if enteric coating on components of LMN-201 is sufficient to deliver therapeutic proteins to the terminal ileum.	Presence or absence of capsules and/or transit markers in ileostomy fluid by visual observation

OBJECTIVES	ENDPOINTS
Exploratory	
To document the presence of LMN-201 therapeutic proteins at the terminal ileum	Detect presence of LMN-201 therapeutic proteins (VHHs and lysin) in collected ileostomy fluid by EIA
Exploratory	
To determine variability between individuals in the quantity of LMN-201 therapeutic proteins at the terminal ileum	Quantitate LMN-201 therapeutic proteins (VHHs and lysin) in collected ileostomy fluid by EIA

5. STUDY DESIGN

5.1 General Study Design

This is a Phase 1, multi-site, open label, nonrandomized, exploratory study to assess delivery of LMN-201 components via enteric capsules.

The trial will be evaluated through 2 cohorts of up to 6 subjects each. The first cohort will utilize specific components to allow analysis of individual component digestion. Eligible subjects with mature ileostomies will be consented, enrolled, assigned to treatment sequentially, and asked to swallow the following:

	Number of capsules administered to subject—First cohort					
Subject	**Anti-toxin B VHH-1**	**Anti-toxin B VHH-2**	**Anti-toxin B VHH-3**	**Lysin capsules**	**Capsule with tube-shaped transit markers**	**Capsule with ring-shaped transit markers**
1	**3**	—	—	**1**	**1**	**1**
2	**3**	—	—	**1**	**1**	**1**
3	—	**3**	—	**1**	**1**	**1**
4	—	**3**	—	**1**	**1**	**1**
5	—	—	**3**	**1**	**1**	**1**
6	—	—	**3**	**1**	**1**	**1**

Every hour after ingestion, ileostomy fluid will be collected, weighed, filtered, and analyzed for the presence of capsules and/or transit markers. This procedure will be repeated for four hours after the capsules and/or transit marker are observed in the ileostomy collection, or 12 hours after ingestion, whichever time is shorter.

The trial will be adapted between the first and the second cohort in the following manner:

- If intact enteric capsules are observed in the ileostomy fluid of more than one participant
  - And the transit time is less than 4 hours, then a fluid restriction to less than 150 ml per hour will be implemented for the second cohort.
  - And the transit time is greater than 4 hours, then immediate release capsules will be utilized for the second cohort.
- If the number of enteric capsules that remain encapsulated in the ileostomy fluid is less than 20%
  - Then the number of subjects in the second cohort will decrease to three.

The second cohort, allowing for the above changes, will utilize a 'cocktail' formulation of VHHs. Subjects will be asked to swallow the following:

	Number of capsules administered to subject—Second cohort					
Subject	**Anti-toxin B VHH-1**	**Anti-toxin B VHH-2**	**Anti-toxin B VHH-3**	**Lysin capsules**	**Capsule with tube-shaped transit markers**	**Capsule with ring-shaped transit markers**
1	1	1	1	1	1	1
2	1	1	1	1	1	1
3	1	1	1	1	1	1

Any changes not described above will only be implemented once a protocol amendment has been submitted to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC), and has been reviewed and approved.

5.2 Study Duration and Enrollment

Estimated duration for the main protocol (i.e., start of screening through to data analysis) is anticipated to be approximately 1-2 months. Subjects will be screened for eligibility within 15 days before the start of the study. The estimated time it will take for each individual participant to complete all study visits is less than or equal to 12 hours.

5.3 Justification of Dose

The dose chosen for this preliminary evaluation is primarily convenience-based for each component and is the amount that can adequately fit into one capsule.

5.4 End of Study Definition

Each subject will complete the study in a single calendar day. Each cohort will be considered completed when the total number of participants have completed their participation. The study will be considered completed when both cohorts have completed their participation and the data has been delivered and approved.

6. STUDY POPULATION

6.1 Inclusion Criteria

Individuals must meet all of the following criteria to be eligible to participate in this study:

- Willing to participate in the clinical trial
- Able and willing to provide informed consent
- Stable ileostomy (no revisions in the last 6 months)
- At least 19 years old
- Medically stable, but may be on medications for chronic conditions

6.2 Exclusion Criteria

Individuals will be excluded from this study if they meet any of the following criteria:

- Unable or unwilling to provide adequate informed consent
- Non-English speakers
- Clinically significant disease

- Women who are pregnant, intending to become pregnant, or breastfeeding
- Use of anti-diarrheal medicine
- Suffer gastroparesis
- Opioid use

6.3 Recruitment, Screening, and Enrollment

Healthy volunteers with mature ileostomies will be recruited by the site PI using advertising approved by the appropriate IRB/IEC. Volunteers who express interest in participating in the study will be asked to complete a pre-screen to assess general health status and basic eligibility. Potential volunteers determined to have an ileostomy and otherwise be generally healthy and meeting basic eligibility requirements will be scheduled for an in-person screening. Volunteers will be carefully screened on the details of the protocol and their time commitment.

7. STUDY SCHEDULE

7.1 Screening (within 15 days prior to study visit)

Volunteers will be screened for eligibility within 15 days before the study visit. Volunteers will be screened according to predefined inclusion criteria as described in section 6.1. See section 6.2 for a list of exclusion criteria. The following procedures will be performed at screening:

- Informed Consent
- Medical history, including existing medical conditions
- Record concomitant medications
- Physical exam
- Vital signs including heart rate, respiratory rate, seated blood pressure, and temperature
- Urine sample

7.2 Study Visit

Subjects will be asked to refrain from eating after 11 p.m. the night before arrival at study facility. The following procedures will be performed upon arrival:

- Assessment of inclusion/exclusion criteria
- Record concomitant medications
- Vital signs including heart rate, respiratory rate, seated blood pressure, and temperature
- Physical exam
- Urine sample
- Collect ileostomy fluid
- Administer study product

After IP is administered, the following procedures will be conducted every hour until study staff observe capsules or transit markers in ileostomy fluid collection:

- Collect ileostomy fluid for analysis as described in MOP
- Monitor for AEs and measure vital signs

After any transit markers is observed in the ileostomy fluid, study staff will repeat ileostomy fluid collection procedures hourly for a minimum of 4 additional hours or 12 hours total study participation, whichever comes first.

Participants can start eating 2 hours after dosing.

7.3. Concomitant Medications

Concomitant medication use will be documented.

7.4 Early Termination

Subjects have the right to withdraw from the study at any time and for any reason. Subjects who withdraw their consent will not receive any further study drug but will be offered all follow-up safety assessments.

Subjects who withdraw from the study prior to treatment will be replaced per recruitment and enrollment processes outlined above in 6.3.

8. STUDY EVALUATIONS

8.1 Specimen Preparation, Handling, and Shipping

Ileostomy fluid is collected prior to the administration of study capsules, filtered, and aliquoted (either unadulterated or supplemented with purified proteins and protease inhibitor to use as a positive control). Once study capsules are administered, ileostomy content is collected hourly for the duration of the protocol (up to 12 hours). Upon collection, they are filtered, and the retained material is examined for the presence of intact capsules, capsule remnants, and transit markers. If these are observed, a photograph is taken to record the findings. The pH and volume of the filtrate are measured and recorded. Five 10 mL aliquots are prepared, supplemented with a protease inhibitor, and immediately flash frozen and stored at -80 ˚C until shipment. For shipment, one positive control, half of the pre-treatment samples, and 1 tube from each timepoint are assembled and transported on dry ice to Lumen Bioscience at the end of the study.

9. INVESTIGATIONAL PRODUCT

9.1 Investigational Product (IP)

The investigational product (IP), individually encapsulated components of LMN-201, will be supplied by Lumen Bioscience. LMN-201 is being developed to be a cocktail consisting of a bacteriophage lysin specific for degrading the *C. difficile* organism and three VHH-derived proteins designed to bind and inhibit *C. difficile* toxin B, delivered in whole, spray-dried spirulina biomass.

The LMN-201 drug substance is manufactured using four stable cell lines engineered to express the respective lysin and VHHs. The substance is manufactured under Current Good Manufacturing Practices (cGMP) using recombinant DNA processes and controls. The cells are cultured using chemically defined, animal-product-free basal medium under photoautotrophic growth conditions, using bicarbonate and CO2 as the carbon source. After harvesting and rinsing with a dilute solution of trehalose, cells are spray dried to produce drug substance. The drug substance is fully tested against established specifications prior to release for further processing and use in clinical studies. Each strain contains a single

prophylactic protein, and the prophylactic protein 'cocktails' are generated by growing these strains separately, spray drying them separately, and finally dry-mixing the resulting powders together.

The LMN-201 drug product is manufactured at Lumen Bioscience's cGMP manufacturing facility in Seattle, Washington, US. The individually encapsulated components of drug substance are provided in pre-formulated capsules. The individually encapsulated components of LMN-201 drug product are tested for potency and purity defined by established specifications. Lumen Bioscience's cell banking protocols are designed to comply with ICH guideline Q5D for microbial cells. LMN-201 drug products and the tube-shaped transit markers will be filled into Vcaps Enteric intrinsically enteric vegetarian capsules size 00 (Capsugel). Ring-shaped transit markers will be provided in manufacturers non-enteric capsules (Medifactia AB).

Transit markers (Transit-Pellets™ Radiopaque Markers, manufactured by Medifactia AB) will also be provided by Lumen Bioscience.

9.2 Dosing Regimen

Subjects will receive individually encapsulated components of LMN-201, taken as four (4) capsules (500 mg biomass in each capsule), orally. In addition, they will receive an immediate release capsule containing ring-shaped transit markers and an enteric capsule containing tube-shaped transit markers to allow calculation of transit time and encapsulation dissolution visually.

9.3 Dispensing of IP

The investigational team will dispense individually encapsulated components of LMN-201 and transit markers-containing capsules according to the study protocol.

9.4 Dosage Form

LMN-201 ingredients are spray-dried spirulina biomass and trehalose. Individually encapsulated components of LMN-201 doses (500 mg) are packaged in size 00, white, opaque capsules (Capsugel, Morristown, NJ, US), Vcaps Enteric (first cohort) and Vcaps Plus (second cohort, if adapted). Vcaps Enteric capsules incorporate pH-controlled release technology designed to release encapsulated components at or before the terminal ileum. Vcaps Plus capsules are immediate release capsules designed to release encapsulated components in the stomach. No capsules contain any materials of human or animal origin.

9.5 Route of Administration

Individually encapsulated components of LMN-201 and transit markers must be administered orally and will be taken with water only.

9.6 Timing of Dose

Capsules are to be self-administered by subjects upon confirmation of subject desire for participation.

9.7 Packaging and Labelling

The IP will be provided in a single dose packet with the appropriate labels.

9.8 Storage and Handling

All IPs will be kept in a locked area with limited access. Capsules containing IP should be stored at room temperature, 59-77°F (15-25°C) and protected from moisture, light, and extreme heat during storage.

Only subjects enrolled in the study may receive the IP in accordance with all applicable regulatory requirements. Upon the completion of the study, this material will be subjected to final inspection and reconciliation. At that time, all unused, partially used, and fully used (empty) container(s) along with a packing slip must be destroyed as per Pharmacy Manual. Documentation of destruction will be retained by the investigational pharmacy with the study files.

9.9 Study Intervention Compliance

A member of the study team will witness the ingestion of the IP.

10. SAFETY MANAGEMENT

10.1 Adverse Events (AEs)

The Principal Investigator (PI) is responsible documenting AEs according to the guidelines below.

An AE is any untoward medical occurrence or change in a clinical trial subject having received a biologic or medicinal product, whether or not considered treatment related. This may occur in any phase of the clinical study.

Events meeting the AE definition include:

- Any noxious, pathological, or unintended change in anatomical, physiologic, or metabolic functions as indicated by physical signs, symptoms, and/or clinically significant laboratory abnormalities
- Exacerbation or worsening of pre-existing conditions or events
- Intercurrent illnesses, injuries, or vaccine or drug interaction
- Worsening of abnormal clinical laboratory values

Stable, pre-existing conditions and/or elective procedures are not AEs.

10.2 Documenting and Reporting AEs

All observed or volunteered AEs regardless of suspected causal relationship to the IP will be recorded on the AE page(s) of the case report form (CRF). The investigator must assess all AEs for seriousness, severity, and relation to IP.

The PI will follow all AEs, regardless of seriousness or severity, until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

The investigator is responsible for ensuring appropriate clinical management of all AEs until they are resolved or stabilized at a level acceptable to the investigator. Appropriate clinical management of AEs is at the discretion of the investigator.

10.3 Expedited Recording of Serious Adverse Events (SAEs)

Any SAE must be reported to the Sponsor within 24 hours.

Instructions:

The following information should be sent via email (preferred) or telephone:

- *Protocol IND number, IP, PI name, and contact number*
- *Subject identification number*
- *Serious adverse event (SAE), onset date, date of IP administration, severity, relationship, and subject's status*

AND email the following documents to Medical Monitor, Lumen Bioscience:

- *Cover sheet*
- *Adverse Event (AE) CRF*
- *Supplemental SAE Report Form*
- *Concomitant Medication CRF or a list of concomitant medications*
- *Medical record progress notes including pertinent laboratory/diagnostic test results*

The PI will assess all SAEs as being either related or unrelated to the administered product.

Investigators are required to forward safety information provided by the Sponsor's representative to the IRB/IEC. All SAEs will be reported to the IRB/IEC within 24 hours of the PI becoming aware of the event:

Bellberry Limited HREC
123 Glen Osmond Road Eastwood Adelaide
South Australia 5063
Phone: (08) 8361 3222
Email: bellberry@bellberry.com.au

11. STATISTICAL CONSIDERATIONS

11.1 Introduction

Safety, clinical outcomes, and outcome data will be entered into the data system. Data will be edited with standard strategies for range and consistency checks. AEs for all subjects will be included in the safety analysis.

11.2 Sample Size Considerations

No statistical hypothesis is required to be tested. Therefore, no formal sample size calculations have been made. The sample size has been determined to be up to six (6) per cohort to provide preliminary information.

Overall, up to 12 human subjects will be exposed to the IP.

11.3 Safety

Preliminary analysis of safety and tolerability will include all subjects who received study drug. Safety will be evaluated from reported AEs, physical examination findings, and vital signs.

12. DATA HANDLING AND RECORD KEEPING

The PI will maintain complete and accurate documentation for the study. All required study data will be clearly and accurately recorded by authorized study personnel in the electronic CRFs (eCRFs). Only designated study site personnel shall record or change data in an eCRF. The PI will be responsible for the procurement of data and for quality of data recorded in the eCRFs. Original observations entered directly into the eCRFs are considered source data. Study-specific procedures detail how each form will be completed. The study coordinator will ensure accuracy of the CRFs. All source documents will be retained at the site.

A detailed data management plan will be written and approved by the study team and the PI. The plan will be drafted prior to study initiation but will be finalized before study close-out and database lock.

13. CLINICAL TRIAL MATERIAL ACCOUNTABILITY

The site PI is responsible for maintaining accurate records of the processing and use of all clinical trial materials. All used, unused, or undispensed study medication must be accounted for by the site PI.

Drug accountability will be conducted during monitoring visits to ensure appropriate receipt, storage, dispensing, and documentation of returned Clinical Trial Materials.

14. QUALITY CONTROL (QC)/QUALITY ASSURANCE (QA)

14.1 QC/QA Monitoring

During the study and at the close-out, a monitor from Lumen Bioscience or its representative will have regular contacts with the investigational site for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, data is being accurately recorded in the CRFs, and IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts)
- Record and report any protocol deviations not previously sent to Lumen Bioscience
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Lumen Bioscience or its representative and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC and/or FDA

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice. The PI assumes ultimate responsibility for the conduct of the study and remains readily accessible throughout the duration of the study.

14.2 Audits and Inspections

Authorized representatives of Lumen Bioscience or a regulatory authority may visit the site to perform audits or inspections, including source data verification. The purpose of a Lumen Bioscience audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately

reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Lumen Bioscience immediately if contacted by a regulatory agency about an inspection.

The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

To ensure compliance with GCP and all applicable regulatory requirements, Lumen Bioscience may conduct one or more quality assurance audits.

14.3 Protocol Deviation Management

Other than minimal-risk changes, all unanticipated major problems involving human subjects or others will be reported promptly to the IRB/IEC. No such changes will be made to the research without IRB/IEC approval unless necessary to eliminate apparent immediate hazards to human subjects. Minor minimal-risk deviations necessitated during the trial will be made on site as needed and documented for subsequent review within a reasonable time period.

Deviations from the protocol that potentially impact on subject safety will be promptly reported to the Medical Monitor, IRB/IEC, and the Sponsor. Other deviations will be reported at the time of continuing review.

14.4 Clinical Research Monitoring

Lumen Bioscience monitoring responsibilities will be provided by an independent Clinical Research Associate (CRA). Monitoring will be conducted according to an approved monitoring plan and applicable SOPs. The CRA or other authorized representatives of the Sponsor may inspect all documents and records maintained by the PI. The clinical study site will permit access to such records. The PI will obtain, as part of informed consent, permission for authorized representatives of the Sponsor, or regulatory authorities, to review, in confidence, any records identifying individuals in this clinical study.

The PI will notify the Sponsor within 24 hours following contact by a regulatory agency. The PI and study coordinator will be available to respond to reasonable requests and audit queries made by authorized representatives of regulatory agencies. The PI will provide the Sponsor with copies of all correspondence that may affect the review of the current study or his/her qualification as a PI in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance in responding to regulatory audits or correspondence. The PI will permit independent auditors (employees of the Sponsor or an external company designated by the Sponsor) to verify source data validation of the regularly monitored clinical trial. The auditors will compare the entries in the CRFs with the source data and evaluate the study site for its adherence to the clinical study protocol and GCP guidelines and applicable regulatory requirements. The Sponsor will arrange local monitoring prior to beginning, at initiation, during the study, and at closeout by the study monitor or designee.

14.5 Medical Monitor

The Medical Monitor shall be available for consultation with the PI and serves as liaison between the clinical study site and the Sponsor. The study investigators will consult with the Medical Monitor on issues related to subject enrollment and continued participation as needed. The Medical Monitor is required to review all unanticipated problems involving risk to subjects, SAEs, and all subject deaths

associated with the protocol, and provide an unbiased written report of the event. At a minimum, the Medical Monitor should comment on the event outcomes, and in the case of a SAE or death, comment on the relationship to participation in the study. The Medical Monitor should indicate concurrence or non-concurrence with the details of the report provided by the PI. Reports for events determined by either the PI or Medical Monitor to be related or unrelated to participation and reports of events resulting in death should be promptly forwarded to the ethics board.

15. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

15.1 IRB/IEC

The PI must verify that the ethics board has approved the clinical protocol, Informed Consent Form (ICF), and recruitment materials for the investigation prior to conducting study evaluations. Initial ethics board approval, and all materials approved by the ethics board for this study including the ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

All amendments to the protocol, ICF, and/or questionnaires, including a change of PI, will be submitted to the ethics board for review and approval prior to implementation. The PI is responsible for informing the ethics board of any amendment to the protocol.

The PI is also responsible for providing the ethics board with reports of any reportable serious adverse reactions from any other study conducted with the IP. Lumen Bioscience will provide this information to the PI.

15.2 Written Informed Consent

The ICF will be prepared by the Sponsor. The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the subject understands. The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and will include any additional elements required by the Investigator's institution or local regulatory authorities. The ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the study, the Sponsor will obtain the IRB/IEC's written approval/favorable opinion of the written ICF. The IRB/IEC approved ICF will be given to each volunteer. The volunteers will be given adequate time to discuss the study with the PI or site staff and to decide whether or not to participate. Each volunteer who agrees to participate in the trial and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The ICF and any other information provided to subjects will be revised whenever important new information becomes available that is relevant to the subject's consent. The PI will obtain the IRB/IEC's written approval/favorable opinion prior to the use of the revised documents. The PI, or person designated by the PI, will fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. Subjects will read and sign any and all revised ICFs.

The PI or research staff designee will ensure that the volunteer or legally authorized representative is given full and adequate oral and written information about the nature, purpose, possible risks, and

potential benefits of the study. The subject or legally authorized representative must also be notified that the subject is free to discontinue from the study at any time. The subject or legally authorized representative should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent, or the signed and dated informed consent of a legally authorized representative, must be obtained before conducting any study procedures. The PI must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject or legally authorized representative.

15.3 Subject Compensation

Compensation for participation will be provided only for completed study procedures designated for compensatory payment. If a volunteer is eligible to participate in the investigational protocol after screening, the subject will be compensated for study participation-associated time and travel.

15.4 Privacy and Confidentiality

The PI will exercise all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of subjects' identities. On exported electronic source data or any other documents submitted to the Sponsor, subjects will only be identified by subject number. Documents not for submission to the Sponsor, e.g., subject identification log and original ICF, will be maintained by the PI in strict confidence.

15.5 Regulatory Documentation

Before the trial starts, Essential Documents as defined in ICH E6 will be generated and placed in both the Investigator's and Sponsor's files. Additional Essential Documents will be added to both files as new information becomes available and at the completion or termination of the trial as defined in ICH E6.

15.6 Protection of Human Subjects

Declaration of Helsinki

The Investigator will conduct this study in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision.

Good Clinical Practice and Regulatory Compliance

The Investigator will conduct this study in accordance with the principles of GCP (current ICH guidelines) and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

The study will be conducted as described in the approved protocol in accordance with the obligations of clinical Investigators set forth in the Form FDA 1572.

16. REFERENCES

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