A Phase 1a, randomized, double-blind placebo-controlled study to evaluate safety and tolerability and to characterize the pharmacokinetic profile of single ascending doses of fenretinide oral capsules in healthy adult volunteers

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Protocol Amendment #1 dated 18October2023

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1a, randomized, double-blind placebo-controlled study to evaluate safety and tolerability and to characterize the pharmacokinetic profile of single ascending doses of fenretinide oral capsules in healthy adult volunteers
Study Number:	ISLA101-P01-CT001
Study Phase:	Phase 1a
Product Name:	ISLA101 (fenretinide oral capsules)
IND Number:	142758
Indication:	Prophylaxis of dengue fever
Sponsor:	Island Pharmaceuticals Ltd Suite 201, 697 Burke Road, Camberwell Victoria 3124, Australia
Sponsor Contact:	David Foster, PhD, JD dfoster@islandpharmaceuticals.com

	Date
Original Protocol	31 March 2023
Amendment 1	18 October 2023

SYNOPSIS

Sponsor	Island Pharmaceuticals, Ltd
Study Title	A Phase 1a, randomized, double-blind placebo-controlled study to evaluate safety and tolerability and to characterize the pharmacokinetic profile of single ascending doses of fenretinide oral capsules in healthy adult volunteers.
Protocol Number	ISLA101-P01-CT001
IND Number	142758
Indication	Prophylaxis of dengue fever
Sites	One study center located in Australia. A contract research organization will oversee operational aspects of this study on behalf of Island Pharmaceuticals, the sponsor of the study.
Phase of Development	Phase 1a
Study Type	Interventional
Objectives	The primary objective is to: • Evaluate the safety and tolerability of single ascending doses (SAD) of ISLA101 in healthy adult volunteers (fasted). The secondary objective is to: • Characterize the pharmacokinetic (PK) profile (fasted) of fenretinide after administration of SAD of ISLA101 in healthy adult volunteers (fasted). The exploratory objective is to: • Assess the PK profile of fenretinide in healthy adult volunteers under fed conditions.
Endpoints	The primary endpoints are: • Vital signs, clinical laboratory tests, changes from baseline in physical examinations, adverse events (AEs), and treatment emergent adverse events (TEAEs). The secondary endpoints are: • Single dose PK parameters for fenretinide in plasma: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, and others as relevant. The exploratory endpoints are: • Single dose PK parameters for fenretinide in plasma under fed conditions: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, and others as relevant.
Study Design and Treatment	This study is a randomized, double-blind, placebo-controlled SAD study. There are 3 planned dose-level cohorts (Cohorts 1-3). Each dose-level cohort will consist of 8 subjects (6 active + 2 placebo), who will be treated under fasted conditions. The subjects in the highest tolerated dose-level cohort will also be administered ISLA101 under fed conditions, in a cross-over manner (Cohort 4). Proposed doses are 300, 600, and 900 mg/m^2 (equivalent to 8.1, 16.2, and 24.3 mg/kg). Each subject will be allocated to 1 dose level only. The study will include a 5-day stay in the clinical research unit followed by a final safety follow-up visit at Day 8. An independent Safety Review Committee (SRC) will review available safety data up to 96-hours post-dose for subjects enrolled in each dose-level cohort. After safety review, the dose level may be escalated to the next planned or lower than

	planned dose level, de-escalated to an intermediate dose level, or repeated at the same dose, if needed. The first 3 dose-level cohorts will be treated under fasting conditions. A single dose of study drug will be administered on the morning of Day 1, after an overnight fast of approximately 10 hours, followed by an additional 4-hour fast after dosing. Study drug will be taken with up to 8 oz/240 ml of water. Water will be allowed ad libitum except the interval from 1 hour before to 1 hour after dosing. Following review of the safety data of the highest tolerated dose level, the subjects enrolled in this dose-level cohort will be recalled to evaluate the PK of ISLA101 dosed under fed conditions (Cohort 4; 8 subjects). These data will support a planned Phase 2 study. Subjects will be informed and will be provided a consent form prior to the participation in the food effect cohort (Cohort 4) of the study. Subjects in Cohort 4 will be dosed after a meal. They will fast overnight for at least 10 hours and will then consume a high-fat, high-calorie meal prior to administration of study drug, as outlined in the FDA's Guidance for Industry- Assessing the Effects of Food and Drugs in INDs and NDAs – Clinical Pharmacology Considerations. The study drug should be administered approximately 30 minutes after start of the high-fat meal. No food consumption will be permitted for at least 4 hours post-dose. Water will be allowed ad libitum except the interval from 1 hour before to 1 hour after dose.
Study Population	Approximately 24 healthy male and female volunteers who are 18–65 years of age (inclusive).
Inclusion Criteria	Subjects must meet the following criteria to be enrolled in the study: 1. Healthy male or female volunteers not of childbearing potential, who are 18 years to 65 years of age (inclusive) at the time of signing the informed consent form (ICF). 2. Females not of childbearing potential, as defined in the following criteria: a. History of hysterectomy. b. Post-menopausal. i. Natural post-menopausal females with at least 12 months from natural spontaneous amenorrhea and a serum follicle-stimulating hormone (FSH) concentration ≥ 40 IU/L. ii. Post-surgical females must have undergone bilateral oophorectomy at least 6 weeks prior to study. 3. Male subjects with female partners of childbearing potential must agree to practice abstinence or use a combination of 2 of the following acceptable birth control methods during the study and for at least 90 days after dosing: a. Partners have an intrauterine device (IUD) without hormones in place for at least 3 months. b. Barrier method (condom or diaphragm) for at least 14 days prior to screening and 90 days after dosing with study drug. c. Partners using stable hormonal contraceptive for at least 3 months prior to screening and for 90 days after dosing with study drug. d. History of vasectomy at least 3 months prior to signing the ICF. 4. Must be able to understand and provide signed informed consent for study participation. 5. Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

	6. Body mass index (BMI) 18.0 to 32.0 kg/m^2 (inclusive), and a body weight ≥ 50 kg. 7. Normal renal function, defined as estimated glomerular filtration rate (eGFR) ≥ 70 mL/min/1.73 m^2 at screening and Day -1. 8. Clinical laboratory values should be within the laboratory's stated normal range. If not within this range, they must be without clinical significance, as determined by the Investigator. 9. No history of clinically relevant medical disorders, as determined by the Investigator.
Exclusion Criteria	A subject will be excluded from the study if he or she meets any of the following criteria: 1. Known or suspected pregnancy (confirmed via a positive serum human chorionic gonadotropin [hCG] pregnancy test at screening), planned pregnancy during the study period, nursing, or lactation. 2. Women of childbearing potential or men who intend to father a child or donate sperm during the study period and for 3 months after study drug administration. 3. Known allergy to fenretinide or any of the components of ISLA101. 4. Evidence or history of clinically significant medical conditions, such as hematological, renal, endocrine (e.g., polycystic ovarian syndrome or other anovulatory states), immunologic, pulmonary, metabolic, gastrointestinal (e.g., Crohn's disease, acute or chronic pancreatitis, and others) and surgery (except for simple appendectomy or repair of a hernia), which all can influence the absorption of study drug; cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing), or any other illness that the Investigator considers exclusionary or that could interfere with the interpretation of the study results. 5. History of severe infectious disease or recurrent infections. 6. Aspartate transaminase (AST), alanine aminotransferase (ALT), or total bilirubin above the 1.5 x upper limit of normal (ULN) at screening and Day -1. 7. Clinically significant electrocardiogram (ECG) abnormalities or vital sign abnormalities at screening and Day -1, long QT syndrome, or a history of cardiac disease. 8. Abnormal diet that may affect absorption, distribution, metabolism, or excretion of drugs, for example, lacking standard nutrients (e.g, cleansing diet 2 weeks before or during the study). 9. Positive result for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening. 10. History of positive test for tuberculosis (TB) at screening. 11. A subject who has donated 1 unit of blood of over 500 mL within 56 days prior to the study drug administration, or donated plasma within 14 days prior to study drug administration. 12. Use of systemic antibiotics within 30 days prior to dosing. 13. Any use of drugs that inhibit or induce CYP enzymes within 30 days prior to administration of study drug and for the duration of study participation. 14. Use of any tobacco products, e-cigarettes, and/or nicotine replacement products in the 3 months preceding screening. 15. Any food allergy, intolerance, or restriction that, in the opinion of the Investigator, could contraindicate the subject’s participation in this study.

	16. Recent history of (within the past 12 months), or strong potential for, alcohol or substance abuse. Alcohol abuse will be defined as > 14 drinks per week (1 drink = 10g of ethanol). 17. History of drug or alcohol abuse within 5 years before screening or positive result of UDS (e.g, amphetamines, benzodiazepines, cannabinoids, cocaine, hallucinogens, opiates) or alcohol breath test at screening. 18. Exposure to any investigational agent or used an invasive investigational medical device within 30 days or within a period less than 5 drug half-lives prior to study entry (whichever is longer). 19. Study site employees, Sponsor's employees, or immediate family members of a study site or Sponsor employee. 20. Previously enrolled in this study. 21. Vaccination within 14 days from screening or plans to get a vaccine within 30 days after dosing. 22. Acute infection (such as influenza) or relevant lesion at the time of Screening or Day -1. Subjects can be rescreened once they have recovered. 23. Criteria at the discretion of the Investigator: a. Chronic medical condition that impacts subject safety. b. Clinically significant abnormal physical examination or vital signs at screening. c. Condition believed to interfere with the subject's ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk. d. History or evidence of a clinically significant disorder, condition, or disease that that is believed to significantly impair pain perception (e.g., history of stroke, history of neuropathy), would pose a risk to subject safety or interfere with evaluation, procedures, or study completion.
Duration of Treatment	The study participation will last for a total duration of approximately 6 weeks, including screening, confinement, and a follow-up period. The screening period may last up to 28 days. The confinement period will be approximately 5 days. The follow-up period is up to 3 days. The follow-up period after highest tolerated dose cohort will serve as the washout period for the food effect cohort. For the food effect cohort, an additional confinement period of approximately 5 days will be required, followed by a follow-up period of up to 3 days.
Study Drug, Dose, and Mode of Administration	Dosing will begin with a dose level of 300 mg/m^2 of fenretinide administered via oral capsules. The decision to advance to the next cohorts (600 mg/m^2 and 900 mg/m^2) will be based on safety and tolerability data reviewed by the SRC.
Number of Subjects	Approximately 24 subjects will be enrolled in total. Subjects who withdraw or are removed from the study, except for safety reasons, may be replaced at the discretion of the Sponsor.

Safety and Tolerability Evaluation	This study will assess the safety and tolerability of the chosen doses of ISLA101 (fenretinide oral capsules) as assessed by AEs, TEAEs, vital signs, physical examinations, and clinical laboratory tests. As clinical studies from IND38892 and from the published literature showed ocular toxicity upon treatment with fenretinide (eye irritation, dryness of eyes, nyctalopia), an ophthalmologist will be available to evaluate all significant ocular complaints. Discontinuation from the study will be at the discretion of the ophthalmologist. Due to teratogenic risks, all initial reports of pregnancy in female subjects or partners of male subjects must be reported to the Sponsor by the site personnel within 72 hours of their knowledge of the event. The safety and tolerability data will be reviewed by an independent SRC before proceeding to the next dose cohort.
Dose-limiting Adverse Events	The incidence and nature of any AEs, dose-limiting AE, SAEs, vital sign changes, ECG changes, and laboratory abnormalities will be assessed on an ongoing basis by the Investigator. Dose-limiting AEs are defined as clinically significant AEs or abnormal laboratory values that are Grade 3 or 4, based on toxicity grading scales as specified in FDA's Guidance for Industry and Investigators – Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. The following signs of drug toxicity will be deemed to be of special interest: • sustained respiratory depression that results in oxygen saturation below 92% • seizure • protracted nausea and vomiting • any AE deemed by the Investigator to be dose-limiting or Grade 3 and above • signs of drug-induced liver injury based on the following criteria from FDA guidance (Drug-Induced Liver Injury: Premarketing Clinical Evaluation): ALT or AST > 8 x ULN • ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN or international normalized ratio > 1.5) • ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) Escalation from one dose level to the next will occur following the safety review by the SRC. If blinded study drug demonstrates an acceptable safety profile in the previous cohort, enrollment of the next higher dose cohort may begin. In the case of dose-limiting AE, dose reduction or repeat of the cohort with the previously tested dose may occur.
Dose Escalation Criteria	The decision to enroll the sequential cohort at the next dose level will be based on the safety data from previous dose cohorts. Dose escalation will depend on the emergence of dose-limiting AEs and review of the safety data. Progression to the next higher dose will only occur if the previous dose level was deemed to be safe and well tolerated by the SRC. Safety data sets to be reviewed by the SRC for dose escalation determination will include all available data up to 96 hours post-dosing for subjects enrolled into each dose-level cohort. A minimum of 7 subjects' data will be evaluated to make dose escalation decisions.

	Doses will be flexible during the study to allow for reductions in the planned escalation based on safety. When it is not appropriate to escalate the dose, then a previous dose, or an intermediate dose may be given following discussion between the Investigator and Sponsor.
Stopping Criteria for the Study	Further enrollment and study drug administration will be stopped if any of the following events occur: • A single SAE regardless of organ system if it is possibly, probably, or definitely related to the study drug; • Grade 3 or higher AEs and laboratory abnormalities determined to be possibly, probably, or definitely related to study drug should result in prompt discontinuation of study treatment; • Death of any subject considered related to study drug unless the SRC determines it is unrelated to study drug; • An anaphylactic reaction to study drug in any subject; • A potentially life-threatening AE or SAE, unless the SRC determines it is unrelated to study drug; • A pattern of significant symptoms, physical findings, or laboratory abnormalities that, although individually minor, collectively may represent a safety concern in the opinion of the Investigator or the medical monitor and are judged by the SRC to be at least possibly related to study drug; or • Sponsor's decision to terminate the study for any reason. The human research ethics committee (HREC),), the FDA and local regulatory agencies as required will be notified if the study hold criteria are met.
Pharmacokinetic Evaluation	Blood samples will be collected at the pre-determined time points pre- and post-dosing to characterize the PK profile of plasma fenretinide and its metabolites N-(4-methoxyphenyl) retinamide (MPR) and 4-oxo-N-(4-hydroxyphenyl) retinamide (oxo-HPR) and to capture appropriate PK parameters. PK samples will be analyzed and evaluated after completion of all cohorts. The PK sampling time points will be: pre-dose and 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12,24, 36, 48 ,72 and 96 hours post-dose.
Statistical Methods	A statistical analysis plan (SAP) describing all statistical analyses will be provided as a separate document prior to data base lock. <u>Sample Size Considerations:</u> The study is considered to be exploratory with a sample size of 8 subjects per cohort (2 placebo + 6 active); this is considered sufficient to evaluate the safety profile and provide sufficient PK information for future development of the compound. <u>General Statistical Methodology:</u> Demographic data will be summarized using descriptive statistics. Descriptive statistics will be used to provide an overview of the safety results. For categorical parameters, the number and percentage of subjects will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation, median, minimum, and maximum. No imputations will be made for missing data.

	Analysis Populations Two analysis populations will be used to summarize the results from this study: • Safety Population: All subjects who receive at least 1 dose of study drug. • PK Population: All subjects in the safety population who have a pre-dose PK sample, and at least 1 post-dose analyzable PK sample. Subjects disposition will be summarized and will include all subjects who have received one dose of study drug in the safety population, subjects in the PK population, and number and percent of subjects who complete or prematurely discontinue the study, along with reason for discontinuation. Baseline demographic data will be summarized for all subjects who were randomized in this study and took at least 1 dose of study drug. Safety Analysis Safety will be assessed by the evaluation of AEs, TEAEs, laboratory test results, vital sign measurements, physical examination findings, and tolerability assessment. Safety variables will be tabulated and presented for all subjects in the Safety Population by dose. The AEs will be summarized and presented by dose and visit and overall. Change from screening in clinical laboratory parameters and vital sign parameters will be summarized by visit and overall. Shifts from baseline in continuous laboratory assessments will be tabulated. PK Analyses Pharmacokinetic and statistical analysis will be done using validated software (eg, Phoenix® WinNonlin® version 8.0 or higher). Pharmacokinetic parameters will be derived following noncompartmental analysis based on concentration-time data for fenretinide and its metabolites N-(4-methoxyphenyl)retinamide (MPR) and 4-oxo-N-(4-hydroxyphenyl)retinamide (oxo-HPR). On the day of dosing, the following parameters will be derived: C_{max}, AUC_{last}, AUC_{inf}, T_{max}, $T_{½}$, Cl/F, and V/F. Other parameters will be estimated as applicable. Dose proportionality for key exposure parameters for fenretinide (C_{max}, AUC_{last}, and AUC_{inf}) will be calculated based on the dose-normalized parameters. Descriptive statistics (n, mean, SD, geometric mean, %CV, median, minimum, and maximum) will be used to summarize the calculated PK parameters by dose level. For T_{max} and $T_{1/2}$, only n, median, minimum, and maximum will be presented. Analyses of variance (ANOVA) will be performed on ln-transformed PK parameters AUC_{last}, AUC_{inf}, and C_{max} to evaluate fenretinide food effect for the recalled cohort. The ANOVA will include a calculation of least-squares means (LSMs), the differences between adjusted means, and the standard error associated with these differences. Ratios of means will be calculated using the LSM for ln-transformed AUC_{last}, AUC_{inf}, and C_{max}. The 90% confidence interval (CI) for the difference between fed and fasted conditions will be calculated for the parameters AUC_{last}, AUC_{inf}, and C_{max} using ln-transformed concentration data. The CIs will be expressed as a percentage relative to the LSM.

SCHEDULE OF ASSESSMENTS

Table 1 Study Procedures and Assessments to Dose Under Fasted (Cohorts 1-3) and Fed Condition (Cohort 4)

Study Procedure		Cohorts 1-3								Cohort 4						
	Study Period	**Screening**	**Clinic Check-in**	**Treatment Period**					**Follow-up/ET**	**Clinic Check-in**	**Treatment Period**					**Follow-up/ET**
	Study Day	-28 to -2	-1	1	2	3	4	5	8	9[9]	10	11	12	13	14	17
	Visit Window (days)	N/A	Inpatient						+/-1	+/-3	Inpatient					+/-1
Informed Consent		X								X						
Inclusion/Exclusion Criteria		X	X							X						
Demographics		X														
Height and weight		X								X						
Medical History		X	X							X						
Vital Signs[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)[2]		X	X	X						X	X					
Full Physical Exam		X	X						X	X						X
Hep B, Hep C, HIV		X														
Safety laboratory tests (chemistry, hematology, coagulation, urinalysis)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[3]		X	X						X	X						X
FSH[4]		X														
Urine screen for drugs of abuse[5]		X								X						
Alcohol breath test		X	X							X						
Admission			X							X						

Study drug administration				X							X[6]					
High-fat, high-calorie breakfast											X					
PK blood samples[7]				X	X	X	X	X			X	X	X	X	X	
Adverse events[8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge								X							X	

ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; Hep = hepatitis; HIV =human immunodeficiency virus; PK = pharmacokinetic(s);

1 Vital signs include blood pressure, pulse, respiration and temperature.

2 12-lead ECG will be performed in triplicate at screening, and on Day -1 (check-in) to confirm eligibility, and on Day 1 at 5 hours (±15-minute) post dose. A single ECG will be performed on Day 9 (check-in) and on Day 10 at 5 hours (±15-minute) post dose.

3 A serum pregnancy test will be performed at screening and urine pregnancy test will be performed at check-in and at follow-up for all female subjects.

4 For all female subjects to confirm or refute postmenopausal status.

5 A nicotine urine or breath test may be utilized for tobacco use testing at site discretion.

6 Study drug will be administered approximately 30 minutes after start of a high-fat, high-calorie meal; 100% meal consumption is preferred.

7 PK sampling to assess the PK of fenretinide will be performed at the time points as specified in Table 2.

8 Monitoring for serious adverse events begins when the informed consent form is signed; and treatment-emergent adverse events begins after the first dose is administered.

9 Study day is relative to study drug administration for the subjects in Cohort 3.

Table 2 Study Schedule and Sampling Time Points for Pharmacokinetic Analysis

		Time Relative to Dose (hours)[a]	-1	0.5	0.75	1	1.5	2	3	4	5	6	8	10	12	24	36	48	72	96
		Assessment Window (minutes)[b]	+/-2				+/-5			+/-15					+/-30					
Study Day	**Cohorts 1-3**	1	X	X	X	X	X	X	X	X	X	X	X	X	X					
		2														X	X			
		3																X		
		4																	X	
		5																		X
	Cohort 4	10	X	X	X	X	X	X	X	X	X	X	X	X	X					
		11														X	X			
		12																X		
		13																	X	
		14																		X

a: Time from dose begins when first capsule is consumed

b: Vital signs should be assessed prior to PK samples taken

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC	Area under curve for pharmacokinetic concentration vs time profile
AUC_{inf}	Area under curve from time 0 extrapolated to infinity
AUC_{last}	Area under curve from time 0 to the last measured concentration
BID	Twice daily
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum observed concentration
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CRU	Clinical research unit
CSR	Clinical study report
DENV	Dengue virus
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
HED	Human equivalent dose
HREC	Human research ethics committee
ICF	Informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug application
INR	International Normalized Ratio
IUD	Intrauterine device
J&J	Johnson & Johnson Pharmaceutical Research & Development, LLC
LSM	Least-squares means
MPR	N-(4-methoxyphenyl) retinamide
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	No-observed-adverse-effect level
OTC	Over-the-counter
PD	Pharmacodynamics
PK	Pharmacokinetics
QTC	QT interval corrected for heart rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal elimination half-life
TB	Tuberculosis
T_{max}	Time to achieve maximum concentration

TEAE	Treatment-emergent adverse event
UDS	Urine drug screen
ULN	Upper limit of normal
US	United States

1 INTRODUCTION

1.1 Background

An estimated 3.9 billion people in more than 125 countries are at risk of dengue fever, with approximately 390 million infections occurring annually. These infections lead about 500,000 persons to require hospitalization due to dengue each year, and about 20,000 deaths occur due to severe dengue every year (WHO, 2018). Dengue is a mosquito-borne infection caused by the dengue virus (DENV) and is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas. The severe form of the disease is a leading cause of serious illness and death in some Asian and Latin American countries (WHO, 2021). Endemic areas include some United States (US) territories and freely associated states. In 2021, 63 dengue cases were reported in the US and 435 cases were reported in US territories (CDC, 2021; CDC, 2022). Importantly, there is no specific treatment for dengue infection.

Dengue prevention and control is based on vector control measures, which require sustained community involvement and usually are not highly effective in preventing disease transmission. The first dengue vaccine, Dengvaxia® (CYD-TDV), developed by Sanofi Pasteur, was licensed in 2015 and has now been approved in about 20 countries, including the US (Food and Drug Administration [FDA]-approved in 2019) (FDA, 2020; WHO, 2021). The vaccine was considered a major breakthrough in the prevention of DENV infection; however, results of a retrospective analysis showed that trial subjects who were seronegative at time of first vaccination had a higher risk of more severe dengue and hospitalizations from dengue compared with unvaccinated subjects. In addition, the vaccine is not licensed for people younger than 9 years and older than 16 years of age. Thus, the use of Dengvaxia is restricted to children (9 to 16 years) living in endemic areas who have previously had at least 1 documented DENV infection (WHO, 2018; WHO, 2021; CDC, 2022).

Recently, a new dengue vaccine, QDENGA®, was approved for use regardless of prior exposure and without the need for pre-vaccination testing. Approval was based on results across 19 Phase 1, 2, and 3 trials with more than 28,000 children and adults, including 4.5 years of follow-up data showing sustained efficacy and no important safety risks. This vaccine is approved for use in Brazil, Indonesia, and in Europe, and was granted priority review for its Biologics License Application by the FDA (Takeda, 2023).

In view of the current situation, there is an unmet medical need for therapies focusing on the prophylaxis of dengue infection, aiming to minimize viral transmission in endemic areas. To answer to this need, Island Pharmaceuticals Ltd (also referred to as the Sponsor) is developing the ISLA101 product, an immediate-release oral capsule of fenretinide (100 mg), for the prophylaxis of dengue fever.

1.2 Fenretinide

Fenretinide (4-[hydroxyphenyl]retinamide; also known as 4-HPR) is an analog of all-trans-retinoic acid, first synthesized in the 1960s as an alternative to naturally occurring retinoids to treat skin diseases. Since then, nonclinical and clinical studies have demonstrated that this drug has lower toxicity when compared to other retinoids and exhibits cytotoxic

activity in a variety of cancer types (Cooper et al., 2017). According to the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (also known as the "Orange Book"), there are currently no marketed or discontinued drug products in the US that include fenretinide as the active ingredient.

Fenretinide has been used to treat cancer patients for decades with a favorable safety profile. To strategically support the development of ISLA101 for the prophylaxis of dengue fever, the Sponsor obtained the right of reference to Investigational New Drug application (IND) 38892, which focused on fenretinide for the treatment of cancer, psoriasis, and acne. IND 38892 was initially sponsored by Johnson & Johnson Pharmaceutical Research & Development, LLC (J&J), and later by the National Cancer Institute (NCI) and was withdrawn in 2003 due to non-satisfactory efficacy data. The Sponsor developed a formulation very similar to the previous formulation, to facilitate bridging and reliance on safety information from IND 38892.

While tumor responses have been minimal, the established safety profile makes fenretinide a desirable candidate for drug repurposing. In a high-throughput screen to identify compounds that inhibit the binding of the DENV NS5 to host nuclear import proteins, IMP-α and IMP-β1, fenretinide was identified. Using a lethal mouse model of DENV, it was demonstrated that fenretinide is effective in protecting against DENV1-4 infections, possibly by targeting NS5 (Fraser et al., 2014). In a second study that targeted the identification of anti-DENV compounds, the screening of a library of bioactive lipids and modulators of lipid metabolism also identified fenretinide as an inhibitor of DENV replication in vitro and within an in vivo mouse model, through an unknown mechanism (Carocci et al., 2015). These studies unveiled the potential of fenretinide as an anti-dengue therapy.

1.2.1 Clinical Experience

To date, there are no studies in humans that evaluate the efficacy of fenretinide to prevent DENV infection. However, the safety profile of fenretinide has been thoroughly described in 5 clinical pharmacology studies conducted under IND 38892, to which Island has right of reference, and in clinical studies from the published literature.

Clinical studies conducted under IND 38892 and the published literature characterize fenretinide as well-tolerated and did not identify major safety concerns. A total of 3487 healthy subjects (3273 from the literature and 214 from IND 38892, including approximately 150 pediatric subjects) have been exposed to fenretinide. Of the subjects exposed, 3188 healthy subjects (2974 from the literature and 214 from IND 38892) were treated with the oral capsule formulation provided by the NCI or J&J, which was the subject of IND 38892. Despite the high number of exposed subjects, at doses up to 4000 mg/m^2/day, the most common adverse events (AEs) reported for all subjects treated with oral fenretinide were mild and included headache, diarrhea, nausea, skin irritation, and nyctalopia. No deaths or serious adverse events (SAEs) were reported in studies with fenretinide administered orally.

1.2.1.1 Teratogenicity

Oral retinoids, such as isotretinoin (13-cis retinoic acid), are known to produce teratogenic effects in animals and in humans, therefore representing a clinical concern when used to treat female patients of childbearing potential. Isotretinoin is approved in the US for the treatment of severe recalcitrant nodular acne in non-pregnant patients 12 years of age and older, although due to its teratogenicity, isotretinoin is marketed only under a special restricted distribution program (FDA, 2021).

Fenretinide is a retinoid, and teratogenicity risks are a concern, even though the teratogenic effects of fenretinide have been shown to be milder at higher doses when compared with other retinoids such as isotretinoin. In reproductive and developmental toxicity studies conducted under IND 38892, the most biologically significant events in the offspring of rats involved ocular toxicity and delayed ossification of skull bones (doses up to 800 mg/kg, HED = 4774.2 mg/m^2). In rabbits, a low incidence of tail, cleft/palate, and limb malformations were observed in the offspring from mid- and high-dosage groups (doses up to 800 mg/kg, HED = 9548.4 mg/m^2).

Clinical studies in healthy volunteers from IND 38892 were conducted in males, to avoid the risk of teratogenic effects. In studies in patients with ichthyosis, psoriasis, multiple basal cell carcinoma, and treatment-resistant acne, 16 females and 79 males were exposed to 600 and 800 mg daily doses of fenretinide (370 and 493.3 mg/m^2 for 60 kg humans) for up to 16 weeks (mean length of therapy was 66.57 days for all patients). No pregnancy cases were reported. Fenretinide has also been tested in clinical research for decades without significant teratogenic events being reported. In over 30 clinical studies in the published literature, approximately 2560 female subjects were exposed to fenretinide at doses ranging from 61.7 to 4000 mg/m^2/day for up to 5 years; no teratogenicity issues were reported in these studies.

1.3 ISLA101

ISLA101 is an oral capsule formulation of fenretinide. Island plans to submit a New Drug Application (NDA) for ISLA101 for the prophylaxis of dengue fever via the 505(b)(2) regulatory pathway. To support the ISLA101 NDA, Island intends to rely on clinical and nonclinical studies from IND 38892 and from the published literature, in addition to Sponsor-conducted studies.

The current Phase 1 study will evaluate the safety, tolerability, and pharmacokinetics (PK) of single ascending doses of fenretinide after administration of ISLA101 (at doses of 300, 600, and 900 mg/m^2) in healthy subjects. This study will also assess the dose proportionality of systemic exposure of ISLA101 and food effect as an exploratory objective. To safeguard against the possible risk of teratogenicity, the study will evaluate male subjects and female subjects who are not of childbearing potential. Contraception requirements compliant with local regulations and clinical practices are included as part of the inclusion criteria for the study.

1.4 Risk and Benefits

The well-tolerated safety profile of fenretinide in clinical studies conducted under IND 38892 and in published literature, as evidenced by the absence of SAEs and low incidence of mild AEs, supports the safety of ISLA101. The healthy subjects who enroll in this study are not expected to derive direct benefit from study participation. The safety, tolerability, and PK data obtained in this study, however, are expected to support the development of a prophylactic for the treatment of dengue fever, thereby addressing an unmet medical need.

Previous nonclinical and clinical data indicate that retinoids have teratogenic potential, although the teratogenic effects of fenretinide have been shown to be milder compared to other retinoids. To promote subject safety, this study will only evaluate male subjects and female subjects of nonchildbearing potential. Female subjects will be excluded if they are pregnant or lactating, taking hormonal contraceptives (due to potential drug-drug interactions with fenretinide), or are less than 12 months postmenopausal or have had less than 6 weeks elapse following bilateral oophorectomy. As a safety measure, pregnancy testing will be conducted frequently during the study. Male subjects with female partners must agree to use appropriate contraceptive measures during the study, in keeping with the special restricted distribution program for isotretinoin (FDA, 2021), and in compliance with local regulations and clinical practice. If subject or partner pregnancy occurs, study drug will be discontinued, and the pregnancy will be promptly reported to the Sponsor for appropriate follow-up. Collectively, these safeguards and monitoring processes will promote subject safety, and the potential benefit of developing a therapy for the prophylaxis of dengue fever is thought to outweigh a potential teratogenic risk.

Overall, there is no potential benefit to healthy subjects, while the risks appear to be minimal based on the available safety data, study inclusion criteria, and study monitoring procedures.

2 STUDY OBJECTIVES

2.1 Primary Objective and Endpoints

2.1.1 Primary Objective

The primary objective is to:

- Evaluate the safety and tolerability of single ascending doses of ISLA101 in healthy adult volunteers (fasted).

2.1.2 Primary Endpoints

The primary endpoints are:

- Vital signs, clinical laboratory tests, changes from baseline in physical examinations, AEs, and treatment-emergent adverse events (TEAEs).

2.2 Secondary Objective and Endpoints

2.2.1 Secondary Objective

The secondary objective is to:

- Characterize the PK profile (fasted) of fenretinide after administration of single ascending doses of ISLA101 in healthy adult volunteers.

2.2.2 Secondary Endpoints

The secondary endpoints are:

- Single dose PK parameters for fenretinide in plasma: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, and others as relevant.

2.3 Exploratory Objective and Endpoints

2.3.1 Exploratory Objective

The exploratory study objective is to:

- Assess the PK profile of fenretinide in healthy adult volunteers under fed conditions.

2.3.2 Exploratory Endpoints

The exploratory endpoints are:

- Single dose PK parameters for fenretinide in plasma under fed conditions: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, and others as relevant.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

The study is a randomized, double-blind, placebo-controlled single ascending dose (SAD) study of ISLA101 (fenretinide oral capsules) to evaluate safety, tolerability, and pharmacokinetics in healthy human subjects. The study will consist of up to 4 cohorts that will evaluate dose levels of 300 mg/m^2 (fasted), 600 mg/m^2 (fasted), and 900 mg/m^2 (fasted). The highest tolerated dose level cohort will then be evaluated in a fed condition (in a cross-over manner). Eight subjects will be enrolled per dose cohort, with 6 subjects receiving active drug and 2 subjects receiving placebo treatment in a blinded manner. Each subject will be allocated to 1 dose level only.

After completing screening activities, eligible subjects will enter the clinical research unit (CRU) on Day -1 for 5 days. Subjects will receive a single dose of study drug in the morning of Day 1 after an overnight fast of approximately 10 hours, followed by additional 4 hours fast after dose for PK sampling. Cohorts 1 through 3 will receive 300 mg/m^2, 600 mg/m^2, and 900 mg/m^2, respectively, under fasted conditions. After the safety review by the independent safety review committee (SRC), the dose level can be escalated to the planned or lower than planned dose level or de-escalated to an intermediate dose level. Decisions to proceed to the next cohort will be made by the Investigator, SRC, and Sponsor based on the safety data from previous cohort(s).

Safety data will be reviewed to identify the cohort that received the highest dose level under fasted condition. The subjects in this cohort will be recalled to evaluate the PK of ISLA101 under fed conditions (8 subjects; Cohort 4). In Cohort 4, subjects will fast for approximately 10 hours overnight and will consume a high-fat, high-calorie meal approximately 30 minutes prior to administration of study drug. No food consumption will be permitted for at least 4 hours post-dose.

For all cohorts, study drug will be taken with up to 240 mL of water. In fasted cohorts, water will be allowed ad libitum except the interval from 1 hour before to 1 hour after the dose. In the fed cohort, water will be allowed ad libitum except the interval from 1 hour before to 1 hour after dose.

Subjects will be discharged from the clinic on Day 5. At the discretion of the Investigator or designee, the confinement time can be extended to ensure the safety of each subject. Subjects will have up to 3 days of follow up. For Cohort 4 (the food effect cohort), the confinement and follow-up visit will be repeated. Subjects who are dosed but withdrawn prior to study completion will participate in an Early Termination visit and may be replaced if needed to obtain sufficient information as possible based on the timing.

In all cohorts, safety will be assessed via vital signs, clinical laboratory tests, physical examinations, AEs, and TEAEs. Pharmacokinetic data will be collected and analyzed at the end of the study but will not be used for dose escalation decisions. A description of study assessments is provided in Table 1.

3.2 Rationale for Study Design

A randomized, double-blind study in healthy subjects is considered appropriate to evaluate the safety, tolerability, and PK of ISLA101. Single ascending doses of ISLA or placebo will be administered under fasting conditions, and safety and tolerability data will be evaluated in each cohort to guide doses administered to future cohorts. The highest tolerated dose will also be administered under fed conditions to assess any potential food effect (in a crossover manner). A rationale for dose selection is provided in Section 3.2.1.

3.2.1 Dose Rationale for SAD

The starting dose of 300 mg/m^2 was selected based on the safety profile of fenretinide, which was extensively studied in multiple animal species in IND 38892:

- ***Single-dose oral toxicity studies (Good Laboratory Practice [GLP]):***
  - Dogs: doses up to 3000 mg/kg (human equivalent dose [HED] = 61666.7 mg/m^2); the maximum determinable non-lethal dosage was > 1350 mg/kg (HED = 27750 mg/m^2); observed clinical signs included emesis (> 2000 mg/kg), black tarry stool (2000 mg/kg), and loose stool (1350 mg/kg).
  - Rats: dose of 5000 mg/kg (HED = 29838.7 mg/m^2); the median lethal dose was > 5000 mg/kg; clinical signs included diarrhea, unkempt appearance, yellow stool, hunched posture; no mortality was observed.
  - Mice: dose of 7000 mg/kg (HED = 21056.9 mg/m^2); no clinical signs or mortality were observed.

  These studies provided safety margins for the 300 mg/m^2 ISLA101 starting dose ranging from 70.2- to 99.5-fold.

- ***Repeat-dose oral toxicity studies (GLP):***
  - Dogs: doses up to 800 mg/kg/day (HED = 16444.4 mg/m^2). The no-observed-adverse-effect levels (NOAEL) from these studies were 90 mg/kg (HED = 1850 mg/m^2) for a 12-month study, 600 mg/kg (HED = 12333.3 mg/m^2) for a 20-day study, and 800 mg/kg (HED = 16444.4 mg/m^2) for a 3-month study.
  - Rats: doses up to 800 mg/kg/day (HED = 4774.2 mg/m^2). The NOAEL from these studies was 800 mg/kg (HED = 4774.2 mg/m^2) for a 3-month study and 70 mg/kg (HED = 417 mg/m^2) for a 12-month study.

  Although ISLA101 is not intended for chronic use, studies for up to 3 months in IND 38892 provide safety margins for a ISLA101 starting dose of 300 mg/m^2 ranging from 15.9- to 54.8-fold.

  Therefore, in this study, a starting dose of 300 mg/m^2 is believed to be safe for administration to healthy subjects.

The starting dose and systemic safety of ISLA101 for the SAD study will be based on the rationale that the highest exposure in humans in the SAD study will not exceed the exposure levels derived in the nonclinical studies. Human equivalent doses of the NOAEL of selected studies with related exposure caps are shown in Table 3.

Table 3 Summary of Fenretinide NOAEL Data and PK Exposures to be Used to Determine Starting Dose and Exposure Caps in the ISLA101 Study

Species	Duration (weeks)	NOAEL (mg/kg/day)	Through Concentrations (ng/mL; mean ± SD)	C_{max} (ng/mL; mean ± SD)	Human Equivalent Dose* (mg/m^2)
Dogs (Study 1084)	12	800	1383 ± 908 (male); 819 ± 294 (female)	2299 ± 1456	16444.4
Rats (Study 1077)	12	800	183 ± 83 (male); 186 ± 82 (female)	NA	4774.2

* Assumes a 60 kg human.
NA = not available; NOAEL = no-observed-adverse-effect level; SD = standard deviation

The doses in this study were chosen based on the dose-response relationships described in nonclinical mouse models of dengue fever, and on the correlation between nonclinical and clinical exposures to fenretinide. In vivo, an oral fenretinide at 20 mg/kg (HED = 60.2 mg/m^2) given at the time of infection and BID for 5 days protected 70% of mice from death (Fraser et al., 2014). At 180 mg/kg (HED = 541.5 mg/m^2), given 24 hours prior to 10 days post-infection, there was a significant reduction in mice peak viremia (Carocci et al., 2015). In vitro and ex vivo, concentrations from 5 to 10 µM exhibited highly specific and potent anti-dengue virus activity, with an average EC_{50} of 1.6 µM and EC_{90} of 2 µM (Fraser et al., 2014; Carocci et al., 2015). In humans, plasma concentrations produced by doses near 300 mg/m^2 ranged from 0.87 to 2.8 µM, and by doses near 600 mg/m^2, from 2.1 to 5.2 µM. The doses selected for inclusion in this study are therefore expected to be therapeutically relevant for the treatment of dengue fever.

3.3 Dose and Dosing Regimen

The starting dose for the SAD study is 300 mg/m^2. The proposed dose escalation paradigm for SAD is shown in Table 4. Briefly, the doses to be tested are 300 mg/m^2 (fasted), 600 mg/m^2 (fasted), and 900 mg/m^2 (fasted). The highest tolerated dose level cohort will then be evaluated in a fed condition. Subjects will initially receive a dose of 300 mg/m^2, and the decision to advance to the next cohort will be based on safety and tolerability data.

Table 4 Proposed Single Ascending Dose Escalation

Cohort 1	Cohort 2	Cohort 3
300 mg/m^2	600 mg/m^2	900 mg/m^2

Actual doses may be decreased from the planned doses based on emerging safety and tolerability data, as recommended by the independent SRC and agreed by the Investigator

and Sponsor. The initiation of the next cohort with a higher dose level will be decided during the interim safety review by the SRC. The recommendation of the SRC will be documented in a memo that will be filed in the Trial Master File (TMF). The SRC memo will serve as a source document for the clinical study report (CSR) and all supporting information can be presented to the human research ethics committee (HREC) if required. A description of the SRC is provided in Section 3.6.1.

If an acceptable safety profile is demonstrated in the previous cohort, enrollment of the next higher dose cohort may begin. For dose progression to occur, a minimum number of 7 subjects per cohort must have data from at least 96 hours after dosing, to ensure availability of placebo data.

Additional cohorts may be added as needed to test lower or repeat doses. Any changes to the dosing will made following discussions between the Sponsor and Investigator. The number of added cohorts will not exceed four. If the decision to enroll additional cohorts is made, an amendment will be submitted describing the safety and PK data from the portion of the study conducted to date. Enrollment of any additional cohorts will be initiated following HREC review and approval. The timing of vital sign assessment and PK sampling may be modified by SRC based on the emerging data after SAD dosing.

The incidence and nature of any AEs, dose-limiting AEs, SAEs, vital sign changes, and laboratory abnormalities will be assessed on an ongoing basis by SRC. Depending on the severity of these and/or other AEs or the occurrence of more than 1 AE in the same subject, the subject(s) may be unblinded if it is deemed necessary for the treatment of AEs.

3.4 Study Duration and Dates

The study will involve participation for a total of approximately 6 weeks. This includes up to 28 days for screening and approximately 5 days of confinement,and up to 3 days of follow-up after discharge from the clinic. For subjects in Cohort 4 (the food effect cohort), there will be an additional up to 5 days of confinement, and up to 3 days of follow-up.

3.5 End of Study

The clinical study is considered completed when the last subject’s final study visit has been completed.

3.6 Study Oversight

The study will be overseen by the Sponsor or an appropriate designee.

3.6.1 Safety Review Committee

An SRC will be comprised of, but not limited to, the Investigator, Medical Monitor, and an independent clinical representative. Other members of the SRC will be added on an as need basis, such as a PK scientist. The SRC will be responsible for reviewing data and deciding on:

- The continued safety of the study subjects.

- The continued validity of the trial.
- The continued scientific merit of the trial.
- Recommended dose for next cohort, as applicable.

The SRC will facilitate management and identification of potential safety concerns, will review safety data, and will determine if dosing of each cohort should continue, if dose escalation should continue following completion of each cohort, or if dose de-escalation or repeating a dose level should be performed.

4 STUDY POPULATION SELECTION AND WITHDRAWAL

4.1 Study Population

This study will enroll up to 24 healthy, male and female subjects who are 18 to 65 years old at the time of consent. Subjects who withdraw or are removed from the study, except for safety reasons, may be replaced at the discretion of the Sponsor.

4.2 Inclusion Criteria

Subjects must meet the following criteria to be enrolled in the study:

1. Healthy male and female volunteers not of childbearing potential who are 18 years to 65 years of age (inclusive) at the time of signing the informed consent form (ICF).
2. Females not of childbearing potential as defined in the following criteria:
    a. History of hysterectomy.
    b. Post-menopausal:
        i. Natural post-menopausal females with at least 12 months from natural spontaneous amenorrhea and a serum follicle-stimulating hormone (FSH) concentration ≥ 40 IU/L.
        ii. Post-surgical females must have undergone bilateral oophorectomy at least 6 weeks prior to study.
3. Male subjects with female partners of childbearing potential must agree to practice abstinence or use a combination of 2 of the following acceptable birth control methods during the study and for at least 90 days after dosing:
    a. Partners with an intrauterine device (IUD) without hormones in place for at least 3 months.
    b. Barrier method (condom or diaphragm) for at least 14 days prior to screening and for 90 days after dosing with study drug.
    c. Partners using stable hormonal contraceptive for at least 3 months prior to the study and for 90 days after dosing with study drug.
    d. History of vasectomy at least 3 months prior to signing the ICF.
4. Must be able to understand and provide signed informed consent for study participation.
5. Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.
6. Females must have a negative serum hCG pregnancy test at screening.
7. Body mass index (BMI) ≥ 18.0 to 32.0 kg/m^2 (inclusive) and a body weight ≥ 50 kg.
8. Normal renal function, defined as estimated glomerular filtration rate (eGFR) ≥ 70 mL/min/1.73 m^2 at screening and Day -1.

9. Clinical laboratory values should be within the laboratory's stated normal range. If not within this range, they must be without clinical significance, as determined by the Investigator.
10. No history of clinically relevant medical disorders.

4.3 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Known or suspected pregnancy (confirmed via a positive serum hCG pregnancy test at screening), planned pregnancy during the study period, nursing, or lactation.
2. Women of childbearing potential or men who intend to father a child or donate sperm during the study period, and for 3 months after dosage of study drug.
3. Known allergy to fenretinide or any of the components of ISLA101.
4. Evidence or history of clinically significant medical conditions, such as hematological, renal, endocrine (e.g., polycystic ovarian syndrome PCOS or other anovulatory states), immunologic, pulmonary, metabolic, gastrointestinal (e.g., Crohn's disease, acute or chronic pancreatitis, and others), and surgery (except for simple appendectomy or repair of a hernia), which all can influence the absorption of study drug; cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies but excluding untreated, asymptomatic, seasonal allergies at the time of dosing), or any other illness that the Investigator considers exclusionary or that could interfere with the interpretation of the study results.
5. History of severe infectious disease or recurrent infections.
6. Aspartate transaminase (AST), alanine aminotransferase (ALT), or total bilirubin above the 1.5 x upper limit of normal (ULN) at screening and Day -1.
7. Clinically significant electrocardiogram (ECG) abnormalities or vital sign abnormalities at screening and Day -1, long QT syndrome, or a history of cardiac disease.
8. Abnormal diet that may affect absorption, distribution, metabolism, or excretion of drugs, for example, lacking standard nutrients (e.g., cleansing diet 2 weeks before or during the study).
9. Positive result for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening.
10. History of positive tuberculosis (TB) test at screening.
11. Has donated 1 unit of blood of over 500 mL within 56 days prior to the study drug administration, or donated plasma within 14 days of study drug administration.
12. Use of antibiotics within 30 days prior to dosing.
13. Use of drugs that inhibit or induce CYP enzymes within 30 days prior to administration of study drug and for the duration of study participation.
14. Use of tobacco products, e-cigarettes, and/or nicotine replacement products in the 3 months before screening.

15. Any food allergy, intolerance, or restriction that, in the opinion of the Investigator, could contraindicate the subject's participation in this study.
16. Recent history of (within the past 12 months), or strong potential for, alcohol or substance abuse. Alcohol abuse will be defined as > 14 drinks per week (1 drink = 10g of ethanol).
17. History of drug or alcohol abuse within 5 years before screening or positive result of UDS (e.g., amphetamines, benzodiazepines, cannabinoids, cocaine, hallucinogens, opiates) at screening, or alcohol breath test at screening or Day -1.
18. Exposure to any investigational agent or used an invasive investigational medical device within 30 days or within a period less than 5 drug half-lives prior to study entry (whichever is longer).
19. Study site employees, Sponsor's employees, or immediate family members of a study site or Sponsor employee.
20. Previously enrolled in this study.
21. Vaccination within less than 14 days from screening or plans to get a vaccine within 30 days after dosing.
22. Have an acute infection (such as influenza) or relevant lesion at the time of screening or admission. Subjects can be rescreened once they have recovered.
23. Criteria at the discretion of the Investigator:
    a. Chronic medical condition that impacts subject safety.
    b. Clinically significant abnormal physical examination or vital signs at screening.
    c. Condition believed by Investigator to interfere with the subject's ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk.
    d. History or evidence of a clinically significant disorder, condition, or disease that that is believed by Investigator to significantly impair pain perception (e.g., history of stroke, history of neuropathy), would pose a risk to subject safety or interfere with evaluation, procedures, or study completion.

4.4 Discontinuation of Treatment and Withdrawal of Subjects

Subjects are free to withdraw from the study at any time for any reason. Subjects who withdraw from the study early will be asked to complete the Early Termination procedures, as described in Table 1.

In addition, subjects are required to be withdrawn from the study by the Principal Investigator or sub-Investigator for the following reasons:

- Any unacceptable or intolerable AEs
- Difficulties in blood collection
- Non-compliance with study restrictions

- Study terminated by Sponsor
- Personal decision by the subject
- A subject who vomits immediately after study drug administration or up through 6 hours after administration or within 2 x T_{max} (once the T_{max} is known) after dosing.

The CSR will include reasons for subject withdrawals as well as additional details relevant to the subject withdrawal. Withdrawn subjects can be replaced if timing permits unless the withdrawal happened due to safety reasons related to the drug.

4.4.1 Documenting Subject Withdrawal

If a subject prematurely withdraws from the study, either at her/his request or at the Investigator's discretion, the Investigator will record the reason for withdrawal on the relevant case report form (CRF) page. Subjects prematurely discontinuing the study, regardless of cause, should have all Early Termination study assessments performed.

It is important to obtain follow-up data for any subject withdrawn because of an AE,or abnormal laboratory test, vital sign measurement, or physical examination. In any case, every effort must be made to undertake safety follow-up procedures.

4.5 Subject Replacement

Subjects who withdraw or are removed from the study, except for safety reasons, may be replaced at the discretion of the Sponsor.

5 STUDY TREATMENT

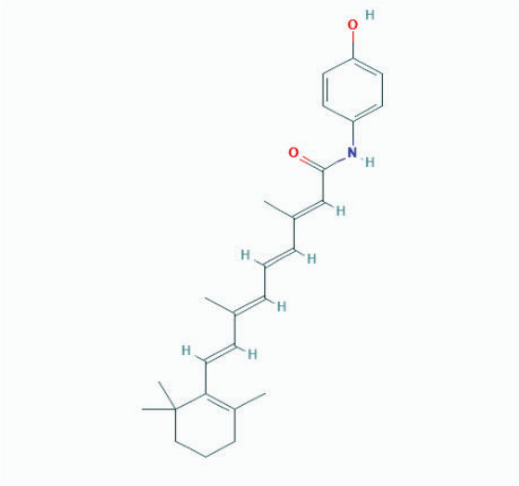
The CRU's Standard Operating Procedures will be followed with respect to the preparation, proper labeling, storage, and dispensing of investigational study drugs. A summary of appropriate procedures is provided below; additional instructions specific to the preparation of ISLA101 will be provided in the ISLA101 Pharmacy Manual.

5.1 Description of Treatment

5.1.1 Study Drug

Fenretinide (N-[4-Hydroxyphenyl] retinamide) is a yellow to orange crystalline powder with molecular weight of 523.32 g/mol. The chemical name and structure of fenretinide are shown in Figure 1.

Figure 1 Structure and Chemical Properties of Fenretinide



Chemical name:	N-(4-Hydroxyphenyl)retinamide; 4-HPR; 4-hydroxyphenylretinamide; 4-Hydroxyphenyl retinamide
Formula:	$C_{26}H_{33}NO_2$
Molecular weight:	391.56
CASRN:	65646-68-6

Source: PubChem

Subjects will be randomly assigned to receive either ISLA101 (Fenritinide) or placebo. The ISLA101 and placebo capsules will be indistinguishable from each other in size, shape, and smell. ISLA101 will be administered at doses of 300 mg/m^2 (fasted), 600 mg/m^2 (fasted), and 900 mg/m^2 (fasted). The highest tolerated dose level cohort will then be evaluated in a fed condition. Administration of placebo will be aligned with administration of ISLA101.

5.1.2 Drug Administration

In each cohort, a single dose of study drug will be administered to each subject. Study drug will be taken with up to 8 oz/240 mL of water.

ISLA101 or placebo will be administered orally. The dose will be calculated according to the subject's body surface area (BSA) using the calculation (Mosteller formula):

BSA (m^2) = the square root (√)of ([Height (cm) x weight (kg)]/3600)

For example: Subject: 150 cm, weighing 68 kg

m^2= √ [150*68]/3600 = 10200/3600

m^2= √ 2.83

m^2= 1.68

600mg/m2/d = 600 * 1.68 = 1009 mg/day

1009 mg/day /100mg capsule = 10 capsules per day

The number of capsules will be rounded up if the daily dose is equal to or greater than daily dose = XX51, e.g., 1051 = 11 capsules.

For subjects participating in the fasted cohorts (Cohorts 1 through 3), subjects will receive study drug following an overnight fast of approximately 10 hours. Subjects will continue to fast for no less than 4 hours after study drug administration. Water will be allowed ad libitum except 1 hour before and 1 hour after dosing.

Subjects in the food effect cohort (Cohort 4) will fast overnight for at least 10 hours and will receive a high-fat, high-calorie meal, approximately 30 minutes prior to administration of study drug. No food consumption will be permitted for at least 4 hours post-dose. Water will be allowed ad libitum except the interval from 1 hour before dosing to 1 hour after dosing.

Prior to dosing, subjects will be reminded of the study restrictions:

- Do not speak while trying to swallow capsule(s).
- All capsules need to be consumed within 5 minutes of the start of consumption.
- Report any AEs to the study staff.
- Request an escort to the restroom, if needed, during the first hour after receiving study drug.

5.2 Dose Modification

The decision to enroll the sequential cohort at the next dose level will be based on the safety data from previous dose cohorts. Dose escalation will depend on the emergence of dose-limiting AEs and review of the safety data. Progression to the next higher dose will only occur if the previous dose level was deemed to be well tolerated by the SRC. Safety data sets to be reviewed by the SRC for dose escalation determination will include all available data up to 96 hours post-dosing for subjects enrolled into each dose-level cohort. A minimum of 7 subjects' data will be evaluated to make dose escalation decisions. Decisions to proceed to the next cohort will be based upon the recommendation of the SRC and agreed upon with the Investigator and Sponsor.

Doses will be flexible during the study to allow for reductions in the planned escalation based on safety. When it is not appropriate to escalate the dose, then the same dose, a previous dose, or an intermediate dose may be given following discussion between the Investigator and Sponsor.

5.3 Stopping/Halting Rules

Further enrollment and study drug administration will be stopped if any of the following events occur:

- A single SAE regardless of organ system if it is possibly, probably, or definitely related to the study drug.
- Grade 3 or higher AEs and laboratory abnormalities determined to be possibly, probably, or definitely related to study drug.
- Death of any subject considered related to study drug unless the SRC determines it is unrelated to study drug.
- An anaphylactic reaction to study drug in any subject.
- A potentially life-threatening AE or SAE, unless the SRC determines it is unrelated to study drug.
- A pattern of significant symptoms, physical findings, or laboratory abnormalities that, although individually minor, collectively may represent a safety concern in the opinion of the Investigator or the medical monitor and are judged by the SRC to be at least possibly related to study drug.
- Sponsor's decision to terminate the study for any reason.

Dose-limiting AEs that will halt further enrollment into the affected cohort and study drug administration within the cohort are described in Section 9.1.4. Additionally, if any AEs of special interest (see Section 9.1.5) occur that meet the following criteria, they will be considered dose-limiting:

- Any two ≥ Grade 2 AE of special interest, unless they are clearly and incontrovertibly due to extraneous causes.
- Any one ≥ Grade 3 AE of special interest, unless the event is clearly and incontrovertibly due to extraneous causes.
- Any SAE of special interest, unless the event is clearly and incontrovertibly due to extraneous causes.

The HREC and the FDA will be notified if the study hold criteria are met.

5.4 Packaging and Labeling

- ISLA101 oral capsules and matching placebo capsules will be prepared, labeled, supplied to the clinical site in bulk bottles, and stored as described in Section 5.5, until dispensing by the pharmacist. For each bottle, the following information will be provided on the label, as well as any information required by local regulations: Protocol Number
- Storage Requirements
- Directions for Use
- Contents (i.e., 50 capsules per bottle)
- Investigational New Drug Statement
- Lot Number
- Manufactured by and Date
- Sponsor
- Expiry Date

5.5 Supply, Storage, Dispensing

5.5.1 Supply

ISLA101 capsules, 100 mg (50 count) are packaged in high-density polyethylene bottles with polypropylene seal. Study drug (ISLA101 and placebo) will be supplied by the Sponsor's designated manufacturer in accordance with current Good Manufacturing Practices (GMP).

5.5.2 Storage

ISLA101capsules and placebo should be stored as indicated on the label (59-86°F [15-30°C]) in a secure, limited-access area in tight containers and protected from light.

The study drug will be stored in a safe and locked place with restricted, controlled access. The temperature of the storage units will be monitored daily with a validated temperature monitoring device(s) and documented. Any temperature excursion (i.e., temperature outside the defined range of storage) must be reported to the Sponsor within 24 hours of knowledge of the excursion.

5.5.3 Dispensing Study Drug

Complete instructions regarding the preparation of study drug for dispensing can be found in the ISLA101 Pharmacy Manual. The pharmacy staff will prepare the ISLA101 and placebo tablets for dispensing. Once prepared by the pharmacy team, the study drug will be kept in a limited access area under appropriate environmental conditions. The study drug is to be used exclusively in the clinical study according to the instructions of this protocol.

5.6 Accountability, Retention, and Return

The site Investigator or his/her designee is responsible for receipt of the study drug at the study site. The Sponsor has ultimate responsibility for product accountability. The

Investigator is responsible for and will maintain logs of study drug receipt, storage, reconstitution, accountability by subject, and study drug remaining before final disposition. The Investigator may delegate, in writing, this responsibility to another individual, but the Investigator is ultimately responsible for the study drug and its proper storage upon receipt at the study site until it is transferred back to the Sponsor or designee or is destroyed, as directed by the Sponsor.

All unused study drug provided by the Sponsor will be retained and returned to the Sponsor or their designee at the completion of the study for reconciliation and destruction. The Investigator must provide an explanation for any missing capsules.

The pharmacist will maintain an accurate record of all study drug supplies received and dates of receipt. The dispensing and return of study drug will be documented on a Pharmacist's Dispensing Log that will be maintained for each subject. At the completion of the study, the clinical study monitor must be able to verify and reconcile that all subjects received the correct study drug assignment (according to the randomization schedule), proper dose of study drug, and that the individual subject study medication bottles were properly labeled.

6 ALLOCATION, DOSING AND STUDY DRUG ADMINISTRATION

6.1 Randomization Procedures

Subjects will be randomly assigned to a cohort per the clinical research unit's standard randomization, participation, and blinding protocol. Within each cohort, 8 subjects will be assigned in a 3:1 ratio to receive ISLA101 (6 subjects) or placebo (2 subjects). Subjects participating in Cohort 4, the food effect cohort, will maintain the same treatment assignment from their fasted cohort.

6.2 Blinding

This will be a double-blind study. The study drug, including both ISLA101 oral capsule and matching placebo, will be dispensed using a method that ensures site staff and subjects remain blinded to the study drug being administered.

If a reportable safety issue is detected during the review of unblinded safety data, notification will be sent to designated clinical research unit staff consisting of the unblinded pharmacy team and the designated regulatory compliance specialist for submission to the HREC, per local reporting requirements.

7 PERMITTED THERAPIES AND CONTRAINDICATIONS

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, OTC medications, and non-prescription medications including dietary and herbal supplements.

All medications, taken by subjects 14 days before screening and during the study (starting with the signing of the ICF) will be recorded on the Prior and Concomitant Medication section of CRF. Any additions, deletions, or changes in the dose of these medications will also be entered in the CRF.

7.1 Prohibited Therapies

Subjects should not take prescription medications that may, in the opinion of the Investigator, impact the status of the subject as healthy within 28 days prior to study drug administration and throughout the study. Subjects will refrain from using OTC medications, vitamin supplements, or herbal preparations from 7 days prior to study drug administration and throughout the study; paracetamol, however, is permitted for pain relief. Subjects should not use antibiotics or drugs that inhibit or induce CYP enzymes within 30 days prior to administration of study drug and throughout the study.

Subjects should not receive a vaccine within 14 days of screening or plan to get a vaccine during the study or within 14 days after discontinuation of the study. Subjects should not receive live or attenuated vaccines for 30 days prior to dosing and throughout the study.

7.2 Permitted Therapies

Paracetamol (up to 2 g per day) is permitted for pain relief. Medication use will be controlled by the Investigator or designee during the time of sample collection or during the washout period between drug administrations.

The Investigator may prescribe appropriate medication to treat AEs. The Sponsor and Investigator will confer to determine whether it is appropriate to continue such a subject in the study.

7.3 Lifestyle Restrictions

7.3.1 Dietary Restrictions

Restrictions related to fasting and consumption of water in the day of study drug administration are described in Section 5.1.2.

Subjects should not consume grapefruit, pomegranate, star fruit, or Seville oranges (or juices or products containing these fruits) for 7 days prior to dosing throughout the study. Subjects should not use St. John’s wort within 28 days prior to dosing and for the duration of the study.

Subjects should abstain from food containing poppy seeds within 48 hours prior to clinic check-in. Subjects should not consume food or beverages containing caffeine, xanthine derivatives or xanthine-related compounds, or energy drinks within 24 hours prior to clinic check-in.

Subjects should abstain from consumption of alcohol-based products from 24 hours prior clinic check-in until after the last study assessments are performed at the Follow-up/Early Termination Visit.

7.3.2 Tobacco Restrictions

Subjects should not use tobacco products for 3 months prior to the screening visit and during the study.

7.3.3 Exercise Restrictions

Subjects should abstain from strenuous exercise for 48 hours prior to Day -1 and throughout the study.

Vigorous activity will be prohibited at all times during the confinement. Subjects will be escorted by clinical staff to the restrooms or to other restricted areas of the clinic during the 1 hour after study drug administration. Any deviation to these restrictions should be recorded.

7.4 Treatment Compliance

Study drug must be used exclusively in the clinical study according to the instructions of this protocol. Study drug will be administered in the clinic under the supervision of site staff. Any deviations from planned dosing will be recorded.

8 STUDY PROCEDURES

All study procedures will be performed according to the Schedule of Assessments (Table 1). All visits are planned to be conducted at the clinic.

The following is a guideline for the order of assessments when more than 1 of the following assessments is required at a particular timepoint:

- Obtain vital signs, including temperature as applicable
- Perform 12-lead ECG
- Perform physical examination
- Collect blood for safety laboratory tests
- Collect blood for PK analysis

When applicable, the blood draw for PK analysis should be given priority of timing such that it is drawn as close to the scheduled time as possible.

8.1 Study Assessments by Visit

For subjects who participate in Cohort 4 (the food effect cohort), the assessments described on Days -1, 1, 2, 3, 4, 5, and 8 will generally be repeated on Days 9, 10, 11, 12, 13, 14, and 17, respectively, unless noted otherwise in the Schedule of Assessments (Table 1).

8.1.1 Screening (Days-28 to Day -2)

Prior to any study procedure, the subject will read and sign an ICF. All subjects will receive a copy of the signed ICF. The informed consent process will be noted in the subject's medical record.

Within approximately 28 days of the study drug administration, the screening visit should be completed. All subjects will be evaluated for adherence with study inclusion/exclusion criteria. A complete medical history evaluation, including surgical history and demographic data (age, gender, ethnicity, and race) will be completed for each subject. A complete history of all medications taken within 4 weeks of this visit will be obtained. Subjects will be instructed about permitted therapies and study restrictions (see Section 7).

A full physical examination will be performed. Vital signs will be measured (blood pressure, pulse, respirations). Temperature will be measured. Clinical significance will be noted for any abnormal findings. A serum pregnancy test will be done on all female subjects. Follicle-stimulating hormone (FSH) will be measured to confirm postmenopausal status. A urine drug screen will be done on all screening subjects. A breath alcohol test will be administered. Body mass index (BMI) will be determined from height and weight (shoes off) measurements. BMI can be calculated using pounds and inches, or kilograms and centimeters, with the following equations:

- BMI = [Weight in Pounds/ (Height in Inches x Height in Inches)] x 703
- BMI = Weight in Kilograms/ (Height in centimeters x Height in centimeters)

For any out-of-normal range values, clinical significance will be noted. The clinical laboratory tests include:

- Serum Chemistry: alanine transaminase, albumin, alkaline phosphatase, aspartate transaminase, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, magnesium, potassium, sodium, total bilirubin, total protein, uric acid.
- Hematology: differential white blood cell count, hematocrit, hemoglobin, platelet count, red blood cell count, international normalized ratio (INR).
- Serology: hepatitis B surface antigen, hepatitis C antibody titer, HIV.
- Serum Pregnancy Test: hCG will be conducted for all female subjects.
- FSH will be tested for all female subjects to confirm or refute postmenopausal status.
- Urinalysis: bilirubin, blood, clarity, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity. A microscopic test on the urine sample will be done where indicated.
- Urine Drug Screen: Methamphetamine, morphine, cocaine, tetrahydrocannabinol, phencyclindine, benzodiazepines, barbiturates, methadone, tricyclic antidepressants, amphetamine, urine cotinine or breath CO test for use of tobacco, MDMA metabolite (ecstasy) and opiates.
- Alcohol breath test.
- Coagulation: prothrombin time.

8.1.2 Check-in (Day-1)

Subjects will enter the facility the day before study drug administration for each study period. All subjects will be domiciled and under medical supervision in the CRU. All subjects will be confined to the clinical unit for the entire treatment period, up to Day 5.

A pregnancy test (females), alcohol breath test, and urine cotinine or breath CO test will be performed at each study period check-in. Results must be negative to continue in the study. Any untoward changes in medical history of the subject since the screening visit will be documented and added to the medical history. For female subjects, start and stop date of last menstrual period will be collected. Untoward changes in medical history since dosing will be recorded as AEs. Subjects will be asked about any medications taken since the screening visit or previous study period and adherence to restrictions. Vital signs (in a semi-recumbent position) and temperature will be measured. A full physical exam will be performed. Blood and urine will be collected for safety laboratory testing (chemistry, hematology, coagulation, urinalysis).

The clinical laboratory tests for check-in are the same as at screening.

The Investigator will review this information and determine continuing eligibility of the subject prior to each study drug administration.

A supervised fast of at least 10 hours will start after the evening meal. The subjects will have free access to drinking water until at least one hour before dosing and one hour after dosing.

8.1.3 Treatment/Confinement Period Procedures

8.1.3.1 Days 1 through 5

On Day 1 of the confinement period, each subject will be randomized to receive study drug or placebo, at a dose determined by the part and cohort into which the subject is enrolled. The next cohort will only be dosed after completing the safety review of the previous cohort as per the schedule of assessments.

ISLA101 will be administered on Day 1 as described in Section 5.1.2. Meals and snacks will be provided at standard times throughout the confinement period in accordance with the site's usual procedures.

Vital signs, temperature, clinical laboratory testing and physical examinations will be performed.

Monitoring for TEAEs will begin as soon as the subject is dosed and continue for the last Follow-up Visit after the final dose of the study drug. Blood draws for PK sampling to assess the PK of ISLA101 will be performed.

The safety laboratory parameters for the confinement days (Day 1 to Day 5) are the same as at screening.

8.1.4 Early Termination/Safety Follow-up Visit

At follow up or at early withdrawal from any cohort, subjects will complete the Follow-up/ET visit. Vital signs and temperature will be measured, and clinical laboratory tests will be performed. A physical exam will be performed, and clinically significant abnormalities will be reviewed by the Investigator. For females, urine pregnancy test will be performed. A review of AEs and concomitant medications will be performed.

8.1.5 Unscheduled Assessments

If a subject reports any AE(s) that present cause for concern during the study, they may be asked to complete further assessments. Any other procedures necessary to monitor the AE may be performed at the Investigator's discretion.

8.2 Safety Assessments

This study is designed to assess the safety of ISLA101. Safety will be determined by evaluating physical examination findings, vital signs, clinical laboratory parameters, AEs, and TEAEs. Scheduled safety assessments will be performed at the time points shown in Table 1. If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator, or Sponsor representative.

Adverse events will be assessed as described in Section 9.

8.2.1 Vital Signs

Vital signs will consist of respiratory rate, heart rate, and semi-recumbent blood pressure. Subjects should be resting in a semi-recumbent position for at least 3 minutes prior to and during vital signs measurement. When the time of vital signs measurement coincides with a blood draw, the vital signs will be taken before the scheduled blood draw where possible while ensuring the blood draw is within the window specified in the protocol. Additional vital signs may be performed at other times if deemed necessary.

If temperature measurement is oral, subjects should not eat or drink hot or cold foods or beverages within 15 minutes of oral temperature measures. On dosing days, temperature will be taken prior to dosing.

8.2.2 Physical Examination

A complete physical examination includes evaluation of the following: General Appearance, Head, Ears, Eyes, Nose, Mouth, Throat, Neck (including thyroid and lymph nodes), Cardiovascular, Respiratory, Gastrointestinal, Renal, Neurological, Musculoskeletal, Skin, and Other. Symptom-directed physical examinations may also be performed at any time.

As clinical studies from IND38892 and from the published literature showed ocular toxicity following treatment with fenretinide (eye irritation, dryness of eyes, nyctalopia), an ophthalmologist will be available to evaluate all significant ocular complaints.

8.2.3 Clinical Laboratory Assessments

Standard clinical laboratory profiles for serum chemistry, hematology, and urinalysis will be evaluated. Specific laboratory tests to be performed at each study visit are described in Section 8.1.

All clinically significant laboratory abnormalities beginning with Day 1 must be recorded as an AE in the subject's source documents and on the appropriate CRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

Tests for hepatitis B surface antigen, hepatitis C virus antibodies, and HIV will be completed at screening to determine eligibility.

A UDS, an alcohol breath test, and a urine cotinine test or breath CO test will be performed at screening. An alcohol breath test and urine cotinine or breath CO test will be performed at Day -1.

8.2.4 Pregnancy

An FSH test will be performed at screening for all female subjects to confirm or refute postmenopausal status. A serum pregnancy test will be performed for all females at screening. Urine pregnancy tests will be performed at check-in and at follow-up for all females.

Due to teratogenic risks, all initial reports of pregnancy in female subjects or partners of male subjects must be reported to the Sponsor by the site personnel within 72 hours of their knowledge of the event.

If a female subject is suspected or known to become pregnant during the study, she should be discontinued from the study. If a female subject, or if a female partner of a male subject, becomes pregnant while enrolled in the study, information regarding the pregnancy should be submitted to the Sponsor or designee within 72 hours of the treating physician's/research personnel's awareness of the pregnancy. Every effort should be made to follow the pregnancy until completion or until pregnancy termination and, if applicable, the health of the child for 1 year post-birth.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the Investigator should follow the procedures for reporting SAEs described in Section 9.1.3.

8.2.5 Electrocardiogram

A 12-lead ECG will be performed at the screening visit, Day -1, and Day 1 for subjects in Cohorts 1-3, and again at the clinic check-in (Day 9) and Day 10 for subjects in the fed cohort (Cohort 4).

8.3 Pharmacokinetic Assessments

Blood samples will be collected to characterize the fasted and fed PK profiles of ISLA101, as described in Table 2.

Blood samples will be taken by fresh venipuncture or indwelling catheter; IV cannula may be utilized on days requiring intensive sampling.

The following is a listing of the PK plasma sampling times relative to the time of study drug administration, defined as the time at which the first capsule is consumed:

- At pre-dose (approximately 1 hour before study drug administration) and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours after dosing.

The total amount of blood sampled from a subject will be up to approximately 185 mL during the study. This will include 72 mL (18 total blood draws × 4 mL per blood draw) for PK assessments; approximately 25 mL for screening evaluations and 12.5 mL each for other laboratory evaluations (Days -1, 1, 2, 3, and 8); and approximately 25 mL for 2 repeat lab assessments (approximately 12.5 mL each), if needed. For subjects in Cohort 4 (the food effect cohort), additional 160 mL of blood will be collected, including samples for PK assessment, laboratory evaluation (Day 9, 10, 11, 12, and 17) and repeat lab assessments.

Plasma samples will be collected and processed as per the instructions developed by the bioanalytical laboratory and aliquoted into at least 2 separate tubes. The plasma samples (split into 2 different aliquots) from each subject will be shipped in 2 separate shipments to the selected bioanalytical laboratory for analysis. The second shipment will be sent after receipt in good condition of the first shipment. The address of the selected bioanalytical laboratory will be supplied to the clinical research organization for shipment of the samples.

9 ADVERSE EVENTS

The incidence and nature of any AEs, dose-limiting AEs, SAEs, vital sign changes, and laboratory abnormalities will be assessed on an ongoing basis by the SRC.

9.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition, regardless of whether it is considered casually related to the study treatment.

The term also covers laboratory findings or results of other diagnostic procedures which are considered clinically relevant. Vital signs or laboratory abnormalities that show shifts from baseline which the Investigator considers clinically significant must be reported as AEs if they are symptomatic, require either corrective treatment or consultation, and/or lead to study drug discontinuation.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which surgery is required may be an AE, if it occurs or is detected during the study period. Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was known before the subject signed the ICF. In these instances, the condition should be reported as medical history.

9.1.1.1 Reporting Adverse Events

All AEs, whether or not they are considered by the Investigator to be related to the study drug, must be recorded in the subject's source documents and in the electronic CRF. For each AE, the reported term, onset and end dates, severity, consequences on study drug intake (action taken), relationship to study drug, treatment provided, outcome, and information on seriousness of the event will be recorded.

The severity of the AE, relationship of the AE to study drug, and the outcome of the AE will be assessed by the Investigator.

Subjects will be monitored throughout the study for adverse reactions to the study drug and/or procedures. The subjects will be instructed to inform the study staff of any AEs that may occur at any time during the study. Observation of AEs extends from the time of ICF signing until the subject has left the study. Any AEs presenting within 30 days after the last scheduled visit will be followed up with a phone call or a visit until an outcome has been determined. After that time point, the need for additional follow-up of ongoing AEs or SAEs will be discussed between the Investigator and Sponsor.

9.1.2 Treatment-Emergent Adverse Events

A TEAE is defined as any event that was not present prior to the initiation of study treatment, or any event already present which worsens either in intensity or frequency following exposure to study treatment.

9.1.3 Serious Adverse Events

9.1.3.1 Definition

A SAE is an AE occurring during any study phase that fulfils one or more of the following:

- Results in death.
- Is immediately life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Is a medically important event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

In this context, "life-threatening" means that the subject is at immediate risk of death at the time of the SAE; it does not refer to an event that hypothetically might have caused death if it was more severe. "Hospitalization" is defined as inpatient care that covers more than one calendar day. "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions, compared to the person's ability prior to the study. Medical judgment should be exercised in deciding whether AEs may be considered serious because they jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. The list of critical terms (1998 adaptation of World Health Organization Adverse Reaction Terminology Critical Terms List) should be used as guidance for AEs that may be considered serious because they are medically important.

9.1.3.2 Reporting Serious Adverse Events

All SAEs, whether or not they are deemed drug-related or expected, must be reported to the Sponsor immediately (or within 72 hours) of becoming aware of the event. The Investigator must inform the site monitor, and if required by local regulations or procedures, the Investigator should report these events to the HREC and/or national regulatory authority. The Investigator must report all SAEs on the eCRF regardless of relationship to study drug. If the site experiences a temporary disruption of the eCRF system, a back-up paper SAE report form will be available for site staff to complete.

Any SAEs should be submitted to CRO's Pharmacovigilance & Safety Services to the email listed below. CRO's Pharmacovigilance & Safety Services should be supplied with the name of the Investigator and the name, title, and contact information (email and telephone) of person submitting the report.

safety@beyonddrugdev.com is the safety reporting email address for the CRO overseeing this study.

Site staff must enter the SAE information into the eCRF system as soon as the system becomes available. Should a back-up SAE form be used, the original SAE form should be kept at the study site.

Any additional follow-up including medically relevant follow-up information must be reported within the same timelines.

The SAE reports should include a detailed written report including all available data allowing the event to be documented and using only anonymized copies (with only the subject identification code: treatment number and initials) from hospitalization reports and additional examination(s). The Investigator should also report all elements concerning the follow-up of the SAE.

When reporting a death, the Investigator should supply any additional requested information such as autopsy reports (if available) and final medical reports.

The back-up SAE report form and the instructions on completion will be provided to the sites. The "Instructions for Completing the SAE Form" document provides detailed guidance on the reporting of SAEs, and AEs initially reported as non-serious which become serious.

The Sponsor will ensure compliance with all regulatory reporting requirements and notify the authorities, ethics committees, and Investigators as appropriate. All safety reporting responsibilities, timelines, and procedures will be described in detail in the Safety Management Plan.

9.1.4 Dose-limiting Adverse Events

Dose-limiting AEs are defined as clinically significant AEs or abnormal laboratory values that are Grade 3 or 4 in severity, based on toxicity grading scales as specified in FDA's Guidance for Industry and Investigators – Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

9.1.5 Adverse Events of Special Interest

The following signs of drug toxicity will be deemed to be of special interest and may be dose-limiting:

- Sustained respiratory depression that results in oxygen saturation below 92%.
- Seizure
- Protracted (> 1 hour) nausea and vomiting.
- Any AE deemed by the Investigator to be dose-limiting or ≥ Grade 3 in intensity.
- Clinical investigations indicating signs of drug-induced liver injury based on the following criteria from FDA guidance:

- Alanine aminotransferase (ALT) or aspartate transaminase (AST) > 8 x the upper limit of normal (ULN).
- ALT or AST > 5 x ULN for more than 2 weeks.
- ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN or international normalized ratio > 1.5).
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

- Any clinically significant findings of blood chemistry and hematology.

Depending on the severity of these and/or other AEs or the occurrence of more than 1 AE in the same subject, the subject(s) may be unblinded if it is deemed necessary for the treatment of AEs.

9.1.6 Severity

The severity (intensity) of each AE must be assessed according to the following classification:

- Mild: does not interfere with routine activities.
- Moderate: interferes with routine activities.
- Severe: subject is unable to perform routine activities.

9.1.7 Relationship

The relationship of any AE to the study drug must be assessed, according to the following rating, by the clinician who examines and evaluates the subject based on temporal relationship and clinical judgment:

- Definitely: The AE is clearly related to the study drug.
- Probably: The AE is likely related to the study drug.
- Possibly: The AE may be related to study drug.
- Unlikely: The AE is doubtfully related to study drug.
- Unrelated: The AE is clearly not related to the study drug.

9.1.8 Outcome

The outcome of each AE may be classified as resolved (spontaneously or with treatment) or unresolved.

Any subject who experiences an AE (whether serious or non-serious) or has a clinically significant abnormal laboratory test values will be evaluated by the Investigator or a monitoring physician and will be treated and/or followed up until the symptoms or values return to normal, or acceptable levels, as judged by the Investigator. Where appropriate, medical tests and/or examination) will be performed to document resolution of events.

9.1.9 Expectedness

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (as described in the Investigator's Brochure for ISLA101).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The Sponsor and/or CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and HREC within 7 days after the Sponsor becomes aware of the event. Relevant follow-up information will subsequently be communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and HREC within 15 days after the Sponsor becomes aware of the event. All Investigators should follow SUSARs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Suspected unexpected serious adverse reactions that occur after the subject has withdrawn from the clinical study must be reported by the Investigator to the Sponsor.

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

A statistical analysis plan (SAP) describing all statistical analyses will be provided as a separate document prior to data lock-out.

Descriptive statistics will be used to provide an overview of the safety results. For categorical parameters, the number and percentage of subjects will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation, median, minimum, and maximum. No imputations will be made for missing data.

A brief outline of planned statistical analyses is presented below.

10.2 Determination of Sample Size

No formal sample size calculation was performed. The study is considered exploratory with a sample size of 8 subjects per cohort (2 placebo + 6 active). This cohort size and active/placebo ratio are considered standard to evaluate safety profile and to provide sufficient PK information for future development of the compound.

10.3 Analysis Populations

In fasted and fed cohorts, 2 analysis populations will be used to summarize the results from this study:

Safety Population: All subjects who receive at least 1 dose of study drug (active and placebo). Safety analyses will be based on the safety population.

PK Population: All subjects in the Safety Population who have a pre-dose PK sample and at least 1 post-dose analyzable PK sample.

Subjects who received planned doses of ISLA101 will be included in the PK evaluation and statistical comparisons, based on availability of sufficient PK profiles. Actual treatments will be used for all analyses.

All subjects who receive at least one dose of the study drug (placebo or active) will be included in the safety analyses.

10.4 Disposition and Demographics

Subject disposition will be summarized and will include all subjects who have received one dose of study drug in the safety population, subjects in the PK population, and number and percent of subjects who complete or prematurely discontinue from the study along with reason for discontinuation. Demographic data will be summarized using descriptive statistics for all subjects who were randomized in this study and took at least 1 dose of study drug.

10.5 Safety Analysis

All safety data from the study will be listed by subject, dose, and cohort. Changes in safety assessments from screening to post-dose measurements will be assessed using summary statistics (mean, minimum, maximum, standard deviation, and corresponding sample size [N] for continuous variables, and frequency of category shifts from screening to post-study for discrete variables) for each part/cohort. Additionally, summary statistics for vital signs (blood pressure, pulse, pulse oximetry, and respiratory rate) and oral temperature will be reported.

Adverse events will be coded using the toxicity grading scale tables as specified in Guidance for Industry and Investigators – Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials and Medical Dictionary for Regulatory Activities terminology. The AEs will be summarized by dose and visit and overall. The AEs will be tabulated and summarized by body system, preferred term, severity, frequency, and relationship to study drug. A listing of SAEs will be provided.

Change from screening in clinical laboratory parameters and vital sign parameters will be summarized by visit and overall. Shift tables for key safety parameters including clinical lab investigations will be presented. Frequency descriptors for the safety analyses will be reported as needed.

10.6 PK Analysis

Descriptive statistics for PK concentrations and parameters will consist of number of subjects (n), arithmetic mean, standard deviation (SD), geometric mean, geometric coefficient of variation (%), median, minimum, and maximum. For T_{max} and $T_{1/2}$, only n, median, minimum, and maximum will be presented.

This study will perform PK analysis using validated software, such as Phoenix® WinNonlin® version 8.0 or higher. Pharmacokinetic parameters will be calculated through noncompartmental analysis of fenretinide and its metabolites MPR and oxo-HPR, including C_{max}, AUC_{last}, AUC_{inf}, T_{max}, $T_{½}$, Cl/F, and V/F on the day of dosing. Other relevant parameters will also be estimated.

Dose proportionality for fenretinide exposure parameters (C_{max}, AUC_{last}, and AUC_{inf}) will be assessed statistically based on the natural log (ln)-transformed PK parameters. Proportionality analysis will be done using a Power Model defined as:

$$\ln(\text{PK parameter}) = \alpha + \beta \bullet \ln(\text{Dose}) + \varepsilon$$

where α is the intercept, β is the slope, and ε is the error term. A linear model with ln-transformed dose as a continuous effect will be fitted. A point estimate and a 90% CI will be derived for the slope (β), measure of the proportionality between the dose and the PK parameter. Evidence of dose proportionality for each PK parameter evaluated will be assessed by the 90% CI of each slope.

Appropriate dose-normalized PK parameters will also be assessed graphically for dose proportionality.

An ANOVA will be conducted on ln-transformed PK parameters, including AUC_{last}, AUC_{inf}, and C_{max} to evaluate the effect of food on fenretinide in the recalled cohort (Cohort 4 vs Cohort 3). The study will calculate the differences between adjusted means and the standard error associated with these differences. The ratio of means will be calculated using the LSM for ln-transformed AUC_{last}, AUC_{inf}, and C_{max} values. The 90% confidence interval (CI) for the difference between the fed and fasted conditions will be calculated for AUC_{last}, AUC_{inf}, and C_{max} using ln-transformed concentration data. The CI will be expressed as a percentage relative to the LSM.

11 QUALITY CONTROL AND ASSURANCE

Each clinical site will be responsible for internal quality management of study conduct, data and biological specimen collection, documentation, and completion based on their internal processes.

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database to generate queries to the site(s) where applicable. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures and the Clinical Monitoring Plan, the monitors will verify that the clinical trial is conducted, that data are generated, documented (recorded), and reported, and that biological specimens are collected in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices and GMP).

The investigational site will provide direct access to all study-related locations, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor and inspection by local and regulatory authorities.

12 REGULATORY AND ETHICAL CONSIDERATIONS

12.1 Institutional Review Board or Independent Ethics Committee Approval

The protocol, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an HREC by the Investigator and be reviewed and approved by the HREC before the study is initiated.

Any amendments to the protocol will require HREC approval before implementation of changes made to the study design.

The Investigator will provide written summaries of the status of the study to the HREC annually or more frequently in accordance with the requirements, policies, and procedures established by the HREC. The Investigator will also notify the HREC of SAEs or other significant safety findings as required by HREC procedures.

12.2 Ethical Conduct of the Study

This study will be conducted in accordance with the protocol and with the following:

- current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) National Health and Medical Research Council National Statement on Ethical Conduct in Human Research 2007 (updated 2018).
- International Council for Harmonisation (ICH) Integrated Addendum to E6(R1): Guideline for Good Clinical Practice (GCP) ICH E6(R2), annotated with comments by the Australian Therapeutic Goods Administration (2018).
- Applicable laws and regulations.

12.3 Subject Information and Consent

Consent forms that describe the study drug, study procedures, and risks will be given to each potential subject and the nature and purpose of the study shall be fully explained. Written documentation of informed consent must be obtained from each subject prior to any study procedures being performed.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be approved by the HREC, and the subject will be asked to read and review the document. Consent forms must be in a language fully comprehensible to the prospective subject. The Investigator (or designee as per local regulation) will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects.

Subjects will have the opportunity to carefully review the written ICF and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or

surrogates or think about it prior to agreeing to participate. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subject for their records.

The informed consent process will be conducted and documented in the subject's medical records (including the date), as required by the ICH Integrated Addendum to ICH E6(R1): Guideline for GCP E6(R2), as adopted by the Australian Therapeutic Goods Administration (TGA), and the NHMRC National Statement on Ethical Conduct in Human Research.. Electronic media may be used to replace paper-based informed consent processes (electronic informed consent), utilizing electronic signatures. An electronic informed consent may be used to provide the same information that is contained within the written informed consent document, evaluate the subject's comprehension of the information presented, and document the consent of the subject. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The informed consent form should be updated or amended whenever new important information that may be relevant to the subject becomes available. Modifications must be approved by the Sponsor and by the HREC before being implemented.

12.4 Subject Confidentiality

Subject confidentiality and privacy are strictly held in trust by the participating Investigators, their staff, and the Sponsor. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the HREC, or regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as is dictated by the reviewing HREC, institutional policies, regulatory authorities, or Sponsor requirements.

Subject research data for purposes of statistical analysis and scientific reporting will be transmitted to and stored in the IBM Clinical Development database. A subject's contact or identifying information will not be included.

13 ADMINSTRATIVE CONSIDERATIONS

13.1 Clinical Study Research Agreement

Agreements will be initiated between the Sponsor, Investigator(s), applicable CROs, and any other relevant parties involved in conducting the study to delineate key responsibilities.

The Sponsor is obligated to conduct the study in accordance with strict ethical principles. The Sponsor agrees to provide the Investigator with sufficient material and support to permit the Investigator to conduct the study according to the study protocol.

The Investigator is obligated to read the protocol carefully, fully understand the study requirements, and to conduct the study in accordance with the protocol. Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the study drug, and their specific duties within the context of the study. Investigators are responsible for providing the Sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the Sponsor and the relevant governing authorities.

13.2 Case Report Forms and Study Records

The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF. CRFs are considered confidential documents and should be handled and stored accordingly. The Sponsor or its designee will provide the necessary training on the use of the specific eCRF used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the eCRF according to the completion guidelines provided by the Sponsor or its designee. The eCRFs must be signed by the Investigator or a sub-Investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

Information recorded in the eCRF should be supported by corresponding source documentation. Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained.

13.3 Protocol Violations/Deviations

A protocol deviation is any noncompliance with the clinical trial protocol and associated documents. The noncompliance may be on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

No deviation from the protocol or investigational plan will be made except to protect the life or physical well-being of a subject in an emergency situation. Except in such emergencies, prior approval of the Sponsor, and the regulatory authorities or the HREC, is required before deviating from the protocol. All protocol deviations that occur during the study will be

documented in the eCRF and reported to the Sponsor and to the HREC if applicable, according to regulations. The site Investigator is responsible for knowing and adhering to the reviewing HREC requirements. Further details about the documentation, evaluation, and follow-up of protocol deviations will be detailed in this study's Clinical Monitoring Plan.

13.4 Access to Source Documentation

Source documents provide evidence for the subject's experience in the study and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. A definition of what constitutes source data will be found in the Clinical Monitoring Plan.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, paper diaries, electronic diaries, video recordings, microfiches, radiographs, angiograms, study medication accountability logs, and correspondence. Case report form entries may be considered source data if the eCRF is the repository of the original recording (i.e., there is no other written or electronic record of data). In this case, a source document agreement should indicate which eCRFs are considered source documents for the study. The Investigator may also need to request previous medical records or transfer records to obtain source documents.

Monitors, auditors, and other authorized representatives of the Sponsor, the HREC, and health authorities may be granted access to source documentation as appropriate an in accordance with all applicable laws. Specifically, the study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for HREC or regulatory authorities according to GCP guidelines. The Investigator agrees to cooperate with any audits and to supply the auditor with eCRFs or other files necessary to conduct the audit. Any findings will be strictly confidential.

If a regulatory authority informs the Investigator that it intends to conduct an inspection, the Investigator shall notify the Sponsor immediately.

13.5 Data Generation and Analysis

Clinical data (including AEs and concomitant medications) and clinical laboratory data will be entered into an EDC system that complies with regional and national regulatory standards. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

The Investigator, or designated representative, will be trained on the EDC prior to receiving access. Each user will have a unique password to enter or review data. According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. A source data location list will be prepared and updated during the study. This list will be filed in both the trial master file and the Investigator study file.

Additional information related to eCRF completion is provided in Section 13.2.

13.6 Retention of Data

The Investigator must maintain confidentiality for all study documentation and take measures to prevent accidental or premature destruction of these documents.

All primary data that are a result of the original observations and activities of the study that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period of not less than15 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 15 years have lapsed since the formal discontinuation of the clinical development of the study drug.

The site will maintain a Clinical Study Document Binder, which will be maintained at the study site. In this binder, there will be tabbed sections for study documents including the following: study personnel identification and signature list, subject screening records, subject roster (names omitted), protocol and amendments or administrative changes, study staff Curricula Vitae, HREC documentation, an approved sample ICF, drug accountability records, correspondence, site monitoring reports, blank Data Documentation form, lab accreditations, and normal values. The site must keep this binder current and available for review or audit by the Sponsor, HREC and/or regulatory authority.

13.7 Study and Site Closure

The Sponsor reserves the right to terminate the study but intends to only exercise this right for valid scientific or administrative reasons or reasons related to the protection of subjects. Possible reasons for the study termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue the development of the study drug.
- A request by a relevant regulatory agency.

Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor to study subjects, Investigators, and regulatory authorities. If the study is prematurely terminated or suspended, the Sponsor, or designee, will inform the Investigator and will provide the reason(s) for the termination or suspension. The Investigator will then promptly inform the subjects and the HREC. Subjects will be contacted, as applicable, and will be informed of changes to the study visit schedule including a possible “end of study visit.”

If the study is put on hold, the study may resume once any relevant concerns about safety, protocol compliance, and data quality are addressed, and the resolution satisfies the Sponsor, HREC, and relevant regulatory authorities.

13.8 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study. Details of financial disclosure responsibilities will be provided in a separate agreement between the Investigator and the Sponsor.

13.9 Conflict of Interest

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest for persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.10 Publication and Disclosure Policy

The designated CRO will be responsible for conducting the statistical analysis and for preparing a CSR. The Sponsor must provide a summary of study results to the Investigator.

The Sponsor may publish the results at the end of the study in an international journal on behalf of the study group, including the Investigator site.

The communication or publication of all or part of the results of this study, including ancillary studies, will be only permitted after receiving written agreement from the Sponsor. Any manuscript or presentation should be submitted to the Sponsor at least 30 days before submission for review and approval. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, to allow for filing of a patent application or other measures that the Sponsor deems appropriate to establish and preserve its proprietary rights. The Sponsor has the right at any time to publish the results of the study.

14 REFERENCE LIST

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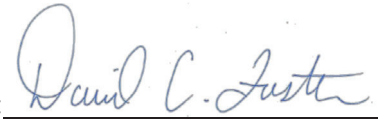
15 APPENDICES

Appendix 1 Sponsor Signatures

Study Title:	A Phase 1a, randomized, double-blind placebo-controlled study to evaluate safety and tolerability and to characterize the pharmacokinetic profile of single ascending doses of fenretinide oral capsules in healthy adult volunteers
Study Number:	ISLA101-P01-CT001
Final Date:	18 October 2023 Ver 2.0

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:  Date: 20 November 2023

David C. Foster, PhD, JD
Chief Executive Officer
Island Pharmaceuticals Ltd

Appendix 2 Investigator's Signature

Study Title:	A Phase 1a, randomized, double-blind placebo-controlled study to evaluate safety and tolerability and to characterize the pharmacokinetic profile of single ascending doses of fenretinide oral capsules in healthy adult volunteers
Study Number:	ISLA101-P01-CT001
Final Date:	18 October 2023 Ver 2.0

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Dr Chrisopher Argent
Principal Investigator
Scientia Clinical Research Pty Ltd