A Dose-Ranging Study Evaluating the Safety and Efficacy of LMN-0801 for Weight Loss

Protocol Number: WT02

Study Product: LMN-0801

Version: 1.~~0~~1

~~February 6,~~March [ ], 2025

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Principal Investigator's Agreement

I have received and read the clinical protocol.

I agree to conduct the study in accordance with this protocol, current Good Clinical Practices, ICH guidelines, the Declaration of Helsinki, and applicable laws and regulations applicable to me and my institution. I will ensure that the rights, safety, and well-being of study participants are protected, and that informed consent is obtained from all participants. I will promptly report any adverse events, protocol deviations, or other issues, as required, and take appropriate corrective and preventative actions to ensure the integrity of the study.

My institution and I agree to maintain the confidentiality of information received or developed in connection with this protocol.

Principal Investigator	Date

Version History

Version	Date	Description
1.0	06-Feb-2025	Original protocol
1.1	[]-Mar-2025	Simplified dosing schedule; increase placebo cohort to 18

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1 Protocol Summary

1.1 Synopsis

Study Title	A Dose-Ranging Study Evaluating the Safety and Efficacy of LMN-0801 for Weight Loss
Study Number	WT02
Study Product	LMN-0801
Sponsor	Lumen Bioscience, Inc.
Study Product; Dosing	Oral therapeutic protein-spirulina in capsules or placebo in capsules; 1-3 doses per day
Study Design	A prospective, randomised, placebo-controlled, single-blind clinical trial using a statistical design of experiments approach to assess the safety and preliminary efficacy of different dosing levels, frequency of dosing, and formulations of LMN-0801 through 24 weeks
Primary Objective	Characterise safety and tolerability by dosing level, frequency of dosing, and formulation
Primary Endpoint	Frequency of moderate to severe adverse events through Week 24 by dosing level, frequency of dosing, and formulation
Secondary Objectives	• Evaluate the efficacy of LMN-0801 on weight loss during treatment • Characterise safety and tolerability by dosing level, frequency of dosing, and formulation after cessation of treatment
Secondary Endpoints	• Change in body weight (kg and %) from baseline to Week 24 • Proportion of subjects achieving >5% body weight reduction from baseline to week 24 • Change in percentage body fat from baseline to Week 24 • Occurrence of adverse events during Week 24 to Week 29
Exploratory Objectives	• Evaluate body weight changes during treatment and after treatment cessation • Evaluate changes in body composition during treatment • Assess blood chemistry changes during treatment • Assess the performance of at-home weight and body composition devices • Assess the predictive validity of *in vivo* rodent models of obesity for oral biologics
Exploratory Endpoints	• Change in body weight (kg and %) from baseline to Day 28 • Change in body weight (kg and %) from baseline to Week 12 • Proportion of subjects achieving >5% body weight reduction from baseline to Day 28, Week 12, and Week 29 • Change in fat mass (kg and %) from baseline to Day 28, Week 12, and Week 24 • Change in lean mass (kg and %) from baseline to Day 28, Week 12, and Week 24 • Change in blood pressure and pulse from baseline to Day 28, Week 12, and Week 24 • Change in body mass index (BMI), waist circumference, percentage body fat, and lean-fat ratio from baseline to Week 24 and from Week 24 to Week 29 • Change (kg and %) in body weight, fat mass, lean mass from Week 24 to Week 29 • Change in HbA1c, TSH, and lipid profile from baseline to Week 24 • Presence of leptin analogue in blood serum, or emergence of anti-drug antibodies • Correlation between measures of weight measured at-home and in clinic • Correlation between measures of body composition measured at-home and in clinic • Correlation between weight loss in diet-induced obese rodents and obese humans using various putative dose-scaling factors
Participants	12~~0~~6 healthy adults with obesity (BMI > 30 and BMI < 40) Patients will be stratified 1:1 by gender and by BMI (< 35/ > 35)

Duration	The expected duration of participant engagement is 33 weeks (approximately 7.5 months), inclusive of 28 day screening window.
Key Inclusion Criteria	• Adults aged ≥ 18 and < 65 years • BMI ≥ 30 and < 40 • HbA1c < 6.5% • In good general health • Females agree to eliminate risk of pregnancy
Key Exclusion Criteria	• Significant illness, abnormal physical exam, lab findings (investigator discretion) • Alcohol abuse or drug dependency or tobacco use • Pregnant, breastfeeding, or planning to become pregnant or breastfeed • Use of weight loss drugs and/or antidiabetic agents in preceding six months • Currently treated with excluded medications • Have previously completed or withdrawn from this study • Participation in another clinical trial now or in the prior three months

1.2 Schedule of Activities

	Screen	**Enrol**	**Treatment Phase**						**Follow-up**
	Days -28 to -1	*Baseline Day 0*	*Wk 1 Day 7*	*Wk 4 Day 28*	*Wk 8 Day 56*	*Wk 12 Day 84*	*Wk 18 Day 126*	*Wk 24 Day 168*	*Wk 29 Day 203*
Scheduling window (days)			±1	±2	±2	±3	±3	±3	±5
In-person clinic visit	•	•	•	•	•	•	•	•	•
Informed consent	•								
Demographics	•								
Health history	•								
Concomitant medications	•	•							
Adverse events[1]		•[12]	•	•	•	•	•	•	•
Vital signs[4]	•	•[12]	•	•	•	•	•	•	•
Height	•								
Weight and BMI[2]	•	•	•	•	•	•	•	•	•
Waist circumference		•	•	•	•	•	•	•	•
Directed physical exam	•	•	•	•	•	•	•	•	•
Urine pregnancy test[3]	•	•							
Safety labs[5, 7]	•	•	•	•	•	•	•	•	•
Serum for study drug detection, anti-drug antibodies		•		•		•		•	•
Serum for cardiometabolic biomarkers[6, 7]		•		•		•		•	•
Serum for HbA1c, TSH[7]		•		•		•		•	•
DEXA scan[9]		•				•		•	•
Study drug supply and pill count		•[8]	•	•	•	•	•	•	
Weekly questionnaire collection and review[10]			•	•	•	•	•	•	•
Daily questionnaire collection and review[11]			•	•	•	•	•	•	•

[1]Detection and recording of study related AEs and SAEs extend from the signing of the consent form until completion of the last study related procedure (including follow-up for safety assessments).
[2]BMI=Body Mass Index
[3]For females of childbearing potential
[4]Vital signs (systolic and diastolic blood pressure, pulse rate, oral temperature, respiration rate) will be measured at each study visit.
[5]Participant will be asked to fast for at least eight hours; safety labs will include chem-7, liver function tests, amylase, lipid profile
[6]Serum will be collected to determine levels of satiety and cardiometabolic biomarkers, including ghrelin, GLP-1 and glucagon.

[7]*Participants will be asked to fast for at least 8 hours*
[8]*On day of enrolment, participants will receive directly observed study drug; participants are considered enrolled once they take their first dose of study drug. After receiving the first dose of study drugs, each participant will be monitored for two hours to assess for tolerability. At the end of two hours, vital signs and any AEs will be recorded.*
[9]Body composition measurements (including lean mass, fat mass and bone density) by DEXA scan[10]*In the provided weekly questionnaire, participants will record weight, lean mass and fat mass using scale with impedance-based body composition feature provided to each participant.*
[10]*Participants will also record any unexpected symptoms/AEs, healthcare provider visits and new medications in the weekly questionnaire.*
[11]*Participants will be provided with a daily questionnaire to record study drug self-administration; date, time and relationship to meals.*
[12]*Collected at baseline (before drug administration) and 2 hours after drug administration.*

2 Introduction

2.1 LMN-0801 Within the Current Therapeutic Landscape for Obesity

Obesity is a silent pandemic whose sequelae include diabetes mellitus, hypertension, dyslipidaemia, heart disease, stroke, sleep apnoea, and the associated morbidity and mortality (NCD Risk Factor Collaboration 2016). There is an urgent need for effective and safe weight loss interventions that are more affordable and scalable than current options.

In addition to lifestyle and surgical interventions, several drugs are now available for weight loss. Incretin analogue drugs—especially glucagon-like peptide-1 (**GLP-1**) receptor agonists—have generated remarkable results. By stimulating insulin secretion and inhibiting glucagon secretion in response to food intake, GLP-1 regulates postprandial glucose excursions. GLP-1 also stimulates centrally mediated appetite control and satiety (van Bloemendaal et al., 2014). Next-generation dual agonists like tirzepatide (Eli Lilly & Co.) generate even greater weight loss. Incretin analogues appear to be safe enough for mass-market use (in contrast to the older, small-molecule weight loss drugs like fen-phen and rimonabant).

However, significant challenges remain. GLP-1 analogues are costly, with limited insurance coverage in most regions, which blocks access for most individuals with obesity. At least one oral formulation (Rybelsus, Novo Nordisk) has been approved, but most are administered by injection. The U.S. Centers for Disease Control and Prevention estimates that needle fear affects up to 25% of adults (Wolicki; Miller 2023), which further limits access. For those who can access GLP-1 analogues, significant side effects such as nausea and diarrhoea lead ~50% of patients to abandon the drugs within a year. Rebounding with rapid weight gain can follow treatment cessation for all incretin analogues.

More importantly, incretin-analogue developers have encountered profound scaling challenges, to the extent that they have found it necessary to delay launches in second-tier geographies (e.g., Europe) (Fick; Skydsgaard 2023; Müller et al. 2012) and ration supplies (Burger; Matthews 2023). The need for injection-grade sterility and cold-chain distribution drives up costs and limits access for less affluent patients, particularly those living outside the U.S. and Europe. The production bottleneck guarantees high prices for the foreseeable future, but it also means that most cannot get access at any price.

With LMN-0801, Lumen Bioscience aims to fill these gaps. LMN-0801 is an orally consumed monoclonal protein therapeutic—a leptin analogue—produced and delivered within the biomass of the common food algae, spirulina (Jester et al. 2022). Developed initially with funding support from the Bill & Melinda Gates Foundation for global health applications, Lumen's unique GMP biomanufacturing platform enables recombinant protein therapeutics for oral delivery at massive scale and very low cost per dose—inexpensive enough even for low-income, developing-world applications (Finrow 2021). In short, the unique approach promises to solve the scaling and cost challenges that hold back broader adoption of biologic drugs for obesity and weight loss.

2.2 Background on Leptin

Leptin was one of the first identified satiety-inducing hormones. It is constitutively synthesised by adipose tissues and acutely by gastric epithelial cells in response to food intake. Leptin has been studied in dozens of clinical trials dating to 1997 (Farooqi and O'Rahilly 2014). A parenterally delivered leptin analogue (Myalept; Chiesi Farmaceutici S.p.A.) was approved by the U.S. FDA in 2014 for lipodystrophy

(U.S. Food and Drug Administration 2014). LMN-0801 is intended for oral administration, but it is reassuring that even *parenterally delivered* leptin analogues have generally been found to be safe and well tolerated in human clinical trials.

Although systemic leptin is well known to control food intake in lean animals and humans, obese individuals (including diet-induced obese (**DIO**) rodent models) are resistant to systemic leptin. In human trials, injection site reactions with the parenteral formulation were dose-limiting (Heymsfield et al. 1999). These headwinds, and the high cost of manufacturing protein therapeutics for parenteral delivery, resulted in the eventual abandonment of leptin for all but a handful extremely rare diseases (lipodystrophy and congenital leptin deficiency).

Remarkably, Lumen discovered that orally delivered leptin significantly suppresses hunger in the DIO mouse model. Thus, oral delivery of biologic drugs can exploit hunger-modulating circuits in the gastrointestinal (**GI**) tract that are functionally inaccessible to the same biologics delivered parenterally. Importantly, leptin receptors are present on the luminal side of intestinal epithelial cells and on vagal afferent neurons that innervate the GI tract and project to the central nervous system. Lumen has shown that oral spirulina-leptin reduces food intake and induces significant weight loss in DIO rodents. Notably, bioencapsulation within spirulina is required for the bioactivity of oral leptin (and likely the other candidates) to prevent degradation during gastric transit.

The leptin analogue within LMN-0801 is thought to operate by modulating endocrine system receptor targets directly within GI tissues. Preclinical studies by Lumen and unaffiliated labs have also found therapeutic synergies in animal models of obesity with concomitant dosing of leptin with other anti-obesity therapeutic peptides, including GLP-1 analogues (Müller et al. 2012) (Figure 1) and amylin (Roth et al. 2008). The latter finding with amylin replicated in a Phase 2 clinical trial, which demonstrated that dosing parenteral leptin with amylin deepened weight loss compared with amylin monotherapy (Roth et al. 2008). Parenteral leptin monotherapy has also been shown to sustain weight loss in mice after withdrawal of GLP-1 analogue treatment (Müller et al. 2012).

2.3 Potential Therapeutic Uses for LMN-0801

Preclinical data developed by Lumen and its collaborators indicates that a spirulina-expressed, orally delivered leptin analogue—LMN-0801—may be effective as a monotherapy weight loss agent.

In addition to superior affordability and convenience, there may also be significant tolerability advantages over systemically dosed incretin analogues. At approximately 16 kilodaltons (kDa), the protein is far larger than the two kDa size typically cited as the upper limit for intact absorption, and systemic absorption has not been observed *in vivo*. Preferential activation of leptin receptors in GI tissues likely explains the differential therapeutic outcomes in animal models compared with parenteral delivery. It also enhances the expected safety profile of the product, as leptin therapy (even when injected) does not appear to carry the same GI side effects—nausea, emesis, and diarrhoea—that

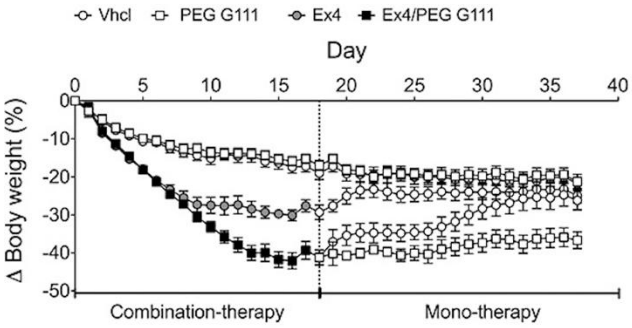

Figure 1: *Therapeutic synergies of parenteral pegylated leptin (PEG G111) with the GLP-1 analogue exendin-4. Leptin dosed concomitantly with a GLP-1 analogue deepens weight loss compared with GLP-1 monotherapy, and parenteral leptin can maintain weight loss as a monotherapy (Müller et al., 2012).*

accompany GLP-1 analogue therapy. Lower cost, easier administration (oral), and presumed superior tolerability may make it an important addition to the physician's tools for treating obesity.

These unique features may also facilitate other therapeutic modalities (Figure 1). If the therapeutic synergies demonstrated in *in vivo* studies replicate in humans, LMN-0801 may have utility dosed in combination with GLP-1 analogues, permitting dose titration of GLP-1 analogues below levels associated with deleterious side effects. LMN-0801 may also have utility as a maintenance therapy, helping individuals with obesity maintain the weight loss induced with GLP-1 analogues after they can no longer tolerate the injections and side effects, at lower cost and greater convenience.

The study proposed here aims to generate data to inform future development of LMN-0801 across these varied potential use cases.

2.4 Summary Risk/Benefit Assessment

LMN-0801 brings together three streams of research, each with decades of clinical safety data: spirulina consumed as a food, oral protein therapeutics, and parenterally delivered leptin and leptin analogues. Taken together, these lengthy safety records indicate that there is minimal risk associated with orally ingesting LMN-0801.

Spirulina, the common food algae within whose biomass the leptin analogue is grown and orally delivered, has a well-established and documented tolerability and safety profile from its multi-hundred-year history of use as a food source for humans and animals, and it has been involved in numerous clinical trials with no reports of adverse events (**AEs**). Possible non-serious AEs have been reported with spirulina intended as a nutritional supplement. The FDA MedWatch from January 2001 to July 2009 reported that the most common putative side effects from spirulina consumption are nausea, diarrhoea, 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 food-grade spirulina grown in uncontrolled, outdoor ponds exposed to wildlife and environmental contaminants (Marles et al. 2011). Given its well-established and documented tolerability and safety profile, the FDA's Office of Food Additive Safety has issued "no further questions" responses to numerous Generally Recognised as Safe (GRAS) notification submissions for spirulina-based food products. It has been sold at a mass-market scale in the U.S. since the 1970s.

Orally delivered protein therapeutics also have a long track record of safe clinical trials. Like the leptin analogue expressed within LMN-0801, orally delivered protein therapeutics have been shown to be too large for systemic absorption through the gut lining. As a result, the risk of off-target toxicity in humans is low, an observation that is borne out in clinical trial data. The U.S. FDA has reviewed many human clinical trials using orally delivered protein therapeutics of various classes, including polyclonal (van Dissel et al. 2005; Mattila et al. 2008; Numan et al. 2007) and recombinant antibodies (Jester et al. 2022) and enzymes like lysozyme, a broad-spectrum bacteriolytic enzyme approved for oral administration in several countries (Hashida et al., 2002). Such studies nearly universally report robust safety and tolerability and no treatment-related adverse effects.

Lumen itself has completed clinical trials with seven spirulina-expressed, monoclonal protein therapeutics delivered orally (NCT04098263, NCT04182490, NCT04893239) and intranasally (NCT06030414). A large, multicentre trial was recently initiated in the U.S. to assess four orally delivered, spirulina-expressed protein therapeutics (three antibodies and one endolysin enzyme) for

prevention of *Clostridioides difficile* infection (NCT05330182). To date, systemic absorption of spirulina-expressed therapeutic proteins has not been detected. Likewise, no treatment-related AEs—or serious AEs of any kind—have been reported in any of these trials.

Leptin analogues have been studied almost exclusively through parenteral delivery, often in individuals suffering from obesity, congenital leptin deficiency, and acute lipodystrophy (Araújo-Vilar and Santini 2019; Oral et al. 2002; Rodriguez et al. 2015). Although generally reported to be safe and well tolerated in clinical trials, *injected* leptin analogues have been found to elicit antibody responses (Chan et al. 2016). This raised a concern that anti-leptin antibodies potentially could impair metabolic control and immune function, though clinical evidence for this conjecture is not clear. The U.S. FDA approved metreleptin injection in 2014, subject to a risk evaluation and mitigation strategy (REMS) program requirement. In larger studies of obese individuals treated with metreleptin, these antibodies were rarely found to be neutralising (FDA 2014). Given the tolerogenic nature of the GI tract to exogenous proteins, oral administration is expected to mitigate these risks further. Systemic absorption has not been observed in *in vivo* studies. There is one published announcement of clinical trial result with orally administered leptin (Yaari, Estee 2020), which reported positive results in safety, tolerability, and preliminary efficacy.

In sum, given the lengthy safety record of each research stream—spirulina biomass, orally delivered protein therapeutics, and leptin analogues—culminating in the creation of LMN-0801, it is expected to have a robust safety profile, justifying its exploratory use in the proposed clinical trials.

3 Objectives and Endpoints

3.1 Primary Objective and Endpoint

3.1.1 Primary Objective

Characterise LMN-0801's safety and tolerability by dosing level, frequency of dosing, and formulation.

3.1.2 Primary Endpoint

Frequency of moderate to severe adverse events through Week 24 by dosing level, frequency of dosing, and formulation

The primary objective focuses on evaluating LMN-0801's safety and tolerability across different dosing levels (low, medium, high), dosing frequencies (one time a day (**QD**), two times a day (**BID**), three times a day (**TID**), and formulations, which are crucial for determining the drug's risk-benefit profile and planning subsequent clinical development. The corresponding endpoint measures moderate to severe AEs throughout the 24-week treatment period, providing comprehensive data on tolerability, potential side effects, or unintended consequences. This information is essential for establishing the overall safety profile of the drug and identifying any dose-dependent risks.

3.2 Secondary Objective and Endpoints

3.2.1 Secondary Objectives

Evaluate the efficacy of LMN-0801 on weight loss during treatment

Characterise safety and tolerability by dosing level, frequency of dosing, and formulation after cessation of treatment

3.2.2 Secondary Endpoints

Change in body weight (kg and %) from baseline to Week 24

Proportion of subjects achieving >5% body weight reduction from baseline to week 24

Change in percentage body fat from baseline to Week 24

Occurrence of AEs during Week 24 to Week 29

The secondary objective aims to assess LMN-0801's efficacy in promoting weight loss. The endpoints measure changes in body weight and body fat percentage from baseline to Week 24, offering quantitative data on the drug's efficacy. These metrics will help determine if LMN-0801 produces clinically significant weight loss and improvements in body composition in adults with obesity, which is crucial for establishing its potential as a therapeutic option.

AEs will also be monitored after cessation of treatment.

3.3 Exploratory Objectives and Endpoints (Body Weight and Composition Changes)

3.3.1 Exploratory Objectives (Body Weight and Composition Changes)

Evaluate body weight changes during treatment and after treatment cessation.

Evaluate measures of changes in body composition during treatment.

3.3.2 Exploratory Endpoints (Body Weight and Composition Changes)

Change in body weight (kg and %) from baseline to Day 28

Change in body weight (kg and %) from baseline to Week 12

Proportion of subjects achieving >5% body weight reduction from baseline to Day 28, Week 12, and Week 29

Change in fat mass (kg and %) from baseline to Day 28, Week 12, Week 24

Change in lean mass (kg and %) from baseline to Day 28, Week 12, Week 24

Change in blood pressure and pulse from baseline to Day 28, Week 12, Week 24

Change in weight, body mass index (BMI), waist circumference, percentage body fat, and lean-fat ratio from baseline to Week 24 and from Week 24 to Week 29

Change (kg and %) in body weight, fat mass, lean mass from Week 24 to Week 29

These exploratory objectives delve deeper into understanding how LMN-0801 affects body weight and composition over time. The endpoints track changes in weight, fat mass, lean mass, BMI, waist circumference, and lean-fat ratio at various time points, providing insights into LMN-0801's impact on body weight and composition. This detailed analysis will help elucidate the drug's mechanism of action and its effects on overall body composition.

This objective aims to evaluate weight changes during treatment and after cessation, which is important for understanding the drug's longer-term effects and potential rebound effects. The endpoints measure weight changes at Day 28, Week 12, Week 24, and Week 29, allowing for the assessment of the drug's efficacy over time and potentially identifying any plateau effects or weight regain after treatment stops. Changes in weight would be expected to be accompanied by changes in blood pressure and pulse.

3.4 Exploratory Objectives and Endpoints (Blood Chemistry and Biomarkers)

3.4.1 Exploratory Objective (Blood Chemistry and Biomarkers)

Assess blood chemistry changes during treatment

3.4.2 Exploratory Endpoints (Blood Chemistry and Biomarkers)

Change in HbA1c, TSH, and lipid profile from baseline to Week 24

Change in cardiometabolic biomarkers from baseline to Week 24

Presence of leptin analogue in serum or the emergence of anti-drug antibodies

This objective focuses on assessing changes in blood chemistry, which can provide insights into LMN-0801's effects on metabolic health. The endpoints measure changes in HbA1c, TSH, lipid profiles, and cardiometabolic biomarkers, which can indicate improvements in diabetes risk, thyroid function, and cardiovascular health. Additionally, measuring leptin analogue levels and anti-drug antibodies will provide information on the drug's pharmacokinetics and potential immunogenicity.

3.5 Exploratory Objectives and Endpoints (At-Home Measurements)

3.5.1 Exploratory Objective (At-Home Measurements)

Assess performance of at-home weight and body composition devices

3.5.2 Exploratory Endpoints (At-Home Measurements)

Correlation between measures of weight measured at-home and in clinic

Correlation between measures of body composition measured at-home and in clinic

This objective aims to validate the performance of at-home weight and body composition measurement devices. The endpoints compare measurements taken at home with those taken in the clinic, which could support future remote monitoring strategies and enhance the convenience of long-term weight management programs. This validation is crucial for expanding the use of telemedicine in obesity treatment.

3.6 Exploratory Objectives and Endpoints (Preclinical Model Validation)

3.6.1 Exploratory Objective (Preclinical Model Validation)

Assess the predictive validity of in vivo ***rodent models of obesity for oral biologics***

3.6.2 Exploratory Endpoint (Preclinical Model Validation)

Correlation between weight loss in DIO rodents and obese humans using various putative dose-scaling factors

This objective seeks to assess the predictive validity of rodent models for oral biologics in obesity treatment. The endpoint correlates weight loss in DIO rodents with that observed in obese humans, using various dose-scaling factors. This analysis will help refine preclinical models for future drug development, potentially improving the translation of animal studies to human clinical trials in obesity research.

4 Study Design

4.1 General Study Design

The study aims to assess LMN-0801 across dose levels (low, medium, high), frequency of dosing (QD, BID, TID), and oral capsule formulations (see the Investigator's Brochure for formulation details). The design of experiments methodology is the most efficient way to generate statistically reliable data with the fewest study participants. This approach aligns with the U.S. FDA's model-informed drug development initiative (**MIDD**). The primary goals of the FDA's MIDD program are to leverage newer statistical methods to "accelerate the development of new medical products and enable more informed decision-making" (Madabushi et al. 2022).

Participants will be randomised to one of ten different cohorts with 12-18 participants in each cohort (as indicated in Table 1), treated for 24 weeks, and then followed an additional four weeks. Stratification factors are BMI (<35 and ≥35 kg/m^2) and biological sex (male or female).

Table 1: *Study Cohorts*

Cohort	N	LMN-0801		Capsule Formulation, #	
		Dose†	Frequency*	A§	B§
1	128	Placebo	**BID	B0	0
2	12	Low	QD	A0	3
3	12	Low	TIQD	B3	0
4	12	MediumLow	BID	C0	6
5	12	Medium	TBID	A3	3
6	12	Medium	BID	B6	0
7	12	HighMedium	QTID	C0	9
8	12	High	BTID	A3	6
9	12	High	QTID	B6	3
10	12	High	TID	C9	0

** Frequency: QD is once a day (morning meal); BID is twice a day (morning and evening meals); TID is three times a day (morning, lunch, dinner meals)*
*~~** For placebo, four volunteers will receive QD, four will receive BID, four will receive TID~~*
† Low is 1200 mg; Medium is 2400 mg; High is 3600 mg total daily dose of LMN-0801
§ See Investigator's Brochure for formulation details

In this way, frequency of dosing and type of formulation are ~~also~~ varied such that the combination of daily dosing level, frequency of dosing, and formulation is constructed orthogonally, which enables reliable estimation of the main effects of each formulation and construction of modelling of the predicted two-way interaction effects between dosing level, capsule type, and frequency of dosing. The specific statistical design of experiments approach is a simplex lattice mixture design in three factors (Cornell 2002). Mixture experiments are widely used today in formulation experiments, blending experiments, and marketing choice experiments (Hare, Altan, and Coppenolle 2025)~~definitive screening design , a fractional factorial design that is balanced and orthogonal in factors. Notably, all combinations~~ . In this context, at each daily dosing amount, practical mixtures of ~~LMN-0801 dose levels~~uncoated and coated capsules are tested ~~in a full factorial fashion .~~to determine the optimal weight-loss blend at a given dose intensity.

4.2 Study Duration and Enrolment

In addition to the screening and enrolment visits, each participant will come in for scheduled study visits to monitor safety, undergo study evaluations and measurements, assess study drug adherence, and replenish study drug supplies. Each participant will be in the study for a duration of 29 weeks from enrolment.

Estimated study duration of the main protocol (i.e., start of screening through data analysis) is anticipated to be approximately 24 months.

4.3 End of Study Definition

The study is complete when all study participants have completed their final follow-up visits (or withdrawn), and all data has been accepted by Lumen.

5 Study Population

5.1 Inclusion Criteria

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

1. Adult aged 18-65 years at screening
2. BMI $\geq$ 30.0 kg/m^2 and < 40.00 kg/m^2 at screening
3. In good general health
4. HbA1c < 6.5%
5. Female volunteers must be of non-child-bearing potential or, if of child-bearing potential, must have a negative urine pregnancy test at screening and a negative urine pregnancy test before the first study drug administration. They must agree not to attempt to become pregnant and must agree to use a highly effective method of contraception by signing consent throughout the study and for at least 30 days after the last dose of the study drug
6. Male volunteers must agree not to donate sperm and if engaging in sexual intercourse with a female partner who could become pregnant, must agree to use a condom in addition to having the female partner use a highly effective contraceptive method from signing consent, during the study, and at least 90 days after the last dose of study drug
7. Able and willing to provide written informed consent to participate in the clinical trial before any study-related activities occur

5.2 Exclusion Criteria

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

1. Significant illness or abnormalities per investigator's discretion
2. Alcohol abuse/dependency (defined as more than 10 standard drinks per week or more than 4 standard drinks on any one day, where 1 standard drink is 10 g of pure alcohol) within 3 months prior to screening
3. Recent drug abuse defined as a history of nonprescription use of opioids, benzodiazepines, amphetamines, cocaine, or tranquilisers within 3 months prior to screening
4. Tobacco or nicotine consumption is not permitted from screening and until the end of follow-up
5. Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study

6. Use of weight loss drugs and/or antidiabetic agents in the preceding six months
7. Currently treated with any of the following excluded medications: drugs that directly affect gastrointestinal motility; systemic corticosteroids (excluding topical and inhaled preparations) by oral, intravenous, or intramuscular route used regularly (longer than two weeks) or used within two weeks immediately before screening for this study
8. Use of weight loss drugs and/or antidiabetic agents in the preceding six months
9. Have previously completed or withdrawn from this study
10. Currently or within the last three months, participating in another clinical trial
11. Dietary spirulina allergy
12. Unwilling or unable to comply with all study assessments and adhere to the protocol schedule and restrictions

6 Study Schedule

The schedule of events in Section 1.3 details the study activities that will occur at the screening, enrolment, treatment, and follow-up study visits. In preparation for each study visit, participants will be asked to fast overnight.

6.1 Recruitment and Screening

Healthy, adult individuals with obesity will be recruited by the principal investigator (**PI**) and study team using advertising approved by the Human Research Ethics Committee (**HREC**) as required under Australian law. Volunteers who express interest in participating in the study will be asked to complete a pre-screen questionnaire (Appendix 1) to assess general health status and basic eligibility, including informed consent to the screening procedures. Potential participants meeting basic eligibility requirements will be scheduled for an in-person screening not more than 28 days prior to planned enrolment.

At the in-person screening visit, potential participants' height and weight will be measured, and they will be carefully screened. This will include collecting demographic information, obtaining a health history with current medications, and conducting a physical exam with height, weight, BMI, and vital signs measurements, urine pregnancy testing (for females of childbearing potential), and a blood draw for laboratory analyses (safety labs). Data for screen failure reason, eligibility criteria, and demography will be captured on the appropriate screening and enrolment log. At the discretion of the PI, assessments may be repeated if abnormal values were recorded in the first instance. Values outside the ranges specified in the criteria below may be considered acceptable if determined by the PI (in conjunction with the independent medical monitor) as not clinically significant.

Details of the protocol and necessary time commitment will be discussed. If willing and able to participate in all study activities and visits and to provide written informed consent, eligible volunteers will be invited to enrol.

Individuals not meeting eligibility criteria will be informed of their ineligibility and will not be invited to return to the clinical for enrolment and other study Day ~~0activities~~0 activities.

6.2 Randomisation and Enrolment

On study Day 0, participants will come to the clinic for enrolment.

The following procedures will take place on Day 0:

- Adverse events
- Concomitant medications
- Physical examination
- Vital Signs (systolic and diastolic blood pressure, pulse rate, oral temperature, respiration rate)
- Weight and BMI
- Waist circumference
- Body composition measurements (including lean mass, fat mass and bone density) by DEXA scan
- Urine pregnancy testing (for females of childbearing potential)
- Blood collected for clinical safety labs
- Serum collected for study drug detection and anti-drug antibodies
- Serum collected for HbA1c and TSH
- Serum collected for cardiometabolic biomarkers (including ghrelin, GLP-1 and glucagon)

Additionally, diet, nutrition, and lifestyle counselling, including advice on exercise, will be provided to each participant.

Following this baseline assessment and counselling, each eligible participant will be randomised in a double-blind fashion to one of ten cohort groups (see Table 1 above) and receive an initial oral dose of LMN-0801 or placebo. As noted above, randomised enrolment will be biased to first fill groups 1 (placebo), 8, 9, and 10. Eligible participants will be considered enrolled only once they receive directly observed, orally administered study drug at the enrolment visit. If they do not receive study drug for any reason, they will not be considered enrolled.

After receiving the first dose of study drugs, each participant will be monitored for two hours to assess for tolerability. At the end of two hours, vital signs and any AEs will be recorded. If necessary, participants will be monitored for an additional two to four hours for resolution of AEs.

On departure, each participant will receive:

- a supply of study drugs to administer at home until the Week 4 study visit; and
- study drug self-administration instructions and adherence counselling; and
- an electronic WiFi-enabled scale with an induction-based body composition measurement feature for weekly weight and at-home body composition measurements; and
- weekly and daily questionnaires for the participants to complete at home

6.3 Treatment Phase

During the 24-week treatment phase, participants will take their assigned study drugs orally as directed. A daily questionnaire will be administered with questions on study drug adherence.

A weekly questionnaire will be administered with questions about occurrence of AEs, and concomitant medications. Participants will be asked to record their weight, lean mass and fat mass weekly using the provided WiFi-enabled scale.

Participants also will come to the clinic during Week 1 (Day 7), Week 4 (Day 28), Week 8 (Day 56), Week 12 (Day 84), Week 18 (Day 126), Week 24 (Day 168), and Week 29 (Day 203) for study visits. In preparation for each study visit, participants will be asked to fast overnight (at least 8 hours) the night before and to bring their remaining study drug for counting. To balance endpoint precision against scheduling practicalities, these visits will be set within the scheduling windows noted in the schedule of activities (Table 1).

At the indicated study visits, participants will have their weight, BMI, waist circumference, body composition by DEXA scan, and vital signs measured. They will also have labs drawn. In addition to collecting and performing a pill count of their previous study drug supply, a new supply of study drugs will be provided to the participants to self-administer at home until their next study visit. Site staff will review the questionnaires at each study visit.

6.4 Follow-Up Phase; Study Completion

The treatment phase ends at Week 24, at which time participants will be asked to bring their remaining study drugs to the clinic and fast overnight the night before. At this study visit, in addition to collecting and performing a pill count of their study drug supply, participants will have their weight, BMI, waist circumference, hip circumference, body composition by DEXA scan, and vital signs measured. They will also have labs drawn.

During the four-week follow-up phase, participants will not take study drugs but will continue to take at-home weekly weights and body composition measurements and to complete the same weekly questionnaire.

A final study visit will occur at Week 29, again following a fast the night before. At this final study visit, participants will have their weight, BMI, waist circumference, hip circumference, body composition by DEXA scan, and vital signs measured, and labs drawn.

6.5 Concomitant Medications

Concomitant medication use will be documented at each study visit.

6.6 Early Termination

Participants may discontinue from the study prematurely for several reasons:

6.6.1 Participant Decision to Discontinue Study Drug

If a participant decides to stop taking the study drug, they will be offered the opportunity to continue all other study activities through the end of the five-week follow-up period. The date of last dose should be recorded, and the reason for discontinuation should be documented in the participant's medical record and case report form (**CRF**).

6.6.2 Withdrawal of Informed Consent

Participants may choose to withdraw their informed consent at any time during the study. In this case, no further study procedures or follow-up will be conducted. The date of withdrawal and reason should be documented in the participant's medical record and CRF.

6.6.3 Principal Investigator Decision

The Principal Investigator may decide to discontinue a participant from the study drug if it is deemed to be in the best interest of the participant. In such cases, participants will be offered the opportunity to continue all other study activities through the end of the five-week follow-up period. The date of last dose, reason for discontinuation, and justification should be documented in the participant's medical record and CRF.

For all types of early termination, the following procedures should be followed:

- Schedule an early termination visit as soon as possible after the decision to discontinue;
- Conduct all assessments scheduled for the final study visit, if possible;
- Record any adverse events and concomitant medications;
- Retrieve all unused study drug; and
- Encourage participants to complete follow-up safety assessments when applicable.

Data collected up to the point of withdrawal will be retained and included in the study analyses, unless the participant specifically requests otherwise.

The study team will make reasonable efforts to contact participants who are lost to follow-up to determine their status and reason for discontinuation.

All early terminations will be reported to the human research ethics committee (HREC) in accordance with local requirements at the contact information provided in Section 9.4.

Participants who withdraw from the study prior to their first study drug administration will be replaced per recruitment, screening, and enrolment processes outlined in Section 6.1.

7 Study Evaluations and Measurements

7.1 Weight and Body Composition Measurements

At enrolment, participants will be supplied with a WiFi-enabled scale for at-home use during the study, which will include induction-based measurement of body composition.

Weight, BMI, and waist circumference, , will also be taken at each clinic study visit for comparison and validation purposes. In addition, Dual-Energy X-ray Absorptiometry (**DEXA**) scans will be conducted at Study Day 0, Week 12, Week 24, and Week 29. DEXA scans use low-dose X-rays to measure bone density, lean mass, and fat mass and are commonly found in many clinics.

7.2 Laboratory

7.2.1 Safety labs

For the purposes of this study, safety labs will include serum chemistry and haematology. Participants will be asked to fast for at least 8 hours prior to collection of safety labs. Serum chemistry consists of assays for sodium, potassium, calcium, magnesium, phosphate, creatinine, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, amylase, and lipid profile. Haematology will include assays for haemoglobin, complete blood cell count (with differential), and platelet count. Safety labs will be assessed, and clinically significant results will be reported as adverse events.

7.2.2 HbA1c

The HbA1c assay measures the percentage of haemoglobin molecules in the blood that have glucose attached to them. This test provides an average measure of blood glucose levels over the preceding two to three months, the typical lifespan of red blood cells. In Australia, the common reporting unit is a percentage, with a normal range typically considered to be below 5.7%, prediabetes between 5.7-6.4%, and diabetes at 6.5% or higher.

In this study, HbA1c may provide insight into the participant's glucose metabolism and can indicate whether the weight loss drug affects blood sugar control. For participants who start with prediabetic HbA1c levels, the study can assess whether the drug improves their glycaemic status. The drug's effect on HbA1c might differ between participants with normal baseline values and those with elevated levels, allowing for subgroup analyses. Unexpected increases in HbA1c could signal adverse effects on glucose metabolism, which is crucial for safety assessment.

By including HbA1c measurements, this study can provide a more comprehensive understanding of the drug's effects on overall metabolic health, beyond just weight loss. This data may be valuable for assessing the drug's potential benefits, safety profile, and possible indications for use.

7.2.3 Thyroid-stimulating hormone

The thyroid-stimulating hormone (**TSH**) assay is a blood test that measures the level of thyroid stimulating hormone in the blood. TSH is produced by the pituitary gland and regulates the production of thyroid hormones by the thyroid gland. Modern TSH assays are highly sensitive and can detect very low concentrations of TSH, allowing for accurate diagnosis of both hyper- and hypo-thyroidism. The normal range for TSH can vary slightly between laboratories, but it is it's typically between 0.4 and 4.0 mIU/L (milli-international units per litre) for adults.

In this study, changes in TSH levels could indicate that the weight loss drug is affecting thyroid function, which is crucial for safety assessment. Significant alterations in TSH might suggest a need for further thyroid function tests. Monitoring TSH can help determine if the drug's weight loss effects are related to changes in thyroid function. TSH levels have been shown to correlate positively with leptin in many studies on both adults and children. TSH levels can provide insights into the drug's overall effect on metabolism, complementing other metabolic markers like HbA1c.

By including TSH measurements, the study may provide a more comprehensive understanding of the drug's effects on endocrine function and metabolism. This data will be valuable for assessing the drug's safety profile, potential mechanisms of action, and possible indirect effects on thyroid function, which are closely linked to body weight and metabolism.

7.2.4 Lipid Profile

A lipid profile typically includes measurements of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides in the blood. These components provide valuable information about an individual's cardiovascular health and risk for atherosclerosis. The lipid profile is included in the safety labs.

7.2.5 Pharmacokinetic and Biomarker Analyses

Serum will be collected for potential detection of the presence of the leptin analogue in serum and determination of the presence of antibodies against the leptin analogue. If anti-drug antibodies are confirmed, additional testing on the samples may be performed (e.g., titre and neutralising antibodies)

to gain further understanding. In addition, sera will be collected to determine levels of satiety and cardiometabolic biomarkers (examples include ghrelin, GLP-1, and glucagon). Expression evaluation will improve understanding of the relationship between oral formulation and dosing regimen on circulating obesity-related biomarkers.

8 Study Products

8.1 Study Products Generally

The study drugs, LMN-0801 and placebo, will be supplied by Lumen. LMN-0801 is comprised of a biomass of the common food algae spirulina that has been engineered to intracellularly express a protein that is an analogue of the human gut hormone leptin.

Prior Leptin analogues have been tested in over 65 clinical trials, nearly all of which evaluated parenteral delivery. Lumen's recombinant leptin protein is expressed and delivered within the spirulina biomass for oral delivery. Preclinical data suggest that gut-specific application of this orally administered spirulina-leptin analogue may enhance its weight-loss potential and improve safety. For this study, doses of LMN-0801 will be delivered as a spray-dried powder in capsules without additional excipients.

Placebo will be identical-appearing cornstarch (NF) with colouring in identical-looking capsules.

No capsules will contain any materials of human or animal origin.

8.2 Dosing Regimen

Participants will orally self-administer LMN-0801 or placebo capsules daily as directed (see Section 4.1).

8.3 Timing of Doses

The initial study drug administration date and start and stop times must be recorded in the participant's chart and in the case report form (**CRF**).

The preferred timing of LMN-801 or placebo capsule dosing is as follows:

- Daily (QD) dosing: all capsules consumed first thing in the **morning** (before breakfast, if taken)
- Twice-daily (BID) dosing: means ~~**midday**~~**morning** (before ~~lunch,~~ breakfast, if taken) and **evening** (before dinner, if taken)
- Thrice-daily (TID) dosing: first thing in the **morning** (before breakfast, if taken), **midday** (before lunch, if taken) and **evening** (before dinner, if taken)

Each participant will be provided a daily questionnaire by the study clinic to record study drug administration, date, time, and relationship to meals.

8.4 Rationale for Selected Dose

The standard scaling method for comparable dosing of biologic drugs between experimental animals and humans is on a mg/kg basis. The diet-induced obese mice used in Lumen's preclinical studies averaged 55 grams in weight, and in our clinical studies, we will be scaling to an obese human weight of approximately 90 kg. Therefore, the scaling factor is 1,636 fold.

The highest dose of LMN-0801 administered to obese mice was 0.2mg of leptin daily. At this highest dose, there were no observed adverse effects. There are practical and ethical limitations on

administering even larger doses of oral biologic to animals, particularly daily gavage administration in rodents (which is associated with oesophageal rupture and animal stress) so for planning purposes, we may consider this dosing level the no observed adverse effect level (**NOAEL**).

The human equivalent dose (**HED**) on this conventional scaling metric is 327 mg per dose. The highest leptin dose we will use in this trial is 30mg/dose, more than 10-fold lower. Furthermore, in preclinical studies, none of the doses tested in mouse models resulted in detectable levels of leptin in serum. Consequently, the HED represents an even lower level of systemic leptin exposure than previously tested in parenterally delivered leptin analogue studies in humans. This is also lower than the recommended dosage of the marketed leptin analogue (metreleptin). It is a notable advantage of oral biologic drugs that exposure is limited to the targeted tissues in the GI tract and, in the event dose-related adverse events are observed, the natural processes of the GI tract (peristalsis and proteolysis) will automatically and rapidly remove the biologic drug on treatment cessation.

8.5 Blinding and Dispensing of Study Product

The site pharmacy will dispense LMN-0801 or placebo capsules according to the pharmacy manual. All capsules will be dispensed according to the participant's treatment number and group. Dispensing packets, with appropriate labels, will be provided to each individual participant. The process for preparing LMN-0801 and placebo, as well as blinding and packaging, is detailed in the pharmacy manual.

8.6 Storage and Handling

The study product will be kept in a locked area of the study pharmacy. Pending completion of longer-term stability studies, LMN-0801 should be refrigerated, 35-46°F (2-8°C) and protected from moisture, light, and extreme heat during storage and transport. Study product should not be frozen.

Only enrolled study participants may receive the assigned study product in accordance with all applicable regulatory requirements. In the event the participant loses their assigned study product, replacement doses will be provided. Upon completion of the study, participants will be asked to bring the remaining study product in their possession to the study clinic for collection.

The principal investigator is responsible for maintaining accurate records of the processing and use of all clinical trial materials. Upon completion of the study, study product will be subjected to final inspection and reconciliation.

Unused, partially used, and fully used (empty) containers will be destroyed or returned to Lumen in accordance with instructions provided in the pharmacy manual. Documentation of destruction will be retained by the site pharmacy with the study files.

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

9 Safety Management

9.1 Tolerability; Potential Toxicities

The first dose of study drug will be administrated to each enrolled participant while being directly observed. After receiving the study drug, each participant will be monitored for two hours to assess for tolerability. At the end of two hours, vital signs and any reactions or adverse events (**AEs**) will be

recorded. If necessary, participants will be monitored for an additional two to four hours for resolution of the AE.

The anticipated risks and potential toxicities of LMN-0801 are estimated to be similar to, but less acute than, those reported in parenteral delivery studies with leptin analogues. No toxicities have been published with respect to oral leptin, but it is possible that there may be risks and toxicities generally associated with parenterally administered protein therapeutics. For example, metreleptin—the injection leptin analogue currently on the market—is associated with the development of transient neutralising anti-leptin antibodies in a minority of patients (U.S. Food and Drug Administration 2014). However, since the leptin analogue within LMN-0801 is a protein macromolecule administered orally, systemic absorption is not anticipated, and so the risk of formation of anti-leptin antibodies is thought to be attenuated. The most common (<10%) side effects noted in metreleptin clinical trials were headache, hypoglycaemia and abdominal pain (U.S. Food and Drug Administration 2014). Please see the Investigator's Brochure for additional information.

9.2 Adverse Events

The PI is responsible for documenting AEs according to the guidelines below.

For the purposes of this study, an AE is defined as: "*any untoward medical occurrence or change in a clinical trial participant having received a biologic or medicinal product, whether or not considered treatment related.*"

AEs may occur in any phase of the clinical study. Events meeting the AE definition include:

- a 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; or
- worsening of abnormal clinical laboratory values.

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

A serious adverse event (SAE) is any AE that at any dose:

- Results in death.
- Is life-threatening.
  Note: the term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death, if it were more severe).
- Requires inpatient hospitalisation or prolongation of an existing hospitalisation.
  Note: only hospitalisations that are longer than expected based on Investigator judgement, will be considered prolonged hospitalisations.
- Results in persistent or significant disability/incapacity.
  Note: results in a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
  Note: a congenital anomaly/birth defect that occurs in the offspring of a participant exposed to the IP

Abnormal laboratory findings (e.g., serum chemistry, haematology, coagulation, and urinalysis) or other abnormal assessments (e.g., vital signs, and physical examination findings) that are judged by the PI as clinically significant (CS) will be recorded as AEs or SAEs if they meet the definitions stated above. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected after the first administration of the study drug or are present at baseline and significantly worsen following administration of the study drug will be reported as AEs or SAEs. The PI will exercise his/her medical and scientific judgement in deciding whether an abnormal laboratory finding, or other abnormal assessment, is CS.

9.3 Documenting and Reporting Adverse Events

All observed or volunteered AEs—regardless of suspected causal relationship to the study drug—must be recorded on the AE page of the CRF.

Detection and recording of study related AEs and SAEs extend from the signing of the consent form until completion of the last study related procedure (including follow-up for safety assessments). Any AE reported or observed at or after the start of dosing with study drug will be recorded as a treatment-emergent AE (TEAE) or SAE.

The PI must assess all AEs for seriousness, severity, and relation to the study drugs. The PI will follow all AEs, regardless of seriousness or severity, until the AE or its sequelae resolve or stabilise at a level acceptable to the PI. Clinical management of an AE is at the discretion of the PI.

9.3.1 Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgment. The severity of each AE and SAE will be graded using the most current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) 5-point scale:

Grade		Definition
I	Mild	Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated.
II	Moderate	Minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
III	Severe	Severe or medically significant but not immediately life threatening: hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL.
IV	Life-threatening	Life-threatening consequences: urgent intervention indicated.
V	Death	Death related to AE.

9.3.2 Assessment of Causality

The Investigator will make an assessment as to the relationship between study drug and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine whether or not the AE/SAE is causally related to the study drug. Alternative causes, such as natural history of any underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator will also consult the Investigator's Brochure in the determination of his/her assessment.

The causal relationship of the study drug to an AE/SAE will be rated according to the following 2-point scale:

Causal Relationship	Definition
Not related	Temporal association with study drug administration is lacking or other causative factors (e.g., participant's clinical state or environmental factors or other therapies administered) more likely explain the event
Related	There is a reasonable temporal association with administration of study drug or the event is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern of response consistent with previous knowledge of the study drug).

The causality assessment is one of the criteria used when determining regulatory reporting requirements, therefore, the Investigator must make an assessment of causality based on all available information for every event and prior to transmission of an SAE Form to the Sponsor. The Investigator may change his/her opinion regarding causality in light of followup information and amend the SAE Form and the eCRF accordingly.

9.4 Expedited Reporting of Serious Adverse Events

For the purposes of this study, a serious adverse event (**SAE**) is defined as any untoward medical occurrence that, at any dose:

- Results in death;
- Is life-threatening (i.e., the subject was at immediate risk of death from the event as it occurred; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event that may not result in death, be life-threatening, or require hospitalisation but may be considered serious when, based upon appropriate medical judgment, it may jeopardise the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In the event of an SAE, within 24 hours of becoming aware of an SAE occurrence, the following information must be sent by the PI via email (preferred) or telephone to the Medical Monitor:

- Protocol IND number, study drug, PI name, and contact number
- Participant identification number
- Narrative description of SAE, onset date, most recent date of study drug administration, severity, relationship, and participant's status

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

- Cover sheet
- AE CRF
- Supplemental SAE CRF
- 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.

The PI must also report SAEs to the appropriate HREC that approved the protocol according ~~ot~~to their requirements. All SAEs will be reported to the HREC within 72 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

9.5 Safety Review

9.5.1 Safety Review Committee

A data safety monitoring board (DSMB) will not be established for this study, however safety and tolerability data collected from participants will be reviewed by a safety review committee (SRC) consisting of the principal investigator (**PI**), the independent medical monitor, and the sponsor medical monitor. The SRC will convene when the first 12 participants (10% of recruitment target) complete Day 7. Subsequent SRC meetings will be convened following outcomes and decisions from the first SRC meeting. Safety labs, including lipid profile assessments, AEs/SAEs and concomitant medications collected at the Day 7 visit will be included in the SRC review.

9.5.2 Dose Stopping Rules

AEs that will prompt stopping the investigational product administration for all subjects and review include:

- Any individual experiencing any SAE considered related to the investigational products;
- If two or more subjects experience the same or similar unanticipated adverse event that is Grade 3 in severity or higher;
- If the accumulation of SAEs and/or severe AEs collectively raises a safety concern in the opinion of the PI, independent medical monitor, or sponsor medical monitor;
- If any individual experiences liver function tests or creatinine increased to 3 times the upper limit of normal;
- If any individual experiences significant spontaneous bleeding or platelet count < 100 X 10^9/L;
- If any individual experiences coagulation disorders characterised by prolonged PT; or PTT or abnormal INR greater than 1.5 times the upper limit of normal; or
- If any individual experiences neutrophil values < 1.0 x 109/L.

The decision to restart the study will be made by consensus of the independent medical monitor, the sponsor's medical monitor, and the PI. The decision to stop the study will be communicated to the HREC and, similarly, the decision to re-start a study will also be communicated to the HREC.

Administration of the investigational product will be discontinued for any subject that develops:

- A serious adverse event considered related to the investigational product; or
- An adverse event that is Grade 3 or higher and considered related to the investigational product; or
- The PI deems that stopping the investigational product administration is in the best interest of the subject.

10 Statistical Considerations

10.1 Introduction

The study aims to evaluate LMN-0801 across dose levels, frequency of dosing, and formulations. The design of experiments methodology is the most efficient way to generate statistically reliable data with the fewest study participants. This approach aligns with the U.S. FDA's model-informed drug development initiative (MIDD). The primary goals of the FDA's MIDD program are to leverage newer statistical methods to "accelerate the development of new medical products and enable more informed decision-making" (Madabushi et al. 2022).

See Section 4.1 for more information about the statistical study design.

10.2 Analysis of Safety

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

- The incidence and number of all reported AEs and treatment-related AEs will be tabulated by cohort. AEs will be classified by organ system classification.
- AEs and SAEs will be summarised 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 participant, 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 cohort.
- SAEs will be presented as listings by cohort. 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 cohort.

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

The overall number of participants receiving LMN-0801 is N=108. If no participants (0 of 108) experience moderate to severe treatment-related adverse events, then the 95% confidence interval probability of a moderate to severe treatment-related adverse event is [0.00%, 3.43%]. That is, we can be 95% confident that the true rate of moderate to severe treatment-related adverse events is no more than 3.43% if no participants (0 of 108) experience moderate to severe treatment-related adverse events.

If treatment-related adverse events are reported, prevalence and severity will be reported in tabular form. Additionally, treatment-related adverse events will be analysed for dose, schedule and formulation dependence.

10.3 Sample Size Considerations (Preliminary Efficacy Assessment)

The group size was selected based on simple pairwise comparison of percent weight loss between Cohort 1 (placebo) and active treatment Cohorts ~~5-7 (medium leptin) or between Cohort 1 and Cohorts 8~~2-10 ~~(high leptin).~~ With a significance level of $p<0.05$ ($\alpha=0.05$) and a power of 90% (ß=0.1), a t-test would conclude statistical difference in percent weight loss between active cohorts with n=12 per cohort if Cohen's $d \geq 1.38516$.

In this context, Cohen's *d* is the difference in mean percent weight loss divided by the pooled standard deviation of percent weight loss across both groups (Ghusn et al. 2022; Wilding et al. 2021) report variation in weight loss at different time points to be proportional to mean weight loss in a cohort of patients, and so the variation in percent weight loss is generally 60% (cv=sd/mean=0.6) (Ghusn et al. 2022; Wilding et al. 2021) If the mean percent weight loss in Cohort 1 is 1%, 2% or 3%, then Cohen's *d* ≥ 1.38516 when the mean percent weight loss in an active treatment Cohort ~~4 or 7~~ is ≥ 2.68%, 5.36% or 8.05%, respectively. Wilding (STEP-1) report mean placebo and semaglutide percent weight loss at 28 weeks as 2.84% and 11.7%, respectively; Ghusn reports report mean percent weight loss from semaglutide injection at ~~12 weeks~~6 months as ~~5.92% and 6~~10.9~~%, respectively. Wilding reports mean percent weight loss from placebo at 12 weeks as 2.17~~%. Thus, the study is adequately powered to detect clear differences in LMN-0801 from placebo treatment if the effect size of LMN-0801 is equivalent to half that of semaglutide injection at ~~12~~24 weeks.

~~F~~Additionally, the primary analysis will be performed using repeated-measures, mixed-effects, modelling using the totality of the data set to assess the effects of LMN-0801. These methods provide more power than landmark t-test, so the powering calculations above are conservative.

10.4 Statistical Analysis Plan

A preliminary statistical analysis plan will be drafted prior to enrolling the first participant and finalised prior to unblinding.

11 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 authorised 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 will be considered source data. Study-specific procedures detail how each form will be completed. The study coordinator will ensure accuracy of the eCRFs. All source documents will be retained at the site.

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

12 Quality Control and Quality Assurance

12.1 Monitoring

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

- Provide information and support to the PI.
- Confirm that facilities remain acceptable.
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the CRFs, and study drug accountability checks are being performed.

- Perform source data verification, including a comparison of the data in the CRFs with the participant medical records at the hospital or practice, and other records relevant to the study (requires direct access to all original records for each participant (e.g., clinic charts)).
- Record and report any protocol deviations not previously sent to Lumen.
- Confirm that AEs and SAEs have been properly documented on CRFs, that SAEs have been forwarded to Lumen or its representative, and that SAEs meeting criteria for reporting have been forwarded to the HREC.

The monitor will be available between visits if the PI or other staff need information or advice. The PI assumes ultimate responsibility for the conduct of the study and must remain readily accessible throughout the study.

12.2 Clinical Research Monitoring

Lumen monitoring responsibilities will be performed by an independent clinical research associate (**CRA**). Monitoring will be conducted according to a monitoring plan and applicable standard operating procedures. The CRA or other Lumen representatives may inspect all documents and records maintained by the PI, and the clinical study site will permit access to such records. The PI will obtain, as part of informed consent, permission for authorised representatives of Lumen, or regulatory authorities, to review, in confidence, any records identifying individuals in this clinical study.

The PI will notify Lumen 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 authorised representatives of regulatory agencies. The PI will provide Lumen with copies of all correspondence that may affect the review of the current study and the PI's qualifications to act as a PI in the study.

Lumen will provide any needed assistance in responding to regulatory audits or correspondence. The PI will permit independent auditors (employees of Lumen or an external company designated by Lumen) 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, ICH Good Clinical Practice guidelines, and applicable regulatory requirements.

Lumen will arrange local monitoring prior to beginning, at initiation, during the study, and at closeout by the study monitor or designee.

12.3 Medical Monitor

The designated independent medical monitor shall be available for consultation with the PI and will serve as a liaison between the clinical study site and Lumen. The PI will consult with the medical monitor on issues related to participant enrolment and continued participation as needed.

The medical monitor will be required to review all unanticipated problems involving risk to participants, SAEs, and all participant 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 HREC.

12.4 Protocol Deviation Management

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

Deviations from the protocol that potentially impact participant safety will be promptly reported to the medical monitor, HREC, and Lumen. Other deviations will be reported at the time of continuing review.

13 Regulatory, Ethical, and Study Oversight Considerations

13.1 Human Research Ethics Committee Review

The PI must verify that the HREC has approved the clinical protocol, informed consent form (**ICF**), and recruitment materials for the study prior to conducting study evaluations. Initial HREC approval, and all materials approved by the HREC for this study must be maintained by the PI and made available for inspection.

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

The PI is also responsible for providing the HREC with reports of any reportable SAEs from any other study conducted with the study drug. Lumen will provide this information to the PI.

13.2 Written Informed Consent

The ICF will be prepared by Lumen. The ICF will clearly describe the nature, scope, and potential risks and benefits of the study in a language that the participant understands. The ICF will conform to all the requirements for informed consent according to ICH guidelines on Good Clinical Practice (**GCP**) and U.S. FDA guidelines. The ICF will adhere to the ethical principles of the Declaration of Helsinki.

Prior to study initiation, Lumen will obtain the HREC's approval of the ICF. The HREC-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 to participate. The PI or research staff designee will ensure that the potential participant is given full and adequate oral and written information about the nature, purpose, possible risks, and potential benefits of the study. The participant must also be notified that they are free to discontinue the study at any time.

Each volunteer who agrees to participate in the trial and who signs the ICF will be given a copy of the signed and dated document. Execution of ICF may be completed electronically (e.g., Docusign). The original signed ICF will be retained by the PI in the study files.

The ICF and other information provided to participants will be revised whenever important new and relevant information becomes available. All such revised materials must be re-approved by the HREC prior to use. The PI or site staff will fully inform any affected participants of the changes if relevant to the participant's willingness to continue participation in the study. Participants must read and sign any revised ICFs and the originals must be retained by the PI as above.

13.3 Participant Compensation

Compensation for participation will be provided only for completed study procedures designated for compensatory payment. Participants will be compensated for time and travel associated with study participation.

13.4 Privacy and Confidentiality

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

13.5 Regulatory Documentation

Before trial start, the "essential documents" (as defined in ICH E6) will be generated and placed in both the files of Lumen and the study centre. Additional essential documents will be added to both files as new information becomes available and at the completion or termination of the trial.

13.6 Protection of Human Subjects

Declaration of Helsinki. The PI will conduct this study in accordance with the Declaration of Helsinki.

Good Clinical Practice and Regulatory Compliance. The PI will conduct this study in accordance with the principles of GCP, current ICH guidelines, and the requirements of local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

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Appendix 1: Pre-screening Questionnaire

You are being asked to consider participating in a study of a new oral weight loss drug. Study participants will be overweight adults who are otherwise healthy. Briefly, after enrolment, study participants will receive the new oral weight loss drug or placebo for 24 weeks and be followed for 4 additional weeks for a total of 29 weeks. The weight and body composition of study participants will be followed. This questionnaire will help you and your doctor decide if you are eligible for this study. Before deciding to participate in this study, you will be provided a detailed explanation of the study requirements as well as the risks and benefits. You can also ask any questions you might have.

1. What is your age?
2. What is your current height and weight? (This will be used to calculate BMI)
3. Are you currently pregnant, breastfeeding, or planning to become pregnant in the next six months?
4. Do you have any significant health conditions, such as heart disease, diabetes, liver or kidney problems, or cancer?
5. Are you currently taking any medications for weight loss or diabetes?
6. Have you used any weight loss drugs or antidiabetic agents in the past six months?
7. Do you currently use tobacco products, have alcohol dependency, or use illicit drugs?
8. Are you currently participating in any other clinical trials, or have you participated in one within the last three months?
9. Are you willing and able to attend scheduled study visits and follow study procedures for the next 29 weeks?
10. For females of child-bearing potential: Are you willing to use a highly effective method of contraception throughout the study and for at least 30 days after the last dose of the study drug?