Clinical Protocol:

A Phase 1 Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation, Safety and Pharmacokinetic Study of LMN-101 in Healthy Volunteers

Investigational Product: LMN-101

(VHH-derived binding protein designed to bind and inhibit FlaA, flagellin protein of Campylobacter jejuni, delivered in whole spray-dried, encapsulated spirulina biomass)

Version 1.1

15 October 2019

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigators' Brochure for LMN-101. I have read the Clinical Protocol and agree to conduct the study as outlined in this protocol and according to the International Conference on Harmonisation (ICH) guidelines, the National Statement on Ethical Conduct in Human Research 2007, The Declaration of Helsinki 2000, and relevant Commonwealth and/or State/Territory 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 by me.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone
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ABBREVIATIONS AND SPECIALIST TERMS

Table 2: List of Abbreviations and Specialist Terms

Abbreviation	Full term
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
eGFR	estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRAS	Generally Recognized as Safe
HBsAg	Hepatitis B surface antigen
beta-hCG	beta-human Chorionic Gonadotropin
HCV	Hepatitis C virus
HED	Human equivalent dose
HREC	Human Research Ethics Committee
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
INR	International normalized ratio
IUD	Intrauterine device
IV	Intravenous
kDa	Kilodalton
LMN-101	VHH-derived binding protein designed to bind and inhibit FlaA
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Affairs
mL	Milliliter
mmHg	Millimeters of mercury
NF	National Formulary
NOAEL	No-observed-adverse-event level
NYHA	New York Heart Association
PAD	Pharmacologically active dose
PI	Principal Investigator

Abbreviation	Full term
PIN	Participant Identification Number
PK	Pharmacokinetics
PTT	Partial thromboplastin time
SAE	Serious Adverse Event
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal
VHH	Variable heavy chain (single domain)
VS	Vital signs

CLINICAL TRIAL SYNOPSIS

Sponsor: Lumen Bioscience, Inc.

Investigational Product: LMN-101 *(VHH-derived binding protein designed to bind and inhibit FlaA, flagellin filament protein of Campylobacter jejuni, delivered in whole spray-dried, encapsulated spirulina biomass)*

Study Title: A Phase 1 Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation, Safety and Pharmacokinetic Study of LMN-101 in Healthy Volunteers

Study Center: Nucleus Network, Brisbane, Australia

Principal Investigator: Dr. Paul Griffin, QPharm

Estimated date first subject enrolled: December 2019 Estimated date last subject enrolled: February 2020	Phase 1

Study Objectives	The primary objective of this study is to determine: • The safety and tolerability of LMN-101 The secondary objectives of this study are to determine: • Serum pharmacokinetics of LMN-101; and • Formation of anti-drug antibodies
Study Design	This will be a two-part study: Part A, an open-label administration of a single dose of LMN-101 and Part B, a randomized, double-blind, placebo-controlled, dose-escalation study of 3 dose levels of LMN-101. In Part B, healthy volunteers will take LMN-101 or placebo orally at one of three dose levels three times daily over 28 days. Protocol-specified evaluations and procedures will be performed on Days 1-2 and every one-two weeks during dosing. Study observation will continue until 4 weeks after the last dose of study drug.
Number of Subjects	Enrollment is planned for 2 subjects in Part A and 18 subjects in Part B (LMN-101 12 subjects; placebo 6 subjects), i.e., 6 per dose cohort (LMN-101 4 subjects per dose cohort; placebo 2 subjects per dose cohort).
Inclusion Criteria	1. Male or female between 18 and 50 years, inclusive, at time of informed consent 2. Willingness to participate after written informed consent obtained 3. Available for all planned clinical visits for physical examinations, blood draws, stool collections 4. General good health, without significant medical illness or abnormal physical examination findings as determined by the PI. 5. Adequate safety laboratory results, renal and liver function. a. Absolute neutrophil count ≥ 1.5 x 10^9/L b. Lymphocyte count < 6.0 x 10^9/L c. Platelet count ≥ 150 x 10^9/L d. Hemoglobin ≥ 110 g/L

	e. eGFR ≥ 40 mL/min/1.73 m^2 f. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 3x ULN g. Total bilirubin ≤ 1.5x ULN h. Serum albumin ≥ 28 g/L 6. Females of childbearing potential should be using and committed to continue using one of the following acceptable birth control methods: a. Sexual abstinence (inactivity) or exclusively same-sex partner for 1 month prior to screening through study completion; or b. Intrauterine device (IUD) in place for at least 1 month prior to study through study completion; or c. Stable hormonal contraception for at least 1 month prior to study through study completion; or d. Surgical sterilization (vasectomy) of male partner at least 6 months prior to study. 7. To be considered of non-childbearing potential, females should be surgically sterilized (bilateral tubal ligation, hysterectomy, or bilateral oophorectomy at least 2 months prior to study) or be post-menopausal and at least 12 months since last menses. 8. Male participants must use condoms during the study and through study completion.
Exclusion Criteria	1. Treatment with an experimental compound within 30 days. 2. Treatment within 30 days or planned use within the study period with immunomodulator or immunosuppressant agent. 3. Pregnancy or breastfeeding. 4. Presence of any of the following clinical conditions: a. History of one or more of the following: cardiac insufficiency (NYHA III/IV), uncontrolled cardiac arrhythmias, unstable ischemic heart disease, or uncontrolled hypertension (systolic blood pressure > 170 mmHg or diastolic blood pressure > 110 mmHg). b. History of venous thromboembolic disease within 12 months, myocardial infarction, or cerebrovascular accident. c. Unstable pulmonary, renal, hepatic, endocrine or hematologic disease. d. Gastrointestinal disorder requiring ongoing care by a physician. e. Autoimmune disease, mixed connective tissue disease, scleroderma, polymyositis, or significant systemic involvement secondary to rheumatoid arthritis. f. Evidence of active malignant disease, malignancies diagnosed within the previous 5 years, or breast cancer diagnosed within the previous 5 years (except skin cancers other than melanoma).

	g. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other opportunistic infections, excluding urinary tract infections; or major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks. h. Positive serology for human immunodeficiency virus (HIV) infection or history of other immunodeficiency illness. i. Positive serology results for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) j. Significant neuromuscular disease or neuropathy k. Psychiatric condition l. Alcohol or illicit drug abuse/dependency or positive urine toxicology screen for drugs of abuse other than marijuana. Alcohol and tobacco consumption are permitted. m. Significant food allergy restrictions.
Dosage Form	Lyophilized LMN-101 powder in capsugel (or equivalent) capsules. Active capsules will contain 300 or 500 mg of LMN-101. Placebo capsules will contain equivalent biomass of wild-type spirulina.
Dose and Regimen	Part A: Subjects will be assigned to a single dose of 3000 mg PO given as six 500-mg capsules of LMN-101 (2 subjects). Part B: Subjects will be sequentially assigned to the following dosing regimens and will be randomized within that dose regimen to active or placebo treatment: • 300 mg PO TID given as a single 300-mg capsule of LMN-101 orally three times daily for 28 days (4 subjects) or identical-appearing placebo capsule (2 subjects). • 1000 mg PO TID given as two 500-mg capsules of LMN-101 orally three times daily for 28 days (4 subjects) or identical-appearing placebo capsules (2 subjects). • 3000 mg PO TID given as six 500-mg capsules of LMN-101 orally three times daily for 28 days (4 subjects) or identical-appearing placebo capsules (2 subjects).
Efficacy Parameters	<u>The primary endpoint is</u>: • Safety and tolerability of LMN-101. <u>The secondary endpoints are</u>: • Peak serum VHH concentration following administration of the initial dose and peak serum VHH concentration following a course of treatment (if systemic absorption is observed). • Area under the serum VHH concentration versus time curve (AUC) following administration of the initial dose and following a course of treatment (if systemic absorption is observed). • Induction of serum anti-drug IgG antibodies (if systemic absorption is observed).

Safety Parameters	All dosed subjects will be evaluated for safety, tolerability, and anti-drug antibodies. Repeated adverse event (AE) monitoring, vital signs, physical examinations, and laboratory testing will be performed. Serum will be collected at baseline, end of dosing, and end of study for presence of anti-drug antibodies if systemic absorption of LMN-101 is demonstrated. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and severity graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. AEs will be summarized by treatment group for the number of AEs. Comparisons will be made between baseline, on treatment, and follow-up values. Vital signs and clinical laboratory results will be summarized for each treatment group. Comparisons will be made between baseline, on treatment, and follow-up values. Tolerability will be assessed by the proportion of participants completing study drug and remaining on study and free from possibly drug-related and dose-limiting serious adverse events (SAEs) to the end of follow-up.
PK and PD Assessments	The serum levels of VHH will be determined before, 2 hours, and 24 hours after the first dose; Day 8 (Part B), Day 28 (Part B), and Day 29 (Part B). PK results will be summarized. Stool samples will be collected on Days 1, 2, 8 (Part B), 28 (Part B), and 29 and banked.

1 INTRODUCTION

Diarrheal diseases are a major cause of morbidity and mortality of children in developing countries (Liu *et al.* 2012). Death is due not only to the primary disease itself, but also from secondary gut dysfunction leading to malnutrition, stunting and increased susceptibility to additional infectious diseases. *Campylobacter jejuni* has emerged as a high-priority target among all pathogens responsible for these illnesses (Liu *et al.* 2016; Platts-Mills *et al.* 2015; Platts-Mills and Kosek 2014). There is no significant market in developed nations for prevention of this disease, which disproportionately affects poor and marginalized populations of the developing world. It is particularly hazardous to infants in the developing world, and is a leading cause of infant mortality (Murray *et al.* 2012).

1.1 Burden of *Campylobacter jejuni*

The global health burden of campylobacter diarrhea is estimated to be 88 million cases in children under 5 years of age, resulting in 41,000 deaths annually (Troeger *et al.* 2018). There are 172 million cases globally in all age groups, with 75,000 deaths annually. The fatal attributable fraction is 9.15% in children and 4.58% overall (Troeger *et al.* 2018).

The burden of campylobacter diarrhea in the U.S. is 1.3 million cases per year, of which 310,000 (24%) are resistant to ciprofloxacin or azithromycin, resulting in 13,000 hospitalizations (CDC 2017; Geissler *et al.* 2017; Scallan *et al.* 2011). There are serious sequelae attributable to campylobacter diarrhea, including Reiter's arthritis, Guillain-Barre syndrome, post-infectious inflammatory bowel syndrome, and intestinal perforation (Kaakoush *et al.* 2015).

Fluoroquinolone resistance due to its use in animal feed has led to widespread drug resistance in campylobacter. This resistance can spread to humans. Campylobacter drug resistance has been designated as a serious threat by the World Health Organization and the U.S. Centers for Disease Control (CDC 2013). Ciprofloxacin resistance of campylobacter in the U.S. increased from 13% in 1997 to almost 25% in 2011 (Sproston *et al.* 2018). A European Union survey of 15 EU nations found 58% resistance (ECDC/EFSA 2019). Resistance is so high in some areas of Southeast Asia, reaching as high as 70%, that fluoroquinolones can no longer be used for empiric treatment of diarrhea in these areas (Luangtongkum *et al.* 2009). Drug resistance rates have not decreased despite the regulation of use of ciprofloxacin in animal feed.

1.2 Prevention of *Campylobacter jejuni* Disease

There are several vaccine candidates for prevention of campylobacter diarrhea (Jagusztyn-Krynicka *et al.* 2009; Riddle and Guerry 2016). Human challenge trials following vaccination with ACE393, a *C. jejuni* cell-surface subunit plus alum, failed to demonstrate protection and development was discontinued. A glycoconjugate vaccine consisting of a capsule of *C. jejuni* conjugated to CRM197 as protein carrier, was shown to be poorly immunogenic in a Phase 1 study and was discontinued (NCT02067676). This was hypothesized to be due to the lack of the immunodominant epitopes. A second-generation vaccine candidate with these epitopes is

planned for Phase 1 study. Challenges to vaccine development for campylobacter include the already crowded pediatric immunization schedule, the need to delay pediatric immunization until passively transferred maternal antibodies have waned, and the poor adherence with the later routine pediatric immunization time points. Since previous infection in not necessarily protective against future symptomatic infection, sustained protection from a vaccine may not be observed.

Rifaximin, an antibiotic approved to prevent traveler's diarrhea, did not protect volunteers from a campylobacter challenge (Rimmer *et al.* 2018). There are uncommon but serious side effects of antibiotics used to treat diarrhea, especially fluoroquinolones, which can cause CNS side effects, low blood sugar, tendinitis and tendon rupture. Antibiotic treatment of diarrhea has been associated with increased risk of inflammatory bowel disease and *Clostridium difficile* infection. Furthermore, empiric antibiotic use contributes to the crisis of antibiotic resistance.

Natural colostrum contributes to infant health in part by providing a rich source of antimicrobial substances, including secretory immunoglobulins, that afford protection against common enteric pathogens. Alternative sources of colostrum-protective activities are being sought as therapeutics for infants in developing countries. Hyperimmune bovine colostrum derived from cows immediately post-partum has been shown to be protective against enterotoxigenic *E. coli* (ETEC) challenge in humans (Otto *et al.* 2011; Savarino *et al.* 2017; Sears *et al.* 2017; Steele *et al.* 2013; Tacket *et al.* 1988; Tacket *et al.* 1992). Successful piglet trials for prevention and treatment of *C. difficile* infection have been reported (Hutton *et al.* 2017; Sponseller *et al.* 2015). Despite decades of effort, there remains the challenge of achieving consistent manufacturing compatible with GMP. Other methods for production of immunoglobulins to be administered orally include rice, although GMP manufacturing using plant-based production remains a challenge. There are currently no immunoglobulins for use for prevention of campylobacter diarrhea.

C. jejuni is dependent on cell motility for colonization of the gut and initiation of a disease state (Morooka *et al.* 1985). The antibody binding domain incorporated into the aa682 protein molecule in LMN-101 binds the FlaA protein subunit of the campylobacter flagellin (Riazi *et al.* 2013) and is thought to prevent infection by reduction or elimination of cell motility, thereby preventing colonization of the gut by *C. jejuni*.

1.3 VHH Antibodies

One possibility for prevention of campylobacter disease are camelid antibodies made by camels and llamas. These are heavy chain-only antibodies, versions of which containing only the antigen-binding variable domains (VHHs) can be produced as highly stable recombinant proteins at abundant levels in standard biotechnology platforms. Libraries of VHHs can be screened to identify clones that recognize specific antigens, including those displayed by enteric pathogens. Orally delivered VHHs have also been shown to be effective in preventing pathogen infections in a variety of animal models, including piglet models of ETEC infection (Harmsen *et al.* 2006; Virdi *et al.* 2013; Virdi *et al.* 2019), and mouse models of rotavirus infection (Garaicoechea *et al.* 2008;

Gomez-Sebastian *et al.* 2012; Günaydin *et al.* 2016; Maffey *et al.* 2016; van der Vaart *et al.* 2006). The high cost of manufacturing purified antibodies has impeded commercialization, however.

VHHs have been shown to be effective in preventing rotavirus infection in human infants (Sarker *et al.* 2013). A VHH directed against tumor necrosis factor, V565, has completed Phase 1 studies in healthy volunteers and Crohn's patients (unpublished data). The orally administered drug was safe and well tolerated at high doses in patients with moderately to severely active Crohn's disease with minimal systemic exposure and no drug-induced antibodies. High concentrations of active V565 were delivered throughout the gastrointestinal tract.

These qualities make VHHs outstanding candidates for prevention and treatment of enteric diseases of children, but a low-cost method for synthesis and delivery of VHHs is needed.

1.4 LMN-101, VHH-Derived Binding Protein Designed to Bind and Inhibit FlaA

Lumen Bioscience has discovered and developed a method for efficient and stable genetic engineering of spirulina, a photosynthetic microorganism that is consumed worldwide as a nutritional supplement rich in protein and vitamins. In ongoing work supported by the Bill & Melinda Gates Foundation, Lumen has demonstrated high-level expression of VHHs in spirulina, and that spirulina containing VHHs with specificity against the FlaA, flagellin protein of *Campylobacter jejuni*, can fully protect against campylobacter challenge in two different mouse challenge models developed by researchers at the University of Virginia (Guerrant, *et al*., 2019, personal communication) and the Institute for Research in Biomedicine (Bellinzona, Switzerland) (Grassi *et al.*, 2019, personal communication).

2 PREVIOUS EXPERIENCE WITH LMN-101

2.1 LMN-101 Drug Product

Lumen developed SP1182, a strain of spirulina (*Arthrospira platensis)* that has been stably engineered by chromosomal integration to constitutively express a protein that binds and inhibits the FlaA filament protein on the flagellum of *C. jejuni.* The drug, LMN-101, is orally delivered whole, dried spirulina biomass in capsule form (i.e., the active biologic is not purified from the spirulina biomass). After spray drying, the spirulina powder is non-viable (likely due to the elevated temperature achieved during drying and the low water content of the resulting powder) while the binding activity of the campylobacter binding protein is retained.

The aa682 campylobacter binding protein is constitutively expressed as a soluble protein that remains in the cytosol (not secreted or displayed on the surface of the cell). It is a simple yet highly specific binding protein that is derived in part from the variable binding domain of a llama single-domain antibody (also known as a "VHH") that has been modified for proteolytic stability. For clarity, the binding protein is monomeric and does not contain many of the complex effector functions of conventional antibodies: it does not contain an Fc domain; it is comprised of a single polypeptide chain; it is not glycosylated; and it does not contain multiple disulfide bonds. It binds

to and inhibits a campylobacter flagellin protein whose sequence does not contain any homology to known human proteins and has been demonstrated to lack cross reactivity to a broad panel of human tissues. The aa682 binding protein is engineered as a fusion with *E. coli* maltose binding protein (MBP), which is a chaperone that increases solubility, bioactivity, and expression level in spirulina. MBP is present in all humans as an abundant component of the normal gastrointestinal commensal flora.

Spirulina (a type of blue-green algae) was selected as the expression host because it is Generally Recognized as Safe (GRAS) under FDA regulations, has a well-understood and non-toxic safety profile from its wide use as a food source for humans and animals, has been involved in numerous clinical trials with no reports of AEs, and is highly stable as a spray-dried powder.

The intact spirulina biomass protects the binding protein from gastric acid and proteolytic enzymes during transit through the gastric environment and from degradation during storage.
The drug substance is whole, dried spirulina biomass containing the active component, a bioengineered VHH-derived protein, designed to bind and inhibit a foreign pathogen protein for which there is no corresponding human protein. The drug product consists of the dried powder packaged in vegetable-based capsules for oral delivery. The active biologic, being a 55 kDa macromolecule, is not expected to be systemically absorbed.

2.2 Preclinical Data

Spirulina-VHH directed against FlaA protein, the flagellar filament protein, was tested in murine campylobacter challenge models in two different laboratories (Guerrant, *et al*., 2019, personal communication; Grassi *et al.*, 2019, personal communication). Oral gavage with anti-campylobacter spirulina-VHH fully protected against diarrhea in mice challenged with 10^7 or 10^8 colony-forming units of *C. jejuni.* Campylobacter shedding was reduced by four orders of magnitude. There was no negative effect on weight gain and no observed toxicity.
Taken together these preclinical data provide support for the potential utility for LMN-101 to prevent campylobacter diarrhea.

2.3 Tissue Cross-Reactivity

In vitro tissue cross-reactivity assays demonstrated no binding of LMN-101 to human tissue.

2.4 Prior Clinical Data

LMN-101 has not previously been administered to humans. The spirulina carrier has been extensively used as a food supplement and is safe and well tolerated.

2.5 Dose Rationale and Risk Benefits

Several murine campylobacter challenge studies demonstrated that the NOAEL (no-observed-adverse-event level) was 13.4 mg in 20-gram mice, equivalent to 670 mg/kg (Guerrant, *et al*., 2019, personal communication). The HED is scaled based on a mg/kg conversion for this route of

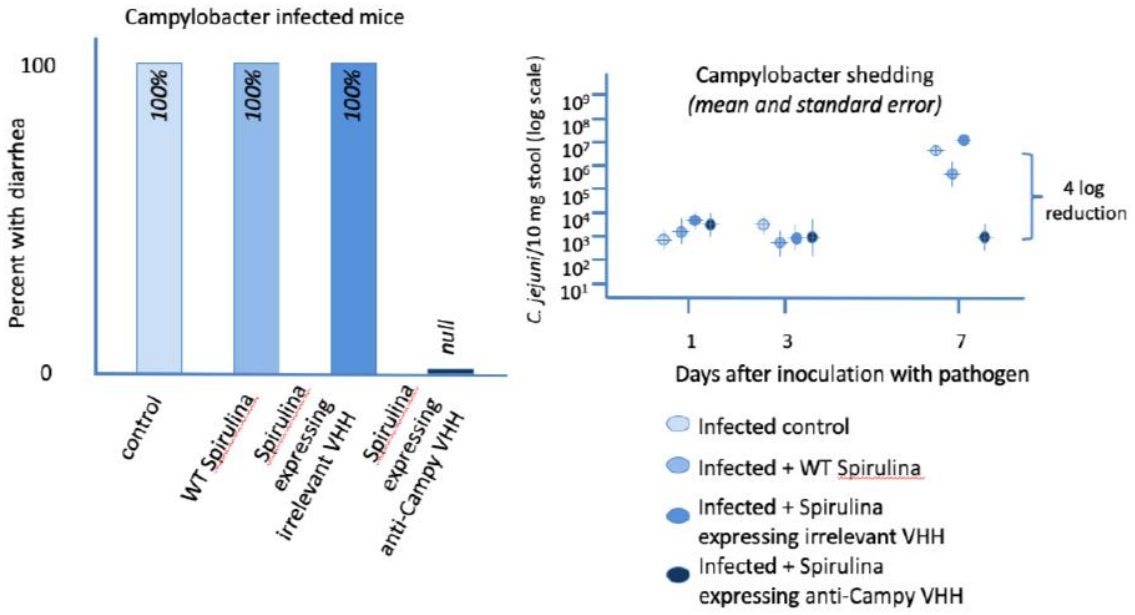

Figure 1: Anti-campylobacter VHH protects against infection in mice challenged with campylobacter (Guerrant, et al., 2019, personal communication)

administration (FDA 2005). The gastrointestinal compartment weight allometrically scales by $W^{0.94}$, approximated as $W^{1.0}$, yielding a HED of 670 mg/kg or 46.9 grams/dose as the NOAEL.

Spirulina has an extensive safety record in the food and nutritional supplement industries. In addition, numerous clinical trials have been conducted with spirulina with no reports of AEs (Karkos *et al.* 2011); one example reports administration of 2 grams of *Spirulina platensis* daily for 2 weeks (Mani *et al.* 2015). A randomized, controlled study of spirulina supplementation on infant growth, morbidity and motor development in 501 Zambian infants age 5-15 months gave 10 g daily of spirulina powder for 16 months (NCT03523182) (Masuda and Chitundu 2019). No safety concerns were reported. Children in the spirulina group had higher scores in gross and fine motor development, language, and social skills. Based on these considerations, Lumen proposes to evaluate the minimal pharmacologically active dose (PAD) as determined by the murine preclinical studies, which was 21.5 mg/kg (Grassi *et al.*, 2019, personal communication). Based on the gastrointestinal compartment weight, the HED is 21.5 mg/kg, i.e., 1505 mg for a 70-kg person.

The highest planned dose in this safety dose-ranging study, 3000 mg, is substantially below the calculated NOAEL, and incorporates a safety factor of 15.6-fold (or 5.2-fold if using the total daily dose). A dose higher than the PAD calculated for a 70-kg individual was selected for this Phase 1 study in order to provide a safety margin for smaller individuals.

3 STUDY OBJECTIVES

The primary objective of this study is to determine:

- The safety and tolerability of LMN-101.

The secondary objectives of this study are to determine:

- Serum pharmacokinetics of LMN-101; and
- Formation of anti-drug antibodies.

3.1 Primary Endpoints

The primary endpoint will be safety and tolerability of LMN-101.

3.2 Secondary Endpoints

The secondary endpoints are:

- Peak serum VHH concentration following administration of the initial dose and peak serum VHH concentration following a course of treatment (if systemic absorption is observed).
- Area under the serum VHH concentration versus time curve (AUC) following administration of the initial dose and following a course of treatment (if systemic absorption is observed).
- Induction of serum anti-VHH IgG antibodies (if systemic absorption is observed).

3.3 Safety Objectives

Safety will be assessed by the occurrence of SAEs, overall rates of AEs, clinically significant abnormal laboratory tests, and changes in vital signs. AEs will be coded using the MedDRA and severity graded according to CTCAE version 5.0. AEs will be summarized by treatment group for the number of AEs. Comparisons will be made between baseline, on treatment, and follow-up values. All hematology, chemistry and coagulation studies will be compared to well established clinical laboratory normal ranges in a certified laboratory. Vital signs and clinical laboratory results will be summarized for each treatment group. Comparisons will be made between baseline, on treatment, and follow-up values. Tolerability will be assessed by the proportion of participants completing study drug and remaining on study and free from possibly drug-related and dose-limiting SAEs to the end of follow-up.

3.4 Pharmacodynamic and Pharmacokinetic Objectives

The serum levels of VHH will be determined before, 2 hours, and 24 hours after the first dose; Day 8 (Part B), Day 28 (Part B), and Day 29 (Part B). Stool samples will be collected on Days 1, 2, 8 (Part B), 28 (Part B), and 29 and banked.

PK results will be summarized. Serum levels are being measured to determine if there is systemic absorption of this orally administered macromolecular protein. Stool supernatants will be banked.

3.5 Anti-Drug Antibodies

Serum samples will be collected at baseline, Week 5, and end of study for measuring for anti-drug antibodies if systemic absorption of LMN-101 is observed. If anti-drug antibodies are observed, additional determinations will be performed for antibodies. If antibodies are observed on confirmatory assays, additional testing will be done to measure antibody titers.

3.6 Study Drug Compliance

Adherence to study drug will be measured by subject diary, study visit assessment, and pill counts.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This will be a two-part study: Part A, an open-label administration of a single dose of LMN-101 and Part B, a randomized, double-blind, placebo-controlled, dose-escalation study of 3 dose levels of LMN-101. In Part A, healthy volunteers will take LMN-101 orally at the 3000 mg dose level once. Protocol-specified evaluations and procedures will be performed on days 1-2 and at one- to two-week intervals during dosing. Study observation will continue until 4 weeks after the last dose of study drug.

In Part B, healthy volunteers will take LMN-101 or placebo orally at one of three dose levels three times daily over 28 days. Protocol-specified evaluations and procedures will be performed on days 1-2 and at one- to two-week intervals during dosing. Study observation will continue until 4 weeks after the last dose of study drug.

Healthy volunteers will be recruited from the community by media and from the existing clinical research center population of healthy volunteers. Individuals meeting all inclusion and exclusion criteria will be sequentially assigned to Part A or Part B.

In Part A, subjects will be assigned to a single dose of 3000 mg PO given as six 500-mg capsules of LMN-101 (2 subjects).

In Part B, subjects will be sequentially assigned to escalating dose regimens will be randomized within that dose regimen to active or placebo treatment:

- 300 mg PO TID given as a single 300-mg capsule of LMN-101 orally three times daily for 28 days (4 subjects) or identical-appearing placebo capsule (2 subjects).
- 1000 mg PO TID given as two 500-mg capsules of LMN-101 orally three times daily for 28 days (4 subjects) or identical-appearing placebo capsules (2 subjects).
- 3000 mg PO TID given as six 500-mg capsules of LMN-101 orally three times daily for 28 days (4 subjects) or identical-appearing placebo capsules (2 subjects).

Enrollment is planned for 20 subjects: Part A, 2 subjects and Part B 18 subjects (LMN-101 12 subjects; placebo 6 subjects), 6 per dose cohort (LMN-101 4 subjects per dose cohort; placebo 2 subjects per dose cohort).

Study Days are defined as consecutive calendar days beginning from the start time of the first study drug administration for each subject (Day 1). Protocol-specified evaluations and procedures will be performed on Days 1, 2, 8, 15, 28 (Part B only), and 29, with an additional evaluation 4 weeks after the final dose. There will be an interim safety review between each dose cohort. Study observations will continue until 4 weeks (± 1 week) after the last dose of study drug.

4.2 Treatment Assignment

Following receipt of signed informed consent from the study subject, completion of baseline assessments at screening and meeting study inclusion and exclusion criteria, the subject will be evaluated by the PI for enrollment eligibility. The Study Manual contains instructions for assigning a randomisation number. The randomisation number will be carefully matched to study drug by a trained member of the Pharmacy team before dispensing study drug. The PI or delegate will maintain a list of contact information for all study participants should additional contact be required. Code-break envelopes will be supplied to the pharmacy if unblinding is required due to a serious or life-threatening adverse event.

4.3 Safety Criteria for Stopping Dosing

Advancing to the next dose cohort will be done after review of safety data by the PI and the Sponsor's Medical Monitor, both of whom are unblinded as to treatment assignment in Part A and blinded as to treatment assignment in Part B. If a dose is safe, then the next dose cohort will be enrolled. Criteria that would result in a pause in active dosing and further investigation by the study team include if any subject experiences a SAE deemed related to the study drug; if two or more subjects experience the same grade 3 or higher AE; if accumulation of SAEs and/or AEs collectively raises a safety concern in the opinion of the investigator, research monitor, or study sponsor; or if any subject experiences an adverse event of special interest (AESI).

If a subject develops a significant allergic reaction or anaphylaxis following study drug administration, the study drug will be immediately discontinued for that subject and no further doses given. The PI should contact the Sponsor's Medical Monitor to determine whether to discontinue study treatment for a given subject. Regardless of communication with the Sponsor, the PI is authorized to discontinue the study drug at any time if it is in the best interest of the safety of the subject. Treatment may also be discontinued at the request of the subject.

4.4 Criteria for Study Termination

Subjects who must discontinue treatment for any reason should continue to complete the study follow-up visits through final study visit. If a subject is not able to comply with study safety monitoring or is significantly non-compliant with study protocol and/or treatment, the PI should inform Lumen Bioscience, Inc. about early termination of the subject's study participation. Criteria for early termination are in the section titled Early Termination of Subjects in this protocol.

5 STUDY POPULATION

Subjects will be required to meet all inclusion criteria to enroll in this study. If any exclusion criteria are met, enrollment will be declined.

5.1 Inclusion Criteria

A subject must fulfill all the following criteria to be eligible for enrollment:

1. Male or female between 18 and 50 years, inclusive, at time of informed consent
2. Willingness to participate after written informed consent obtained
3. Available for all planned clinical visits for physical examinations, blood draws, stool collections
4. General good health, without significant medical illness or abnormal physical examination findings as determined by the PI.
5. Adequate safety laboratory results, renal and liver function.
   a. Absolute neutrophil count ≥ 1.5 x 10^9/L
   b. Lymphocyte count < 6.0 x 10^9/L
   c. Platelet count ≥ 150 x 10^9/L
   d. Hemoglobin ≥ 110 g/L
   e. eGFR ≥ 40 mL/min/1.73 m^2
   f. ALT and/or AST ≤ 3x ULN
   g. Total bilirubin ≤ 1.5x ULN
   h. Serum albumin ≥ 28 g/L
6. Females of childbearing potential should be using and committed to continue using one of the following acceptable birth control methods:
   a. Sexual abstinence (inactivity) or exclusively same-sex partner for 1 month prior to screening through study completion; or
   b. IUD in place for at least 1 month prior to study through study completion; or
   c. Stable hormonal contraception for at least 1 month prior to study through study completion; or
   d. Surgical sterilization (vasectomy) of male partner at least 6 months prior to study.
7. To be considered of non-childbearing potential, females should be surgically sterilized (bilateral tubal ligation, hysterectomy, or bilateral oophorectomy at least 2 months prior to study) or be post-menopausal and at least 12 months since last menses.
8. Male participants must use condoms during the study and through study completion.

5.2 Exclusion Criteria

A subject fulfilling any of the following criteria at screening is to be excluded from enrollment in the study:

1. Treatment with an experimental compound within 30 days.
2. Treatment within 30 days or planned use within the study period with immunomodulator or immunosuppressant agent.
3. Pregnancy or breastfeeding.
4. Presence of any of the following clinical conditions:
   a. History of one or more of the following: cardiac insufficiency (NYHA III/IV), uncontrolled cardiac arrhythmias, unstable ischemic heart disease, or uncontrolled hypertension (systolic blood pressure > 170 mmHg or diastolic blood pressure > 110 mmHg).
   b. History of venous thromboembolic disease within 12 months, myocardial infarction, or cerebrovascular accident.
   c. Unstable pulmonary, renal, hepatic, endocrine or hematologic disease.
   d. Gastrointestinal disorder requiring ongoing care by a physician.
   e. Autoimmune disease, mixed connective tissue disease, scleroderma, polymyositis, or significant systemic involvement secondary to rheumatoid arthritis.
   f. Evidence of active malignant disease, malignancies diagnosed within the previous 5 years, or breast cancer diagnosed within the previous 5 years (except skin cancers other than melanoma).
   g. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other opportunistic infections, excluding urinary tract infections; or major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks.
   h. Positive serology for HIV infection or history of other immunodeficiency illness.
   i. Positive serology results for HBsAg or HCV
   j. Significant neuromuscular disease or neuropathy
   k. Psychiatric condition
   l. Alcohol or illicit drug abuse/dependency or positive urine toxicology screen for drugs of abuse other than marijuana. Alcohol and tobacco consumption are permitted.
   m. Significant food allergy restrictions.

6 DESCRIPTION OF TREATMENT

6.1 Compound

The study drug, LMN-101, and placebo will be supplied by Lumen Bioscience, Inc. (Seattle, Washington, USA). LMN-101 is VHH-derived binding protein designed to bind and inhibit FlaA (a flagellin filament protein of *Campylobacter jejuni*), delivered in whole, spray-dried, encapsulated spirulina biomass. LMN-101 ingredients are spray-dried spirulina biomass (containing the aa682 protein) and trehalose (NF grade) containing 300 mg or 500 mg of biomass. Placebo consists of wild-type spirulina and trehalose (NF grade) packaged into identical capsules containing 300 mg or 500 mg of biomass.

6.2 Dosing Regimen

Subjects will be sequentially assigned to Part A or Part B.

In Part A, subjects will be assigned to a single dose of 3000 mg PO given as six 500-mg capsules of LMN-101 (2 subjects).

In Part B, subjects will be sequentially assigned to the following dosing regimens and will be randomized within that dose regimen to active or placebo treatment:

- 300 mg PO TID given as a single 300-mg capsule of LMN-101 orally three times daily for 28 days (4 subjects) or identical-appearing placebo capsule (2 subjects).
- 1000 mg PO TID given as two 500-mg capsules of LMN-101 orally three times daily for 28 days (4 subjects) or identical-appearing placebo capsules (2 subjects).
- 3000 mg PO TID given as six 500-mg capsules of LMN-101 orally three times daily for 28 days (4 subjects) or identical-appearing placebo capsules (2 subjects).

All subjects will receive background therapy consistent with the local standard of care. The research pharmacy should label study drug according to the Study Pharmacy Manual and using institutional Standard Operating Procedures.

6.3 Dosage Form

LMN-101 doses are packaged in Vcaps Plus® vegetarian capsules (Capsugel, Morristown, NJ, US) or equivalent. Placebo doses are packaged into identical capsules containing 300 mg or 500 mg of biomass. Bulk containers of capsules are provided with a desiccant pouch.

6.4 Timing of Doses

The study drug administration date and start and stop times must be recorded in the subject's chart and in the case report form (CRF). Capsules are to be self-administered by the subject three times daily and may be taken with meals. The subject will be provided a subject diary by the research clinic to record study drug administration, date, time, and relationship to meals.

6.5 Route of Administration

The study drug and placebo must be administered orally and may be taken with fluids or food. For the first dose only, please withhold food for an hour before and after the study drug administration. Please administer the first dose with 240 mL of water.

6.6 Packaging and Labeling

Product labeling states:

LMN-101 Drug Product, 300 mg or 500 mg capsules
For oral use only
Lot No:
Re-test Date: November 2020 Store at 15-25 °C (59-77 °F)

Manufactured by Lumen Bioscience, Inc., Seattle, WA 98103 USA
Tel: +1 (206) 899-1904
Local Sponsor: Lumen Bioscience Australia Pty Ltd, 16 Nexus Way, Southport, QLD 4215
1300 941 908
CAM01 For clinical trial use only
Keep out of reach of children

Placebo, wild-type *Spirulina platensis,* 300 mg or 500 mg capsules
For oral use only
Lot No:
Re-test Date: November 2020 Store at 15-25 °C (59-77 °F)
Manufactured by Lumen Bioscience, Inc., Seattle, WA 98103 USA
Tel: +1 (206) 899-1904
Local Sponsor: Lumen Bioscience Australia Pty Ltd, 16 Nexus Way, Southport, QLD 4215
1300 941 908
CAM01 For clinical trial use only
Keep out of reach of children

6.7 Storage

Capsules containing LMN-101 or placebo should be stored at room temperature, 59° to 77° F (15° to 25° C) and protected from moisture, light, and extreme heat during storage. Capsules contain no preservatives. Any damaged or partially used capsules should be discarded using appropriate drug disposal procedures and documented. To ensure appropriate storage conditions, study drug storage temperatures must be measured and recorded daily. The storage area should restrict access to study personnel only.

For study drug dispensed to the subject, the study drug may be stored at room temperature with a recommendation to protect from moisture, light and extreme heat.

6.8 Study Drug Accountability

The Investigator or delegate will be responsible for implementing a system for documenting drug accountability of clinical supplies at the clinical site in conjunction with the institutional pharmacy. Only pharmacy personnel trained by the Investigator or delegate should receive deliveries. A signature of one of these individuals is required for delivery. Upon receipt of clinical supplies, the trained pharmacy personnel will:

- Confirm (via temperature indicator included in the shipment) that product temperature is within acceptable limits 59° to 77° F (15-25 °C). Document on the receipt form.
- Conduct an inventory of the shipment to verify agreement with the Packing List.
- Acknowledge receipt of the clinical supplies by dated signature of the receipt form.
- Send a copy of the receipt form to Lumen Bioscience or its designee.
- Retain a copy of the receipt for drug accountability records.

6.9 Study Drug Handling and Disposal

Study drug is to be dispensed only to eligible subjects in accordance with the protocol. The Investigator or his designee will maintain the trial drug inventory using an accountability form containing the following information:

- Identification of the subject for whom the drug was dispensed.
- Treatment number, date and quantity of the drug dispensed to the subject and identification of the person dispensing drug.
- Date(s) and quantity of the drug returned as not administered to the subject (if applicable) and identification of the person in receipt of the drug.
- Documentation of any wasted/broken units, including reason and disposition.

Returned study drug must not be administered to another subject. The study drug inventory will be available for periodic inspection/verification.

At the end of the study all unused study drug and placebo will be disposed of appropriately in accordance with study protocol and any institutional Standard Operating Procedures. Reconciliation of shipped, dispensed, and remaining drug will be performed. Any discrepancies noted will be investigated, resolved, and documented.

7 STUDY PROCEDURES

7.1 Duration of Study Drug Treatment

The duration of study drug treatment will be for one dose for Part A and for 4 weeks for Part B. All subjects in Part B will receive a total of 84 doses.

7.2 Duration of Study

Eligibility of subjects for enrollment will be based on the results of screening for inclusion and exclusion criteria. Screening will occur up to 30 days prior to initiation of study treatment. Each subject will continue in the study for 4 weeks (±1 week) after last dose of study drug. The study will be carried out at one site. Enrollment for this trial will occur over a period of 2-3 months with a total of 20 enrolled subjects.

7.3 Screening

Evaluation for eligibility for enrollment will be performed in healthy volunteers at the study site. Screening evaluations must be conducted within 30 days of initiating study drug on Day 1 and will consist of:

- Written informed consent from subject prior to study assessments or procedures
- Screen for inclusion/exclusion criteria
- Medical/surgical history and documentation of comorbidities
- Record concomitant medications

- Record height and weight
- Physical examination, including vital signs (blood pressure, respiratory rate, heart rate and temperature)
- Serum (beta-hCG) pregnancy test for women of childbearing potential
- Measure hemoglobin, white blood cell count with differential, platelet count, serum PTT, INR, sodium, potassium, calcium, magnesium, phosphate, creatinine, albumin, AST, ALT, alkaline phosphatase, total bilirubin, and eGFR
- Collect serum for HBsAg and HCV screen
- Conduct HIV screen
- Collect urine Drugs of Abuse screen
- Send subject home with stool collection kit for sample to be collected as close as possible to Day 1 before study visit.

7.4 Study Day 1 – Pre-Treatment and Post-Treatment

- Record concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate and temperature)
- Prior to first study drug administration (up to 4 hours before):
    - Serum or urine (beta-hCG) pregnancy test for women of childbearing potential. The results of this test must be confirmed negative prior to beginning study drug administration.
    - Collect blood for serum to be stored for baseline pharmacokinetics
    - Collect blood for serum to be stored for baseline anti-drug antibodies
    - Collect urine Drugs of Abuse screen
    - Obtain baseline stool specimen collected by subject (if subject is unable to produce a void, they are still eligible to be admitted to the study)
- Part B only: Supply one-week supply of study drug to subject (except Day 1 first dose)
- Part B only: Instruct subject on self-administration of study drug at home three times daily. The study drug may be taken with meals or liquids. Instruct subject on recording of study drug administration in study drug diary.
- Observe subject self-administer first dose of study drug with 240 mL of water. Subject should be fasting except for water for one hour before and after the first dose only.
- Two hours (± 30 minutes) after administering first dose of study drug:
    - Collect blood for serum to be stored for pharmacokinetics
- History and targeted physical exam for assessment and recording of AEs
- Send subject home with stool collection kit for sample to be collected as close as possible to Day 2 before study visit. Time of collection must be recorded.

7.5 Study Day 2

- Record concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)

- History and targeted physical exam for assessment and recording of AEs.
- Part B only: Review study drug diary with patient and verify study drug compliance with pill count.
- Obtain stool sample collected by subject.
- 24 hours (± 1 hour) after first dose of study drug:
    - Collect blood for serum to be stored for pharmacokinetics
- Part B only: Send subject home with stool collection kit for sample to be collected as close as possible to Day 8 before study visit.

7.6 Study Week 2 (Study Day 8)

- Record concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Part B only: Collect blood for serum to be stored for pharmacokinetics
- Part B only: Obtain stool sample collected by subject to ship to laboratory.
- Measure hemoglobin, white blood cell count with differential, platelet count, serum PTT, INR, sodium, potassium, calcium, magnesium, phosphate, creatinine, albumin, aspartate aminotransferase (AST), ALT, alkaline phosphatase, total bilirubin, and eGFR
- History and targeted physical exam for assessment and recording of AEs
- Part B only: Review study drug diary with patient and collect returned dosing container to return to pharmacy for quarantine and to verify pill count
- Part B only: Supply one-week supply of study drug to the subject

7.7 Study Week 3 (Study Day 15)

- Record concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Measure hemoglobin, white blood cell count with differential, platelet count, serum PTT, INR, sodium, potassium, calcium, magnesium, phosphate, creatinine, albumin, AST, ALT, alkaline phosphatase, total bilirubin, and eGFR
- History and targeted physical exam for assessment and recording of AEs
- Part B only: Review study drug diary with patient and collect returned dosing container to return to pharmacy for quarantine and to verify pill count
- Part B only: Supply two-week supply of study drug to the subject.
- Send subject home with stool collection kit for sample to be collected as close as possible to Day 29 (Part A) or Day 28 (Part B) before study visit. Time of collection must be recorded.

7.8 Part B only: Study Week 4 (Study Day 28, Last Day of Study Drug)

- Record concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Collect blood for serum to be stored for pharmacokinetics

- Collect blood for serum to be stored for anti-drug antibodies
- Measure hemoglobin, white blood cell count with differential, platelet count, serum PTT, INR, sodium, potassium, calcium, magnesium, phosphate, creatinine, albumin, AST, ALT, alkaline phosphatase, total bilirubin, and eGFR
- Serum (beta-hCG) pregnancy test for women of childbearing potential
- Obtain stool sample collected by subject.
- History and targeted physical exam for assessment and recording of AEs
- Review study drug diary with patient and collect returned dosing container to return to pharmacy for quarantine and to verify pill count
- Send subject home with stool collection kit for sample to be collected as close as possible to Day 29 before study visit. Time of collection must be recorded.

7.9 Part A only: Study Week 5 (Study Day 29; 28 days after last dose of study drug ± 4 days)

- Record concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature).
- Collect blood for serum to be stored for anti-drug antibodies
- Measure hemoglobin, white blood cell count with differential, platelet count, serum PTT, INR, sodium, potassium, calcium, magnesium, phosphate, creatinine, albumin, AST, ALT, alkaline phosphatase, total bilirubin, and eGFR
- History and targeted physical exam for assessment and recording of AEs
- Obtain stool sample collected by subject.

7.10 Part B only: Study Week 5 (Study Day 29)

- Part B only: Review study drug diary with patient and verify study drug compliance with pill count.
- Part B only: Collect blood for serum to be stored for pharmacokinetics
- Obtain stool sample collected by subject.

7.11 Part B only: Study Week 8 (28 days after last dose of study drug ± 4 days)

- Record concomitant medications
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature).
- Collect blood for serum to be stored for anti-drug antibodies
- Measure hemoglobin, white blood cell count with differential, platelet count, serum PTT, INR, sodium, potassium, calcium, magnesium, phosphate, creatinine, albumin, AST, ALT, alkaline phosphatase, total bilirubin, and eGFR
- History and targeted physical exam for assessment and recording of AEs

Table 3: Schedule of Evaluations Part A

	Screening	Week 1		Week 2	Week 3	Week 4 End of Study
		Day 1	Day 2	Day 8	Day 15	Day 29 [1]
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Medical/Surgical History, Comorbidities	X					
Record concomitant medications	X	X	X	X	X	X
Pregnancy test[2]	X	X				
Physical Examination	X					
Vital Signs	X	X	X	X	X	X
Height/Weight	X					
Collect serum for pharmacokinetics[3]		XX	X			
Collect serum for anti-drug antibodies		X				X
Collect blood for hematology[4]	X	X[7]		X	X	X
Collect serum for chemistry[5]	X	X[7]		X	X	X
Collect blood for coagulation[6]	X	X[7]		X	X	X
Collect serum for HBsAg, HCV screen	X					
Collect serum for HIV screen	X					
Collect urine for Drugs of Abuse screen	X					
Obtain stool sample		X	X			X
Administer study drug (single dose)		X				
History & targeted physical exam for AEs		X	X	X	X	X

[1] Follow-up at Day 29 (28 days after last dose of study drug ± 4 days) for assessment of adverse events, and blood sampling, including anti-drug antibody and clinical laboratory studies.

[2] Serum beta-hCG pregnancy test from women of childbearing potential at screening. Repeat serum or urine pregnancy test on Day 1.

[3] Serum PK before, and 2 hours and 24 hours (Day 2) after administering first dose of study drug (Day 1). This consists of 3 total samples per subject.

[4] Hematology to include hemoglobin, white blood cell count with differential, and platelet count.

[5] Serum chemistry to include sodium, potassium, calcium, magnesium, phosphate, creatinine, albumin, AST, ALT, alkaline phosphatase, total bilirubin, and eGFR.

[6] Coagulation to include PTT and INR.

[7] Hematology, chemistry and coagulation studies only need to be performed if screening blood tests were performed more than 2 weeks prior to baseline visit.

Table 4 Schedule of Evaluations Part B

	Screening	Week 1		Week 2	Week 3	Week 4	Week 5	End of Study
		Day 1	Day 2	Day 8	Day 15	Day 28	Day 29	Day 56 [8]
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Medical/Surgical History, Comorbidities	X							
Record concomitant medications	X	X	X	X	X	X		X
Pregnancy test[9]	X	X				X		
Physical Examination	X							
Vital Signs	X	X	X	X	X	X		X
Height/Weight	X							
Collect serum for pharmacokinetics[10]		XX	X	X		X	X	
Collect serum for anti-drug antibodies		X				X		X
Collect blood for hematology[11]	X	X[14]		X	X	X		X
Collect serum for chemistry[12]	X	X[14]		X	X	X		X
Collect blood for coagulation[13]	X	X[14]		X	X	X		X
Collect serum for HBsAg, HCV screen	X							
Collect serum for HIV screen	X							
Collect urine for Drugs of Abuse screen	X							
Obtain stool sample		X	X	X		X	X	
Administer study drug (first dose)[15]		X						
Administer study drug po TID daily for 28 days		X	X	X	X	X		
History & targeted physical exam for AEs		X	X	X	X	X		X
Verification of dosing by diary, pill count			X	X	X	X	X	

[8] Follow-up at Day 56 (28 days after last dose of study drug ± 4 days) for assessment of adverse events, and blood sampling, including anti-drug antibody and clinical laboratory studies.

[9] Serum beta-hCG pregnancy test from women of childbearing potential at screening and end of dosing. Repeat serum or urine pregnancy test on Day 1.

[10] Serum PK before, and 2 hours and 24 hours (Day 2) after administering first dose of study drug (Day 1); Day 8; on last day of study drug (Day 28) and on the day following the last dose of study drug (Day 29). This consists of 6 total samples per subject.

[11] Hematology to include hemoglobin, white blood cell count with differential, and platelet count.

[12] Serum chemistry to include sodium, potassium, calcium, magnesium, phosphate, creatinine, albumin, AST, ALT, alkaline phosphatase, total bilirubin, and eGFR.

[13] Coagulation to include PTT and INR.

[14] Hematology, chemistry and coagulation studies only need to be performed if screening blood tests were performed more than 2 weeks prior to baseline visit.

[15] Two subsequent doses for Day 1 are to be self-administered by subject out of the clinic.

7.12 Non-Study Medications

Non-study medications are permitted during this study except for other investigational drugs and those not allowed in the Exclusion Criteria. Any reported non-study medication will be recorded and evaluated by the Investigator. Use of other investigational drugs or drugs prohibited by the study enrollment criteria may be cause for exclusion or discontinuation of a subject (see Exclusion Criteria).

7.13 Study Drug Assignment

Subjects meeting all inclusion and exclusion criteria will be sequentially assigned a randomisation number from a list provided to the designated pharmacist. Pharmacy personnel preparing the study drug for dispensing will be unblinded. The Pharmacist(s) delegated by the PI are responsible for maintaining the randomisation schedule and the name of the subject assigned to that randomisation number.

7.14 Early Termination of Subjects

Subjects who are enrolled in this study may terminate their participation in the study at will. Subjects that have started study drug and are discontinued from the study drug for any reason will continue to be monitored for study endpoints and safety through study completion.

Investigators may terminate the treatment of a subject who:

- Experiences unacceptable toxicity
- Becomes pregnant
- Non-compliance issues including subject's inability to follow the dosing regimen, e.g., missing four or more doses of study drug;
- Subject found to be in violation of Inclusion or Exclusion Criteria subject to consultation with Lumen Bioscience Medical Monitor

Every effort will be made by the investigational site to maintain contact with subjects who are discontinued in order to monitor for study endpoints and safety, including those discontinued based on non-compliance issues.

All subjects receiving at least one dose of study drug will be included in the safety analysis, whether they complete the study or not. Reasons for dropouts will be reported and evaluated for possible introduction of bias into the analysis. AEs reported by subjects or revealed upon examination or lab testing will be included in the analysis.

If a subject was enrolled and discontinued before starting study drug, they will be replaced in the study. Trained pharmacy personnel may automatically replace a participant if they withdraw after randomisation but before starting study drug. A subject who withdraws after dosing but

before completing the full study will be replaced if they have not completed at least three weeks of study drug. The replacement subject will be assigned the same treatment assignment as the subject that they are replacing.

7.15 Subpopulations for Analysis

Modified Intent-to-Treat Population

The modified intent-to-treat analysis will include all randomised subjects meeting inclusion criteria who receive at least one dose of study drug.

Per-Protocol Subjects

An analysis of the per-protocol population will be performed to include all randomised subjects who complete the full course of study drug and who have data collected for the primary endpoint.

7.16 Data Safety and Monitoring Plan

Investigators are responsible for monitoring the safety of subjects who have entered this study. Subjects will be frequently assessed for AEs by the research nurse and PI, with the latter acting as site medical monitor.

The investigator is responsible for appropriate medical care of subjects during the study. The investigator remains responsible to follow, through an appropriate health care option, AEs that are serious, cause the subject to discontinue before completing the study, or are ongoing at the time of study completion. The investigator will maintain responsibility for forwarding of SAEs to the institutional review board. The subject will be followed until the event resolves or stabilizes. Frequency of follow-up is left to the discretion of the investigator.

7.17 Safety Analysis

The analysis of safety will include all subjects who received study drug. Safety will be evaluated from reported AEs, physical examination findings, vital signs, and clinical laboratory values as described below:

- The incidence and number of all reported AEs and treatment-related AEs will be tabulated by treatment group. AEs will be classified by Organ System Classification.
- AEs and SAEs will be summarized by organ system classification, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in the same subject, the AE will be reported as the number of AEs and with the AE counted only once. The incidence of AEs will be tabulated by Organ System Class and treatment group.
- AEs indicative of secondary infection will also be compared between treatment groups.

- SAEs will be presented as listings by treatment group. The event, start and stop dates and times, relationship to study drug, severity, and outcome will be presented. Outcomes attributed to SAEs will be tabulated separately by treatment group.

Tolerability will be assessed by the proportion of participants completing study drug and remaining on study and free from possibly drug-related and dose-limiting SAEs to the end of follow-up.

7.18 Pharmacokinetic Analyses

The serum levels of VHH will be determined before, 2 hours, and 24 hours after the first dose; Day 8, Day 28, and Day 29. If serum levels of VHH are detected, PK results will be summarized. Stool samples will be collected at baseline and on Days 2, 8, 28 and 29, supernatant collected, and the supernatant stored in a stool bank.

7.19 Potential Toxicities

The potential toxicities of LMN-101 are primarily related to the effects associated with monoclonal antibodies (mAbs) in general. As with all drugs and biologics, there is the potential for individual allergic reactions. Considerable human experience has been accumulated with mAb therapy. The adverse effects of treatment with mAbs are diverse and appear to be dependent on the species of origin (murine versus human) and the antigenicity of the antibody. To date, there is no other reported clinical experience with another mAb against campylobacter.

Potential toxicities that may exist with LMN-101 include the formation of antibodies against LMN-101. Since LMN-101 is a protein macromolecule administered orally, systemic absorption is not anticipated so the risk of formation of anti-drug antibodies is low. Please see the Investigator's Brochure for additional information.

Since LMN-101 is a subunit of an antibody and does not contain an Fc domain, there is not a possibility of Fc binding. Since LMN-101 is directed against a bacterial antigen that does not cross-react with human tissue, there is no anticipated non-specific binding to human tissue.

While there is theoretically a remote possibility of a potential effect on the normal gut microbiome, antibodies against the target antigen, FlaA of campylobacter flagellin do not cross react with normal flora of the gut microbiome.

8 ADVERSE EVENTS (AEs)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether considered caused by the product or not. In clinical studies, an AE can include an undesirable

medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after any subject has been enrolled, before treatment, during treatment, or within days following the cessation of treatment, whether they are related to the study or not, must be recorded on forms provided by Lumen Bioscience or its representative. Lumen Bioscience and the investigators must abide by the Australian Health Ethics Committee statement "*Safety monitoring and reporting in clinical trials involving therapeutic goods.*" *http://health.act.gov.au/sites/default/files//REGO/28.%20AHEC%20Position%20Statement%20-%20Safety%20Reporting%20-%20November%202016.pdf*

8.1 Serious Adverse Events (SAE)

A SAE is an AE occurring during any study phase (i.e., baseline, treatment, or follow-up), and at any dose of the investigational product or placebo, that fulfills one or more of the following criteria:

- Results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or within 28 days following the cessation of treatment, whether they are related to the study or not, must be recorded on forms provided by Lumen Bioscience or its representative.

Any serious or unexpected AEs must be reported to Lumen Bioscience or its representative, including death or life-threatening events, disabling or incapacitating conditions, or any event that requires hospitalization. SAEs occurring during the duration of the study or within four weeks of the subject's last treatment must be reported within 24 hours to Lumen Bioscience or its representative, even if the event appears unrelated to the treatment. See the Study Manual for specific instructions for reporting SAEs.

Lumen Bioscience Medical Monitor 24-hour contact information:

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Chief Medical Officer
Lumen Bioscience, Inc.
1441 N. 34th Street, Suite 300
Seattle, WA 98103 USA
JAgosti@LumenBioscience.com
+01(206) 899-1904 business
+01(206) 619-9963 mobile

Lumen Bioscience back-up Medical Monitor 24-hour contact information:

Wayne Tsuji, MD
Cascadia Drug Development Group
321 High School Rd NE, Suite D3
Bainbridge Island, WA 98110 USA
Tsuji@thecddg.com
+1 (805) 559-4971 mobile

Both Lumen Bioscience and Investigators have the right to terminate this study at any time, and to arrange an appropriately agreed upon schedule for termination, if necessary. This information will be provided to each subject or legally authorized representative during the informed consent process.

SAEs will be reported to the FDA and/or relevant national regulatory authorities within the required time frames to meet the safety reporting requirements, i.e., a 7-day IND safety report for unexpected fatal or life-threatening suspected adverse reactions, an IND safety report for 15-day reports, or a follow-up IND safety report for follow-up information.

8.2 Relationship to Treatment

An Investigator who is qualified in medicine must make the determination of relationship to the treatment for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the treatment. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the treatment and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the treatment is determined to be “possible” or “probable” the event will be considered to be related to the treatment for the purposes of expedited regulatory reporting.

8.3 Recording Adverse Events

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs since they will be captured in those data listings. However, abnormal values that constitute an SAE or lead to discontinuation of administration of treatment must be reported and recorded as an AE. Information about AEs will be collected from the signing of the consent form until the end of the study. SAE information will be collected from signing of the consent form until 28 days following the last dose of treatment. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

Intensity will be assessed according to the CTCAE Version 5.0. A pdf of these criteria is attached as Appendix A.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under the Section above entitled Serious Adverse Event. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded in the source documents and Medical History form in the CRF. Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

8.4 Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of the consent form until 28 days following the end of treatment. Any SAEs considered possibly or probably related to the treatment and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Lumen Bioscience within one business day of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a scanned copy by email to Lumen Bioscience

Additional follow-up information, if required or available, should all be scanned and emailed within one business day of receipt, and this should be completed on a follow-up SAE form placed with the original SAE information, and kept with the appropriate section of the CRF and/or study file.

Lumen Bioscience is responsible for notifying the relevant regulatory authorities of certain events. It is the PI's responsibility to notify the HREC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its HREC of these additional SAEs. Lumen is responsible for AE reporting to the FDA and/or other relevant national regulatory authorities.

9 INVESTIGATIONAL RECORD KEEPING

All study records including disposition of the drug (i.e., dates, quantity, use by subjects, and unused supplies) and subject CRFs, source documents, consent forms, and chart notes will be maintained and retained in accordance with local regulatory requirements and U.S. federal regulations set forth by 21 CFR Sec. 312.62. Each subject case history will contain documentation confirming that informed consent was obtained for the subject prior to participation in the study. All personnel associated with this study will make their best effort to ensure anonymity and confidentiality of subject records. Individual electronic CRFs will be collected for each subject. A copy of each CRF will be retained at the clinical site in the Investigator's files until further notice from Lumen Bioscience. All original CRFs will be transferred to Lumen Bioscience or its appointed agent for analysis and storage.

Case histories and study records will be made promptly available upon request to Lumen Bioscience, its representative, Australian Therapeutic Goods Administration (TGA) personnel, or Food and Drug Administration personnel. Lumen Bioscience, with the PI, will furnish required periodic study progress reports to the HREC. Any SAE safety reports will be made available immediately to Lumen Bioscience, the HREC, and the TGA in accordance with regulatory requirements.

The study results will be disseminated through presentations at scientific meetings and submission for publication to a peer-reviewed medical journal and clinicaltrials.gov. All subject identifiers will be removed in order to maintain subject confidentiality. At the conclusion and publication of the study results, a summary of the results will be shared with study participants in a letter from the PI.

Anticipated secondary uses of the data include supporting regulatory applications to other regulatory agencies for investigational or marketing approval and patent applications. In addition, the data from this study will be used in regulatory filings for other indications, for example, safety and PK data.

9.1 Protocol Deviations and Amendments

Any deviation from protocol deemed appropriate to prevent potential harm to an individual subject does not require pre-approval from the clinical site HREC or authorities at Lumen Bioscience or its representative; however, such deviations must be promptly reported to the HREC and Lumen Bioscience or its representative. Please consult the Study Manual for additional instructions.

9.2 Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Lumen Bioscience, Inc. will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Lumen Bioscience or its representatives. This will be documented in a Clinical Study Agreement between Lumen Bioscience and the Investigator.

During the study and at the close-out of the study, 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 investigational product 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, Inc.
- 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 HREC and/or TGA.

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.

9.3 Audits and Inspections

Authorized representatives of Lumen Bioscience, a regulatory authority, or HREC 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, GCP guidelines of the ICH, 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.

9.4 Retention of Records

The Investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Lumen Bioscience or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

10 HUMAN RESEARCH ETHICS COMMITTEE (HREC)

The final clinical protocol, the final version of the Patient Informed Consent Form, and recruitment materials must be approved, or given a favorable opinion, in writing by an HREC as appropriate. The PI must verify that the HREC has approved the clinical protocol, Patient Informed Consent Form, and recruitment materials for the investigation prior to conducting study evaluations. Initial HREC approval, and all materials approved by the HREC for this study

including the Patient Informed Consent Form and recruitment materials must be maintained by the Investigator and made available for inspection.

The PI is responsible for informing the HREC of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the HREC upon receipt of amendments and biannually, as local regulations require.

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

Progress reports and notifications of serious adverse drug reactions will be provided to the HREC according to local regulations and guidelines.

10.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, the National Statement on Ethical Conduct in Human Research, and applicable regulatory requirements.

10.2 Written Informed Consent

The PI or research staff designee will ensure that the subject 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 Patient Informed Consent Form. A copy of the signed Patient Informed Consent Form must be given to the subject or legally authorized representative.

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12 APPENDICES

12.1 Appendix A. Common Terminology Criteria for AEs

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