

COVER PAGE

Study Title: A Phase 1b Study of OPT101 in Patients with Type 1 Diabetes

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CLINICAL STUDY PROTOCOL A Phase 1b Study of OPT101 in Patients with Type 1 Diabetes	
Development Phase:	1b
Investigational Product:	OPT101
Indication:	Type 1 Diabetes
Sponsor:	Op-T LLC 12635 East Montview Blvd., Ste 142 Aurora, CO 80045
Medical Monitor:	Martin Yussman, MD
Principal Investigator(s):	TBD
IND Number:	IND No. 144053
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Statement of Compliance

This study will be conducted in accordance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR) and/or as applicable local regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor, funding agency and documented approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the study. All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether a new consent needs to be obtained from subject who provided consent, using a previously approved consent form.

PROTOCOL SYNOPSIS

Title	A Phase 1b Study of OPT101 in Patients with Type 1 Diabetes
Study Phase	1b
IND Number	IND No. 144053
Investigational Product	OPT101
Active Ingredient Drug	15-mer peptide with sequence based on the CD154 domain interacting with CD40
Storage/Conditions	Frozen at -65 to -85° C; shipped on dry ice.
Indications	Type 1 Diabetes
Objectives and Endpoints: Primary Objectives: - To assess the safety and tolerability of multiple ascending doses of OPT101 in Type 1 Diabetes patients (≥ 18 years of age) Primary Endpoints: - Rate and type of adverse events after infusion of OPT101 or placebo - Change in vital signs after infusion of OPT101 or placebo - Change in plasma histamine levels shortly after infusion of OPT101 or placebo - Change in laboratory clinical chemistry, hematology and coagulation variables after infusion of OPT101 or placebo - Development of antidrug antibodies after infusions of OPT101 or placebo - Definition of maximum tolerated repeated dose of OPT101 Secondary Objectives: - To assess the pharmacokinetics (PK) of OPT101 - To assess the pharmacodynamic (immunologic) effects of OPT101 - To assess the clinical activity of multiple ascending doses of OPT101 Secondary Endpoints: - Determination of PK parameters (AUC_{0-t}, C_{max}, CL/F, t_{1/2}) - Change in immunological variables after multiple infusions of OPT101 or placebo - Change in HbA_{1c} - Change in daily insulin use - Change in C-peptide - Change in fasting plasma glucose - Change in urine glucose	

Subject Eligibility Criteria

Inclusion Criteria:

1. Able and willing to give informed consent for the trial.
2. Male or female aged ≥ 18 years on the day of signing informed consent.
3. Diagnosis of Type 1 diabetes (T1D) within the last 20 years.
4. Is medically stable based on physical examination, medical history, laboratory results, and vital signs performed at screening.
5. Women of childbearing potential must have a negative highly sensitive serum test (beta-human chorionic gonadotropin) at screening and a negative urine pregnancy test at the Visit 1 Day 1 prior to receiving the investigational product.
6. Women must agree to use one of the following methods of birth control for the duration of the clinical trial: systemic hormonal contraceptive (oral, injected, transdermal), intrauterine device, double barrier (e.g., cervical cap or diaphragm with condom or spermicide). Men with female partners must agree to use double barrier contraception, unless their partner is using systemic hormonal contraceptives or has an intrauterine device.

Exclusion Criteria:

1. Is over the age of 60 years old.
2. Current malignancy or history of malignancy.
3. Has an immune deficiency syndrome (for example, severe combined immunodeficiency syndrome, T-cell deficiency syndromes, B-cell deficiency syndromes, or chronic granulomatous disease), or bone marrow or organ transplantation, or a disease associated with lymphopenia.
4. Is currently receiving an immuno-modulatory treatment.
5. Patients with a history of venous and arterial thromboembolic events including, but not limited to, the following: Deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, transient ischemic attack, or arterial insufficiency causing digital gangrene should be excluded. In addition, patients with recent immobilization or recent surgery, should be excluded. Patients with a history of abnormal prothrombotic laboratories such as congenital or inherited deficiency of antithrombin III, protein C, protein S, or confirmed diagnosis of antiphospholipid syndrome are also excluded.
6. Has an active infection, is prone to infections or has chronic, recurrent or opportunistic infectious disease, including but not limited to: Epstein-Barr virus (EBV), cytomegalovirus (CMV) chronic renal infection, chronic chest infection, sinusitis, recurrent urinary tract infection, *Pneumocystis carinii* pneumonia, aspergillosis, latent or active granulomatous infection, histoplasmosis, coccidioidomycosis, or an open, draining, or infected non-healing skin wound or ulcer.
7. Has recent or active hepatitis A infection, current/chronic hepatitis B and hepatitis C infection, or HIV infection. Participants with immunity to hepatitis B from previous infection (defined as negative HBsAg, positive anti-HBc, and positive hepatitis B surface antibody [anti-HBs]) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) may be eligible to participate.
8. Has a history of latent or active TB.
9. Has received a live (attenuated) vaccine within the last 60 days, including patients who plan to receive live (attenuated) vaccines during the study or within 60 days after the final dose of

study treatment.

10. Patients with clinically significant abnormal laboratory test values in screening blood samples. In particular patients with the following should be excluded:
 - i. Patients with abnormal coagulation panel at screening such as abnormal PT or aPTT or fibrinogen
 - ii. Abnormal liver function tests:
 1. Liver enzyme abnormalities (except in the case of known Gilbert's syndrome)
 2. AST or ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN
 3. AST or ALT ≥ 5 x ULN
 4. AST or ALT ≥ 3 x ULN if associated with appearance or worsening of rash or hepatitis symptoms
 - iii. Abnormal platelet counts ($<150,000/\text{mcL}$ or $> 450,000/\text{mcL}$)
 - iv. Abnormal white blood cell counts ($<3\text{mL}$ or $> 11\text{mL}$)
 - v. Abnormal eGFR ($<50\text{mg/dL}$ or $>1.10\text{mg/dL}$)
 - vi. Abnormal Factor VIII ($> 160\%$)
 - vii. Abnormal D-Dimer ($\geq 500\text{ng/mL FEU}$)
11. Patients planning to undergo elective procedures or surgeries at any time after signing the ICF through the follow-up visit.
12. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
13. Recent history of bleeding or bleeding disorders or any condition whereby in the opinion of the treating investigator giving anti-coagulation during treatment would be contraindicated.
14. History of hypersensitivity to antihistamines.
15. Weight is over 250lbs.
16. Patients with active drug or alcohol abuse within one year prior to screening or patients who test positive for required drug testing during screening.
17. Patient is participating in a clinical trial of another investigational drug or device, including patients who have participated in another study for a duration of 5 half-lives of the investigational agent.
18. Patient is a prisoner.
19. Patients with any medical condition, including, but not limited to, cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal, or a psychiatric condition that, in the opinion of the Investigator, could compromise the participant's ability to participate in this study.

Study Rationale

In mice and humans, elevated Th40 cell levels pre-date hyperglycemia onset and more importantly appear to be causal in diabetes pathogenesis. OPT101 has been shown in the non-obese diabetic (NOD) mouse model of T1D to be able to prevent onset of diabetes and to reverse hyperglycemia in most newly diabetic NOD mice. OPT101 may therefore be able to halt the progression or potentially reverse T1D in man in the early stages of the disease.

Potential safety issues with OPT101 have been evaluated in rat and dog non-GLP dose-range-finding studies, and rat and dog IV repeat-dose 8-week GLP studies. When OPT101 was given by slow IV infusion over 30 minutes, once weekly for 8 weeks,

These overall conclusions support further development of OPT101. Refer to the most recent Investigators Brochure (IB).

The study will be performed in T1D patients 18 years or older rather than healthy subjects as the immunological effects of OPT101 can be best evaluated in a population with elevated levels of pathologic CD40 cells, and the risk/benefit ratio is more appropriate.

Study Design

This is a Phase 1b, randomized, multicenter, placebo-controlled, double blinded study that will be conducted as a multiple ascending doses (MAD) study to measure safety, the immunological, and the clinical effects of 1.1 and 2.8 mg/kg doses of OPT101 that were found to be safe in the OPT-100-30 (IND 150941) Phase 1a study performed in healthy volunteers.

OPT101/placebo will be administered by a slow IV infusion over 30 minutes.

Phase 1b: Safety, pharmacokinetics, immunological and clinical effects of multiple-ascending doses (MAD) of OPT101

A total of 8 IV treatments with 1.1 and 2.8 mg/kg doses of OPT101 or placebo, will be administered to a total of 18 subjects, 9 per cohort (6 active:3 placebo) on Days 1, 4, 7, and 14 and then weekly (Days 21, 28, 35, and 42), for a total of 6-weeks. Every subject will be monitored for 8 hours on Day 1 (visit 1) and Day 42 (visit 8) post treatment for safety, but also to allow for PK samples to be collected. For visits 2 through 7, subjects will be monitored up to 2 hours post infusion prior to discharge. Safety data from the lower dose cohort will be reviewed by the Safety Review Committee (SRC) before subjects are enrolled in the higher dose cohort. Safety, tolerability, PK, immunological, and clinical effects will be assessed.

Subjects will be followed for safety, anti-drug antibodies, immunological, and clinical assessments for 14 days after the last (Day 42) treatment. For Cohort 2 subjects an additional 30 day follow up (Day 86) for a ferritin assessment will be required (End of Study). Subjects experiencing immunological and/or clinical effects may be followed for longer, until the immunological or clinical variable returns to normal levels.

Number of Sites and Subjects

18 subjects will be enrolled at up to five sites.

Estimated Treatment Duration

90 days

Study Drug Dosage, and Mode of Administration

Investigational Product:

- OPT101, 1.1 and 2.8 mg/kg doses. USP sterile solution, *or*
- 50 mL of normal saline, USP sterile solution (placebo)

for intravenous (IV) infusion.

Safety Review Committee

A Safety Review Committee (SRC) consisting of clinicians with expertise in relevant clinical specialties for the study, the medical monitor and the Sponsor will provide oversight. The SRC will

review relevant safety data and make recommendations regarding

Schedule of Visits

Subjects will undergo screening procedures during a Screening Visit to determine study eligibility. A subject and must be asymptomatic at the time of enrollment. Subjects enrolled in the study will be randomized and receive the investigational product or placebo at Visit 1. Subjects will remain at Phase 1 unit for 8 hours for evaluation and will need to be onsite for the required study procedures.

Subjects will return for 7 treatment visits (Visit 2 through 8), 1 follow up visit (Visit 9) and an additional follow up/End of Study (Visit 10) for a total of 10 scheduled visits.

See [Schedule of Procedures and Assessments, Phase 1b](#) at the end of this synopsis for detailed information on individual visit procedures and assessments.

SCHEDULE OF PROCEDURES AND ASSESSMENTS: PHASE 1B

	Visit 0 Screening	Visit 1 Randomization and 1 st Infusion	Visit 2 2 nd Infusion	Visit 3 ¹⁸ 3 rd Infusion	Visit 4 4 th Infusion	Visit 5 5 th Infusion	Visit 6 6 th Infusion	Visit 7 7 th Infusion	Visit 8 8 th Infusion	Visit 9 ² Follow up / Early Termination	Visit 10/ Follow up / End of Study	Unscheduled Visit
Study Day(s)¹⁷	-28 to 0	1	4	7+1¹⁸	14 ±3	21 ±3	28 ±3	35 ±3	42 ±3	56 ±3	86 ±3	
Informed consent	X											
Inclusion and exclusion criteria	X	X										
Record demographics, medical history and medication history including T1D onset and history	X											
Urine drug screen (required drug testing)	X											
Total Iron and TIBC ²⁰	X											
Urine dipstick analysis	X	X	X	X	X	X	X	X	X	X		X
Serum pregnancy test	X											
Urine pregnancy test		X								X		
Mixed Meal Tolerance Test	X									X		
Physical examination including height, weight ³ , vital signs ⁴ and body temperature	X	X	X	X	X	X	X	X	X	X		X
Safety laboratory blood ⁵	X	X	X	X	X	X	X	X	X	X		
12-lead ECG ⁶	X	X	X	X	X	X	X	X	X	X		
Randomization via IWRS ⁷		X										

SCHEDULE OF PROCEDURES AND ASSESSMENTS: PHASE 1B (continued)

	Visit 0 Screening	Visit 1 Randomization and 1 st Infusion	Visit 2 2 nd Infusion	Visit 3 ¹⁸ 3 rd Infusion	Visit 4 4 th Infusion	Visit 5 5 th Infusion	Visit 6 6 th Infusion	Visit 7 7 th Infusion	Visit 8 8 th Infusion	Visit 9 ² Follow up / Early Termination	Visit 10/ Follow up / End of Study	Unscheduled Visit
Study Day(s) ¹⁷	-28 to 0	1	4	7+1	14 ±3	21 ±3	28 ±3	35 ±3	42 ±3	56 ± 3	86 ±3	
Investigational product or placebo administration ⁸		X	X	X	X	X	X	X	X			
HbA1c, C-Peptide ⁹	X									X		
Cytokine Measurements ¹¹		X								X		
Research Samples ¹²	X				X				X	X		
ADA blood sample ¹³		X								X		
Lipid panel ¹⁹		X								X		
Glucose ¹⁴ aPTT, PT, INR		X	X	X	X	X	X	X	X	X		X
Subject phone call ²¹			X									
Record Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Record daily insulin dose ¹⁵	X	X	X	X	X	X	X	X	X	X		X
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X

1. All subjects will be monitored for at least 8 hours post treatment at the first visit/treatment (Day 1) and for visit 8 (Day 42).
2. Physical exam at screening, brief or targeted exams thereafter. Height only at screening. Weight recorded at every visit.
3. Comprehensive metabolic panel, hematology and coagulation tests (D-dimer, Factor VIII, Ferritin, Fibrinogen, Von Willebrand Factor) as outlined in [Section 6.2.1](#). Testing for HIV, Hepatitis B and Hepatitis C will be performed and fasting plasma glucose at screening only.
4. ECG will be performed at screening, after IP infusions (30 minutes after end of infusion) and Day 56.
5. Subjects will be randomized to OPT101 or placebo within each dosing group in a 2:1 ratio. Safety data for the first dose group will be reviewed by the SRC before the first patient at the next dose level is treated.
6. The investigational product will be administered as a slow gravity fed infusion.
7. HbA1c and glucose pulled pre MMTT, C-peptide and glucose pulled post MMTT (2 hours)
8. Research samples (blood) will be pulled for CD40 measurements at screening, day 14, day 42 and day 56 (EOS)
9. Serum anti-drug antibody samples are to be collected pre-dose Day 1 and pre-dose on Day 56.

10. Subjects will be required to complete a daily insulin dose log and submit to site at each study visit. Subjects with CGMs should have a report downloaded at the EOS for the study period, deidentified (only use study and subject ID), and provided to sponsor in lieu of daily insulin dose log.
11. Patients must not receive 2 infusions within 72 hours of each other. If an infusion is missed, document the missed infusion as a protocol deviation and keep subjects on schedule.
12. +1 day Window for Visit 3 (day 7) will be allowed for some flexibility.
13. Low- and high-density lipids, cholesterol, triglycerides; total cholesterol, collected pre-infusion on Visit 1 and at EOS (Visit 9) only .
14. Total Iron and Total Iron Binding Capacity collected at screening only.

SCHEDULE OF PROCEDURES AND ASSESSMENTS: PHASE 1B INFUSION DAY ONLY

PRIOR TO INFUSION (All samples should be drawn/assessed within ± 2 minutes of required time)	
Blood collection	Comprehensive metabolic panel, Complete blood count with differential, PK*, Cytokines, Research Samples (CD40)**, Anti-drug antibodies**, Fibrinogen, D-Dimer, Von Willebrand Factor, Ferritin, Factor VIII, Lipid panel**
Vital signs / Body temperature / Weight Cardiac monitor (continuous) – for 8 hours on Day 1 and 1 hour post infusion for all other visits	
Urine pregnancy test Urine dipstick analysis: Glucose, Bilirubin, Ketone, Specific Gravity, Blood, pH, Protein, Urobilinogen, Nitrite, and Leukocytes	
Physical Exam	

** Samples not required at every visit. Please reference [SCHEDULE OF PROCEDURES AND ASSESSMENTS: PHASE 1B](#)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
aPTT	activated partial thromboplastin time
AST	aspartate transaminase (SGOT)
AUC _{0-t}	area under the curve from zero up to time t
ATC	Anatomical Therapeutic Chemical
BUN	blood urea nitrogen
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C _{max}	maximum observed serum drug concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CTCAE	Common Terminology Criteria for Adverse Events
CRO	contract research organization
DLT	dose-limiting toxicity
DRF	dose range finding
ECG	Electrocardiogram
ECL	electro-chemi-luminescent
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylene diamine tetra-acetic acid
EOI	End of Infusion
FDA	Food and Drug Administration
FOB	functional observational battery
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
fGLP	good laboratory practice

GM-CSF	granulocyte-macrophage colony-stimulating factor
HBV	Hepatitis Virus B
HCV	Hepatitis Virus C
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICR	Institute of Cancer Research
ID	Identification
IEC	independent ethics committee
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
INR	International Normalized Ratio
IP	investigational product
IRB	institutional review board
IV	Intravenous
KGYT	lysine glycine tyrosine tyrosine
KGYT15	another designation for OPT101
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAD	Multiple ascending dose
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCP-1	monocyte chemoattractant protein-1
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MPV	Mean Platelet Volume
MRI	magnetic resonance imaging
MSD	Meso Scale Discovery®
msec	Millisecond
MTD	maximum tolerated dose

n	number of subjects with an observation
N	number of subjects in the dataset or population
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NOD	non-obese diabetic
PDF	Portable Document Format
PK	Pharmacokinetic
PT	preferred term
QTcF	Corrected QT interval using Fridericia
RBC	red blood cell
TNF- α	tumor necrosis factor- α
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SD	standard deviation
SOC	system organ class
SOI	Start of Infusion
SOP	standard operating procedure
SRC	Safety Review Committee
T1D	Type 1 diabetes mellitus
TCR	tissue cross-reactivity
TEAE	treatment-emergent adverse event
TK	Toxicokinetics
TNF	tumor necrosis factor
US	United States
WBC	white blood cell
WOCBP	women of childbearing potential

1 INTRODUCTION

1.1 Background to the Disease

Type 1 diabetes mellitus (T1D) is a chronic disease of carbohydrate, fat, and protein metabolism caused by the lack of insulin. A 2011 report from the United States Centers for Disease Control and Prevention (CDC) estimated that approximately 1 million Americans have T1D. It is the most common metabolic disease of childhood. About 1 in every 400-600 children and adolescents has T1D. In adults, T1D constitutes approximately 5% of all diagnosed cases of diabetes. A study by [Mayer-Davis et al \(2017\)](#) indicated that between 2002 and 2012, the incidence of T1D showed a significant rise among youths in the United States. According to the report, after the figures were adjusted for age, sex, and race or ethnic group, the incidence of T1D (in patients aged 0-19 years) during this period underwent a relative annual increase of 1.8%, with the greatest increase occurred among minority youths.

T1D is associated with a high morbidity and premature mortality that are related to short- and long-term complications, including hypoglycemia from management errors and increased risk of infections. Microvascular complications (e.g., retinopathy and nephropathy), neuropathic complications, or macrovascular disease. There are currently no approved treatments for T1D that address the underlying pathology of the disease or that can reverse the islet inflammation or slow its progression. Treatment consists of life-long, invasive, and intensive maintenance of blood glucose levels by injection of exogenous insulin, careful monitoring of diet, and aggressive treatment of concurrent hypertension and hyperlipidemia.

Autoimmune destruction of the insulin-producing pancreatic islet β -cells by infiltration of immune cells results in the gradual loss of insulin secretion. A unique cluster of differentiation (CD)4⁺ T cell subset that expresses CD40 receptors (Th40) is found in high numbers in non-obese diabetic (NOD) mice, a mouse strain that spontaneously develops T1D. The interaction of CD40 with its ligand, CD154, is a critical component of inflammation in many autoimmune diseases including T1D.

There have been multiple attempts over the years to control the CD40-mediated inflammatory pathways during autoimmunity. Initial attempts were to use monoclonal antibodies; to block or interrupt CD40 interaction with its ligand, CD154. When CD40 and CD154 interact, the outcomes include a series of inflammatory events, e.g., production of inflammatory cytokines including interferon (IFN) γ , tumor necrosis factor (TNF) α , granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-6, IL-1 β , and IL-17. In addition, reactive oxygen intermediates that cause direct tissue damage are produced. Antibodies against CD40 did not work because all the available antibodies, 14 for mice and 8 for human, were agonistic; that is, they stimulated a CD40 inflammatory response and thus exacerbated disease. The next approach was antibodies directed to CD154. Anti-CD154 treatment improved disease status substantially in almost all animal models of autoimmune disease including T1D. The anti-CD154 approach was advanced to human trial where initial success was seen in lupus erythematosus, but eventually problems arose. The antibody had an unanticipated effect of binding to platelets and causing emboli, thus the trials were halted ([Kalunian 2002](#)). Another approach was the development of synthetic small molecules, which did not provide necessary protection when tested in animal models.

1.2 Investigational Product

The investigational product, OPT101, is a 15-mer peptide derived from the sequence of mouse CD154, which is 87% identical to human sequences and contains the highly conserved binding KGYT (lysine glycine tyrosine tyrosine) amino acid sequences that are involved in binding to CD40 (Vaitaitis 2014). It has been shown to interfere with the CD40/CD154 interaction, which is involved in autoimmunity, and it is efficacious in both delaying the onset of diabetes and reversing established diabetes in the NOD mouse model of T1D.

The study will be placebo controlled, the placebo being 50 mL of normal saline, USP sterile solution also administered by intravenous

1.2.1 Pharmacology

OPT101 has been shown to be efficacious in the NOD diabetic mouse model. In a prevention experiment, pre-diabetic NOD mice were treated by IV injections at 6 weeks of age with OPT101 at 1 mg/kg or vehicle (control). OPT101 was highly effective in preventing development of T1D (maintaining blood glucose below 250 mg/dL), and during the observation period the OPT101-treated mice remained healthy. In a reversal experiment, OPT101 was tested for its ability to reverse hyperglycemia. NOD mice that were hyperglycemic with a blood glucose level at or greater than 250 mg/dL were treated with OPT101 by IV injections at a dose of 4 mg/kg daily for 5 days. Sixty percent of the OPT101-treated mice had reduced blood glucose levels to normal levels (less than 120 mg/dl) after 1 week of treatment whereas hyperglycemia was not reversed in any control mice.

The ability of OPT101 to influence glucose tolerance and insulin production in pre-diabetic NOD mice was tested. NOD mice were treated at 9 weeks of age (mid/late stage of pre-diabetes) where moderate insulinitis occurs, and blood glucose levels began to increase. OPT101-treated mice had a significantly lower baseline glucose level than untreated NOD mice. OPT101-treated NOD mice responded appropriately to a glucose challenge, and baseline insulin levels in the mice were significantly higher, effectively doubled, compared to untreated NOD mice.

The 15-mer OPT101 derived from mouse CD154 protein is highly conserved between mouse and human (87% identical to human sequences), indicating that it may be efficacious for the treatment of T1D in humans (Vaitaitis 2014). To determine if human Th40 cells are responsive to OPT101 treatment, peripheral lymphocytes from T1D patients were treated *in vitro* with OPT101, and then stimulated with antigen presenting cells in the presence of human islets. The untreated Th40 cells from diabetic subjects produced high levels of IFN γ when stimulated. When Th40 cells were pre-treated with OPT101, the IFN γ response was strongly ablated.

To assess for potential adverse effects in NOD mice, animals were treated with OPT101 for over 12 weeks. In all OPT101-treated mice, the level of infiltration by peripheral immune cells was substantially reduced ($p < 0.01$) when compared to control-treated mice.

1.2.2 Toxicology and Pharmacokinetics

In a preliminary toxicity study rats and dogs were given a single dose of OPT101 as an IV bolus. When OPT101 was administered to beagle dogs at Clinical pathology effects included increases in leukocyte count, erythrocyte and platelet counts.

Noteworthy hematology, coagulation, and serum chemistry changes were seen.

It has been shown that using an anti-CD154 monoclonal therapeutic approach to interfere with the CD40-CD154 interaction there was efficacy in animal models, but in the clinical trial of one of the monoclonal antibodies there was binding to platelets resulting in emboli. Therefore, the clinical trials were halted ([Kalunian 2002](#)). To determine if OPT101 has similar effects as the monoclonal antibody, an *in vitro* study was done with human platelets to determine if OPT101 would affect platelet aggregation, as measured by light transmission aggregometry. Therefore, OPT101 had no impact on human platelet aggregation *in vitro*. Importantly, there was no evidence of thromboemboli in rats and dogs in the 8-week toxicology studies.

OPT101 was negative in the standard reverse bacterial mutation assay (Ames assay).

1.3 Findings from Clinical Studies

Safety and pharmacokinetic (PK) data are available from a single ascending dose, Phase 1a study (Study number OPT101-100-30) in healthy adults.

OPT101 was well tolerated after IV administration of up to and including a 2.8mg/kg single dose. None of the clinical laboratory, vitals or ECG findings suggest a safety concern up to this dose level. Infusion reactions were observed in 2 out of 14 subjects. Drug was cleared very quickly after the end of infusion, with insignificant serum levels seen at 4 hours after infusion.

These overall conclusions support further development of OPT101. Refer to the most recent IB.

1.4 Rationale for the Study

In mice and humans, elevated Th40 cell levels pre-date hyperglycemia onset and more importantly appear to be causal in diabetes pathogenesis. OPT101 has been shown in the NOD mouse model of T1D to be able to prevent onset of diabetes and to reverse hyperglycemia in most newly diabetic NOD mice. OPT101 may therefore be able to halt the progression and potentially reverse T1D in man in the early stages of the disease. Op-T LLC proposes to perform a study in T1D patients (≥ 18 years of age), consisting of a MAD study to measure safety, immunological, and clinical effects of 2 dose levels of OPT101 that were found to be safe in a Phase 1a study in healthy volunteers (IND 150941). The starting dose for the Phase 1b study will be 1.1mg/kg. OPT101 or placebo will be administered by IV infusion.

1.5 Summary of Known Risks and Benefits

Given the high morbidity and mortality of T1D, any treatment, such as OPT101, which could potentially prevent and/or suppress the auto-destruction of pancreatic islet β -cells would be of profound benefit to T1D patients, in terms of both length and quality of life.

Risks of OPT101 include the possibility of infusion reactions likely resulting from histamine release directly caused by the peptide.

A SAD (Phase 1a) stage of a safety and tolerability study in healthy volunteers (14 subjects) is the only stage completed to date. Data from this study indicate that OPT101 has a favorable safety and tolerability profile in healthy subjects after IV administration at single doses of up to and including 2.8mg/kg. No SAEs occurred during the study and all treatment emergent adverse events (TEAEs) were considered mild to moderate in severity by the Investigator. Infusion related reactions occurred in two subjects that received OPT101.

The majority of subjects experienced ≥ 1 TEAE. The majority of events were considered possibly study drug related by the Investigator and resolved without sequelae. No clinically significant trends were observed after review of vital signs, blood chemistry, hematology, urinalysis, and ECG test results. No evidence of clotting concerns was observed.

OPT101 is a small peptide and therefore is unlikely to be significantly antigenic.

Overall, should OPT101 prove to be an effective treatment of the underlying autoimmune pathology of T1D, the risk/benefit balance is favorable and may help patients maintain healthy blood glucose levels without exogenous insulin and avoid the serious morbidities associated with T1D.

Because of the infusion reactions observed in the clinical and nonclinical studies, the initial IV treatment of subjects with OPT101 will be conducted only at sites which are experienced and equipped to treat infusion reactions (i.e. appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, anaphylactic, or infusion-related reactions will be immediately available, and study personnel will be trained to recognize and treat anaphylactic and infusion-related reactions) should they occur.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of multiple ascending doses of OPT101, compared with Placebo (Saline) in T1D patients (≥ 18 years of age).	• Rate and type of adverse events after infusion of OPT101 or placebo • Change in vital signs after infusion of OPT101 or placebo • Change in plasma histamine levels shortly after infusion of OPT101 or placebo • Change in laboratory clinical chemistry, hematology and coagulation variables after infusion of OPT101 or placebo • Development of antidrug antibodies after infusions of OPT101 or placebo • Definition of maximum tolerated repeated dose of OPT101
Secondary	
• To assess the pharmacokinetic (PK) behavior of OPT101 in T1D patients (≥ 18 years of age) under the conditions of this trial. • To assess the pharmacodynamic (immunologic) effects of OPT101 in T1D patients (≥ 18 years of age) under the conditions of this trial. • To assess the clinical activity, compared with Placebo, of multiple ascending doses of OPT101 in T1D patients (≥ 18 years of age).	• Determination of PK parameters (AUC_{0-t}, C_{max}, CL/F, t_{1/2}) • Change in immunological variables after multiple infusions of OPT101 or placebo • Change in HbA1c • Change in daily insulin use • Change in C-peptide • Change in fasting plasma glucose • Change in urine glucose

3 STUDY DESIGN

3.1 Study Design Overview

Phase 1b: Safety, pharmacokinetics, immunological, and clinical effects of multiple- ascending doses (MAD) of OPT101

The Phase 1b is a randomized, double-blind, placebo-controlled, repeat dose study designed to evaluate two dose levels that were identified as tolerated in a Phase 1a in healthy volunteers (OPT101-100-30/IND 150941). The two doses of the peptide will be given to 2 groups of 9 subjects (6 investigational product:3 placebo). The subjects in this part of the study will be ≥ 18 years old with T1D diagnosed within the past 20 years.

Following written informed consent, subjects will undergo screening evaluations within 28 days prior to the investigational product or placebo infusion (Day 1); these evaluations will include complete medical history, drug screen, complete physical examination (including vital signs, weight, and height), clinical laboratory evaluations, serum pregnancy test for females of child-bearing potential (a negative pregnancy test is required within 48 hours prior to the start of drug treatment), diabetes assessment samples, mixed meal tolerance test, 12-lead ECG, urinalysis, concurrent medical conditions, and concomitant medication assessment. A subject may be enrolled 4 weeks after a positive COVID diagnosis and must be asymptomatic at that time of enrollment.

A total of 8 IV treatments with the 1.1 and 2.8 mg/kg doses or placebo, will be administered to a total of 18 subjects on Days 1, 4, 7, and 14 and then weekly (Days 21, 28, 35, and 42), for a total of 7 weeks. Patients should not receive 2 infusions within 72 hours of each other and if an infusion is skipped or missed, this should be documented as a deviation and the subject kept on schedule. Safety and tolerability data of Day 1 to Day 15 obtained in all subjects in the lower dose cohort will be reviewed by the SRC prior to proceeding to the higher dose cohort.

Subjects will be followed for safety, anti-drug antibodies, immunological, and clinical assessments for 14 days after the last (Day 42) treatment. Every subject will be monitored for 8 hours on Day 1 (Visit 1) and Day 42 (Visit 8) post treatment for safety, but also to allow for PK samples to be collected. For all other visits, 8-hour monitoring is not required but may occur at the discretion of the investigator for any patient who experiences clinically important adverse event/s (i.e. infusion reaction, or any other concerning adverse event) that do not recover within the period of observation. For Visits 2 through 7, subjects will be monitored up to 2 hours post infusion prior to discharge. Following the first two infusions, the Investigator or designee is required to contact the subject on the day after the infusion to check on the subject and discuss how they are feeling.

Throughout the study, subjects will be queried regarding AEs and concomitant medication usage.

3.2 Study Duration, Visits, and End-of-Study Definition

The study consists of a screening period and 10 study visits (8 infusion visits and 2 follow-up visits).

The estimated duration of the entire study for each subject is approximately 90 days.

A subject is considered to have completed the study if he/she has completed all visits in the study in which they are enrolled. The end of the study is defined as the date of the last visit (Visit 10 or Early Termination) of the last subject active in the study.

4 SELECTION OF SUBJECTS

4.1 Number of Sites and Subjects

The study will be conducted in up to 5 clinical study sites in the United States.

Screened subjects who do not meet all the inclusion criteria or one of the exclusion criteria will be considered screen failures. Subjects who do not meet eligibility criteria may be re-screened at the discretion of the Sponsor. Any subject who is re-screened will be assigned a new subject identification (ID) number and will be required to repeat the screening items that did not meet the criteria (see [Section 4.5](#)).

For the purposes of this study, medically stable is defined as:

Blood pressure: 120/<90mmHg +/- 20mmHg systolic

Pulse: 60-100bpm

Oxygen saturation: >92%

Respiratory rate: 12-22 breaths per minute

Anything outside of these ranges would require the patient to be evaluated by the Principal Investigator or Sub Investigator with any questions or concerns being referred to the SRC for determination of exclusion.

4.2 Inclusion Criteria

Subjects meeting all of the following criteria will be considered for enrollment into the study:

1. Able and willing and able to give informed consent for the trial
2. Male or female aged ≥ 18 years on the day of signing informed consent
3. Diagnosis of T1D within the last 20 years
4. Is medically stable based on physical examination, medical history, laboratory results, and vital signs performed at screening
5. Women of childbearing potential must have a negative highly sensitive serum test (beta-human chorionic gonadotropin) at screening and a negative urine pregnancy test at the Visit 1 Day 1 prior to receiving the investigational product.
6. Women must agree to use one of the following methods of birth control for the duration of the clinical trial: Systemic hormonal contraceptive (oral, injected, transdermal), intrauterine device, double barrier (e.g., cervical cap or diaphragm with condom or spermicide). Men with female partners must agree to use double barrier contraception, unless their partner is using systemic hormonal contraceptives or has an intrauterine device.

4.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from participating in the study:

1. Is over the age of 60 years old
2. Current malignancy or history of malignancy
3. Has an immune deficiency syndrome (for example, severe combined immunodeficiency syndrome, T-cell deficiency syndromes, B-cell deficiency syndromes, or chronic granulomatous disease), or bone marrow or organ transplantation, or a disease associated with lymphopenia
4. Is currently receiving an immuno-modulatory treatment.
5. Patients with a history of venous and arterial thromboembolic events including, but not limited to, the following: Deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, transient ischemic attack, or arterial insufficiency causing digital gangrene should be excluded. In addition, patients with recent immobilization or recent surgery, should be excluded. Patients with a history of abnormal prothrombotic laboratories such as congenital or inherited deficiency of antithrombin III, protein C, protein S, or confirmed diagnosis of antiphospholipid syndrome should also be excluded.
6. Has an active infections, is prone to infections or has chronic, recurrent or opportunistic infectious disease, including but not limited to, Epstein-Barr virus (EBV), cytomegalovirus (CMV), chronic renal infection, chronic chest infection, sinusitis, recurrent urinary tract infection, *Pneumocystis carinii* pneumonia, aspergillosis, latent or active granulomatous infection, histoplasmosis, or coccidioidomycosis or an open, draining, or infected non-healing skin wound or ulcer
7. Has recent or active hepatitis A infection, current/chronic hepatitis B and hepatitis C infection, or HIV infection. Participants with immunity to hepatitis B from previous infection (defined as negative HBsAg, positive anti-HBc, and positive hepatitis B surface antibody [anti-HBs]) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) may be eligible to participate.
8. Has a history of latent or active TB
9. Has received a live (attenuated) vaccine within the last 60 days including patients who plan to receive live (attenuated) vaccines during the study or within 60 days after the final dose of study treatment.
10. Patients with clinically significant abnormal laboratory test values in screening blood samples. In particular patients with the following should be excluded:
 - 5.4.1. Patients with abnormal coagulation panel at screening such as abnormal PT or aPTT or fibrinogen
 - 5.4.1. Abnormal liver function tests:
 1. Liver enzyme abnormalities (except in the case of known Gilbert's syndrome)
 2. AST or ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN
 3. AST or ALT ≥ 5 x ULN
 4. AST or ALT ≥ 3 x ULN if associated with appearance or worsening of rash or hepatitis symptoms
 - iii. Abnormal platelet counts ($<150,000$ mcL or $> 450,000$ mcL)

- iv. Abnormal white blood cell counts ($<3\text{mL}$ or $>11\text{mL}$)
 - v. Abnormal eGFR ($<50\text{mg/dL}$ or $>1.10\text{mg/dL}$)
 - vi. Abnormal Factor VIII ($> 160\%$)
 - vii. Abnormal D-Dimer ($> 500\text{ng/mL FEU}$)
11. Patients planning to undergo elective procedures or surgeries at any time after signing the ICF through the follow-up visit.
 12. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
 13. Recent history of bleeding or bleeding disorders or any condition whereby in the opinion of the treating investigator giving anti-coagulation during treatment would be contraindicated.
 14. History of hypersensitivity to antihistamines.
 15. Weight is over 250lbs.
 16. Patients with active drug or alcohol abuse within one year prior to screening or patients who test positive for required drug testing during screening.
 17. Patient is participating in a clinical trial of another investigational drug or device, including patients who have participated in another study for duration of 5 half-lives of the investigational agent.
 18. Patient is a prisoner
 19. Patients with any medical condition, including, but not limited to, cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal, or a psychiatric condition that, in the opinion of the Investigator, could compromise the participant's ability to participate in this study.

4.4 Avoidance of Pregnancy

It is important that women of childbearing potential (WOCBP) and the female partners of male subjects do not become pregnant during the study and for a recommended period of 4 months following administration of the investigational product (IP). Any pregnancy within 4 months post-study should be reported to the Principal Investigator and the Sponsor.

All WOCBP participating in this study and male subjects who are partners of WOCBP must agree to use one of the following methods of birth control for the duration of the clinical trial: systemic hormonal contraceptive (oral, injected, transdermal), intrauterine device, double barrier (e.g., cervical cap or diaphragm with condom or spermicide). Men with female partners must agree to use double barrier contraception, unless their partner is using systemic hormonal contraceptives or has an intrauterine device. Acceptable birth control methods are listed in Table 4.1 below.

Table 4.1 Acceptable Methods of Contraception

Established use of hormonal methods of contraception associated with inhibition of ovulation (e.g., oral, injected, implanted). The subject or male subject's partner should have been using that hormonal contraceptive for an adequate time to ensure effectiveness and should plan to use the same method throughout the study
Correctly placed copper-containing intrauterine device (IUD)
Male condom or female condom used with a spermicide product (e.g., foam, cream, or suppository)
Male sterilization with absence of sperm in the post-vasectomy ejaculate
Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure

Note: Male subjects must not have unprotected sexual intercourse with a female partner who is pregnant or breastfeeding during the clinical study. In addition, male subjects must not donate sperm during the study and for at least 6 months after completion of the study.

Rhythm methods will not be considered as highly effective methods of birth control. Subject abstinence from heterosexual intercourse for the duration of the study and 4 months after the last dose of the IP is acceptable without need for any additional method of contraception.

Women of non-childbearing potential are those who are post-menopausal or surgically sterilized (e.g., tubal ligation, hysterectomy in medical history).

Pregnancy Testing:

For WOCBP, a serum pregnancy test will be performed at screening and a urine pregnancy test will be performed at Day 0 before IP administration (see [Schedule of Procedures and Assessments, Phase 1b](#) at the end of the synopsis). Following a negative pregnancy result at screening, appropriate contraception must be commenced or continued, and a further negative pregnancy result will then be required at Day 0 before the subject may receive the IP. Urine pregnancy tests may be repeated whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Serum pregnancy test will be repeated at the end-of-study visit to confirm absence of pregnancy in female subjects. In the case of a positive pregnancy test or confirmed pregnancy, the subject will be withdrawn from the study. Additional pregnancy tests may also be undertaken if requested by IRB/IEC or if required by local regulations.

4.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria,

and any serious adverse event (SAE).

Subjects who do not meet the criteria for participation in this study (screen failure) may be re-screened at the discretion of the Sponsor. Re-screened subjects will be assigned a new subject ID number. The screening items that did not meet the criteria must be repeated within one month of the initial screening, unless approved in advance by the Sponsor.

5 STUDY TREATMENTS

5.1 OPT101 Treatment Instructions

The Principal Investigator and research nurse will conduct the IP infusion blinded and study staff not performing any other study related procedures will be unblinded to prepare the IP for infusion. The IP is to remain frozen at -65 to -85° C until preparation for infusion. Detailed instructions on the preparation and administration of the drug are provided in the Pharmacy Manual that will be provided by the Sponsor. An infusion pump is not to be used for administration of the IP.

5.2 Treatment Assignment

Subjects will be randomized to OPT101 or placebo within each dosing group in a 2:1 ratio. Each patient will be assigned a subject ID and will only be identified by this unique ID. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, all parties will be bound to keep this information confidential. The subject ID will be used for patient identification throughout the study. The numbers will be assigned sequentially. The subject ID should be used on all study documents relating to the subject from screening and throughout the study.

5.3 Dose Modification

The investigational product will be prepared by an unblinded study staff member and administered by the Investigator or authorized study site staff. All subjects will be given the assigned dose level without dose modification. Any preliminary PK and/or immunogenicity data, if available, can be included for SRC review.

5.4 Stopping Criteria

5.4.1. Infusion-related Reactions

Monitor subjects for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. Permanently discontinue OPT101 for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (Mild reaction; infusion interruption not indicated; intervention not indicated):

For Grade 2 symptoms (urticaria or erythema; stable vital signs; moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs], prophylactic medications indicated for ≤ 24 hours):

For Grade 3 or 4 symptoms (hypotension, hypoxia, unstable vitals; severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Life-threatening, Grade 4: pressor or ventilatory support indicated):

5.5. Treatment Compliance

The investigational product will be administered at the site under the supervision of delegated study site staff, and treatment compliance will be verified according to the site's standard operating procedures (SOPs). In the event of an overdose, the Investigator should report the event to the Sponsor's appointed study monitor and/or the medical monitor as soon as possible. Whether or not the subject should be withdrawn depends on the criteria listed in [Section 9](#). Any unfavorable effects caused by the overdose event must be reported as an AE (and an SAE if applicable criteria are met).

5.6 Packaging, Labeling and Storage Condition

All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Each vial of IP is labeled with the following label:

OPTIOI 20 mg/mL Lot#: 050I0819 See protocol for preparation and dosage instructions. Store frozen at -70 °C Caution: New Drug - Limited by Federal (or United States) Law to Investigational Use The University of Iowa Pharmaceuticals - College of Pharmacy The University of Iowa - Iowa City, Iowa 52242

The following information is printed on the label per Regulatory guidelines:

1. Name of the IP, dose strength, lot number, and storage condition
2. The following statement: "Caution: New Drug-Limited by Federal Law to Investigational Use"

3. Name of manufacturer

The investigational product should be stored at -65 to -85° C in the original carton until the time of administration. In addition, the lot # of the IP is 05010819, and not 05010819. All investigational product will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions supplied to the study site, the site's SOPs, and applicable regulations. Appropriate storage temperature and transportation conditions will be maintained for the investigational product from the point of manufacture up to delivery and receipt of the investigational product.

5.8 Supplies and Accountability

On receipt of the investigational product and study supplies, the Investigator (or delegated site staff) will conduct an inventory of the supplies and verify that IP supplies are received intact, at the correct temperature, confirming the correct lot numbers, date received prior to completing a supplies receipt. The Investigator will retain a copy of this receipt at the study site and return the original receipt to the study monitor. The monitor will verify all study supplies have been received at the study site prior to the initiation visit.

It is the responsibility of the unblinded study monitor to ensure that the Investigator (or delegated site staff) has correctly documented the amount of the IP received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at each study site at all times. The site must account for all IP received including IP that was accidentally or deliberately destroyed. Any discrepancies between the actual and expected returned IP counts should be explained. The site will retain and store all IP until inventoried by the unblinded monitor. The unblinded study monitor will perform an inventory of IP at the close-out visit to the study site. At the end of the study, once final accountability and monitor verification are complete, all unused IP will be destroyed by the responsible party at the study site and a certificate of destruction provided or returned to the depot at the Sponsor's request.

5.9 Prior and Concomitant Medications

At screening, the subject's medication history of the past 90 days will be recorded in the electronic case report form (eCRF) on the Concomitant Medications CRF. All medications taken by subjects other than the IP after screening until the completion of the end-of-study visit (Visit 9) are considered concomitant. Changes in concomitant medications relative to the previous visit will be documented according to the [Schedule of Procedures and Assessments, Phase 1b](#). The reported medications will be reviewed and evaluated by the Investigator to determine if they affect a subject's eligibility or continued participation in the study.

Table 5.2 Prohibited Medication/Therapy

Period of Exclusion	Excluded Medication/Treatment
≥60 days prior to Baseline Visit and throughout study	Live vaccination(s). Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, tuberculosis (bacille Calmette-Guerin—BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
≤4 weeks prior to Baseline Visit	Prescription or non-prescription medication, including vitamins, herbal and dietary supplements (except acceptable forms of birth control, and hormone replacement) unless, in the opinion of the Investigator, the product will not interfere with the study procedures or data integrity or compromise the safety of the subject.
≤4 weeks prior to Baseline and throughout study	Immunomodulatory drugs
≤30 days prior to Screening Visit	Any other IP not related to the current study

6 STUDY PROCEDURES

6.1 Description of Study Visits

The visits and the procedures and assessments that will occur at each of the encounters are shown in the [Schedule of Procedures and Assessments: Phase 1b](#).

The following are the approximate study visits based upon the estimated infusions:

Visit 0 Screening Day -28 to Day 0

The following will be collected at the time of patient screening visit:

- Demographic Information: age, race, weight, height
- Document Medical and Surgical History
- Physical exam and vital signs
- 12 Lead ECG
- Urine analysis via dipstick
- Urine Drug Screen (including CAGE questionnaire)
- Mixed Meal Tolerance Test
- Blood tests (see [schedule of procedures and assessments 1](#))
- Record daily insulin dose
- List any concomitant medications taken within the last 90 days

CAGE questionnaire:

The following are the CAGE-AID questions. The CAGE questionnaire is a 4-question screening tool to be used to help in the diagnosis of alcoholism during screening. The questions are as follows:

- Have you ever felt you ought to cut down on your drinking or drug use?
- Have people annoyed you by criticizing your drinking or drug use?
- Have you felt bad or guilty about your drinking or drug use?
- Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (eye-opener)?

Each “no” answer is given a 0 and each “yes” answer is given a 1. If the total sum of the scores for the questions is 2 or higher, it may indicate an alcohol use issue and is considered clinically significant.

Mixed Meal Tolerance Test:

This test measures how effective the patient’s pancreas is at producing insulin. The test usually takes approximately 2 hours to complete.

Drink one Ensure or Boost which contains protein, carbohydrates, and fat (approximately 200 – 300 calories).

Blood is taken pre meal (fasting blood collection) and at 2 hours (2 blood collections). HbA1c and glucose will be assessed pre meal and C-peptide and glucose will be assessed post meal (2

hour timepoint).

Physical Exam:

Details regarding the physical exam (PE) can be found in Section 8.6. The screening PE will not include a genitourinary exam.

Concomitant Medications will be assessed and recorded 90 days prior to infusion/Day 1 within the screening period and throughout the active study period visit 9 /day 56.

Hypoglycemia Guidance for Patients:

Signs and symptoms of hypoglycemia, from milder, more common indicators to most severe are provided below and should be communicated to the patient to be aware of post infusion. Signs are things others can notice, while symptoms are sensations that only the person with diabetes can notice and express.

- Shakiness
- Nervousness or anxiety
- Sweating, chills, and clamminess
- Irritability or impatience
- Confusion
- Rapid/fast heartbeat
- Light-headedness or dizziness
- Hunger and nausea
- Color draining from the skin (pallor)
- Sleepiness
- Blurred/impaired vision
- Tingling or numbness in the lips or tongue
- Headaches
- Weakness or fatigue
- Anger, sadness, or stubbornness
- Lack of coordination, clumsiness
- Nightmares or crying out during sleep
- Bizarre behavior
- Seizures
- Unconsciousness

Steps to perform when blood glucose dips are as follows:

1. Consume simple carbohydrates (example: a small piece of fruit, 7 saltine crackers, ½ a cereal bar)
2. Check blood glucose again.
3. If the level is still, repeat steps 1–3.
4. Repeat until blood glucose is and then consider eating a snack or small meal to keep levels from dropping again.

This stepwise approach can help the patient avoid overtreatment, which can lead to high blood glucose.

6.2 Biological Samples

6.2.1 Blood

Blood samples will be collected for clinical laboratory evaluations, pregnancy, serology, PK, immunological, safety endpoints and immunogenicity analyses. [Table 6.1](#) provides an overview of the sample types and amount of blood samples that will be collected for analysis per subject during the study.

7 ASSESSMENT OF PHARMACOKINETICS, IMMUNOLOGY AND DIABETES

7.1 Assessment of Pharmacokinetics

7.1.1 Pharmacokinetics

Blood samples will be collected to determine the serum concentrations of OPT101. Sampling and handling of PK samples will be performed by qualified study site staff.

The following PK parameters will be calculated from serum concentrations of OPT101 using non-compartmental procedures:

1. Maximum observed concentration (C_{max})
2. Time to reach C_{max} (t_{max})
3. Area under the curve from zero up to time t (AUC_{0-t})
4. Apparent total clearance of the drug from serum (CL/F)
5. Terminal half-life ($t_{1/2}$)
6. Apparent volume of distribution during terminal phase (V_z/F)

PK levels will be collected, processed and shipped according to the instructions provided in the Laboratory Manual.

7.2 Diabetes Assessment

7.2.1 HbA1c

Blood samples will be collected as indicated in the [Schedule of Procedures and Assessments, Phase 1b](#), to determine HbA1c, also known as glycated hemoglobin.

7.2.2 Daily insulin use

Daily insulin use will be collected from each subject as indicated described in the [Schedule of Procedures and Assessments, Phase 1b](#). Ideally subjects with an automated insulin device or continuous glucose monitoring (CGM) device should be included in the study. If the subject is not using a CGM, the subject will be required to complete a daily insulin use log throughout the course of study participation. The study staff will collect the log at each visit and the completed log will be uploaded into the EDC at end of study. Subjects on a CGM should have a report of insulin use from their device downloaded, deidentified and uploaded to the EDC at the end of study. Any required insulin dosing changes during the study should be performed by the patient's primary care physician. The investigator must be notified of these changes.

7.2.3 C-peptide

Blood samples will be collected as indicated in the [Schedule of Procedures and Assessments, Phase 1b](#), to determine C-peptide. This test requires fasting therefore will be obtained when other fasting labs may be drawn.

7.2.4 Glucose

Glucose testing will be performed as indicated in the [Schedule of Procedures and Assessments for Phase 1b](#), via glucometer (iSTAT). It is recommended that glucose monitoring by the patient should occur per ADA guidelines during the study. That is, glucose should be tested before meals and two hours post any meals to include snacks. A daily insulin log will be completed through the course of study participation.

7.2.5 Mixed Meal Tolerance Test

Blood samples will be collected as indicated in the [Schedule of Procedures and Assessments, Phase 1b](#). This test will determine how effective the patient's pancreas is at producing insulin. This test usually takes approximately 2 hours to complete. The test requires fasting, a pre-meal blood draw, drinking a liquid meal beverage (Boost or Ensure) after which blood will be taken 2 hours post meal.

7.2.6 Urine Dipstick Analysis

Urine samples will be collected as indicated in the [Schedule of Procedures and Assessments for Phase 1b](#), and will show any glucose in the urine as well as bilirubin, blood, ketone, leukocyte, nitrite, pH, protein, specific gravity and urobilinogen.

7.3 Immunological Assessment

7.3.1 Cytokine Measurements

Blood samples will be collected as indicated in the [Schedule of Procedures and Assessments, Phase 1b](#) to determine the serum cytokine levels in subjects. Cytokines to be measured include TNF- α , IL-1 β , IL-6, and MCP-1. Samples will be collected, processed, and shipped according to a laboratory manual provided by the Sponsor and/or bioanalytical laboratory. Serum cytokine levels will be determined using the bead-based multiplex immunoassay.

7.3.2 Anti-drug Antibody

Blood samples will be collected as indicated in the [Schedule of Procedures and Assessments, Phase 1b](#) for assessment for anti-drug antibodies.

7.3.3 Tryptase measurements

If an infusion reaction is observed, blood samples will be collected as indicated in the [Schedule of Procedures and Assessments, Phase 1b](#) for assessment of tryptase, an enzyme that is released, along with histamine and other chemicals, from mast cells when they are activated as part of a normal immune response as well as in allergic (hypersensitivity) response.

7.3.4 Histamine measurements

In an infusion reaction is observed, blood samples will be collected as indicated in the [Schedule of Procedures and Assessments, Phase 1b](#) for assessment of histamine, to detect mast cell activation.

7.3.5 Prostaglandin measurements

In an infusion reaction is observed, blood samples will be collected as indicated in the [Schedule of Procedures and Assessments, Phase 1b](#) for assessment of inflammation.

7.3.6 Immunology (Research Samples)

Samples will be collected as indicated in the [Schedule of Procedures and Assessments, Phase 1b](#).

8 ASSESSMENT OF SAFETY

8.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a subject receiving the study drug and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of OPT101, whether related to use of the OPT101. Abnormal laboratory findings without clinical significance (based on the Principal Investigator's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered AEs. From the time the subject signs the informed consent form through the Follow-Up Visits all AEs must be recorded in the subject medical record and AE CRF.

AEs will be assessed according to the CTCAE version 5.0, which has been harmonized to MedDRA (Medical Dictionary for Regulatory Activities) coding. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the OPT101
- Probably: The AE is likely related to the OPT101
- Possible: The AE may be related to the OPT101
- Unlikely: The AE is doubtfully related to the OPT101
- Unrelated: The AE is clearly NOT related to the OPT101

8.1.1 Reporting of AEs

Op-T LLC should be notified of all treatment-related AEs on a regular basis (to be agreed upon by the study team and Op-T LLC). Reports of these should be made to Op-T Clinical Operations.

8.2 Serious Adverse Event

An AE or suspected adverse reaction is considered "serious" if in the opinion of either the investigator or the sponsor it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the two outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct of normal life functions
- Results in a congenital anomaly/birth defect.

8.2.1 Reporting of SAEs

Only AEs that the sponsor and/or Principal Investigator determines to be serious, unanticipated, and related or possibly/probably (i.e., more likely than not) related to the research must be reported to the IRB. Those AEs will be submitted, according the following guidelines:

- Report within 24 hours of learning about any subject's death that was unanticipated and more likely related to the research than unrelated.
- Report within 5 business days of learning about any serious, unanticipated, and related or possibly/probably related AE.
- Report within 10 business day of learning about any other unanticipated problem or event that was more likely related to the research than unrelated.

The Principal Investigator is responsible for compliance with all applicable regulations pertaining to the reporting of AEs to the IRB. To ensure patient safety, each study treatment- related serious adverse event (SAE) will also be reported to the sponsor, Op-T LLC, within 24 hours by the Principal Investigator. Follow-up information on these events shall also be reported to Op-T LLC, within 24 hours. Follow-up information may include hospital admission records, discharge summaries and autopsy reports, where applicable. The initial SAE form should be sent within 24 hours of the Investigator becoming aware.

- Op-T LLC, Medical and Safety Monitor at emergency number to be provided by the Sponsor.

The sponsor must report to the Food and Drug Administration (FDA), in an Investigational New Drug (IND) safety report, any suspected adverse reaction that is both serious and unexpected. Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction (i.e., there is a reasonable possibility that the drug caused the AE)
- Serious
- Unexpected

If the AE does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The sponsor is required to report to the FDA all IND Safety reports in writing within 15 days (7 days for unexpected fatal or life-threatening suspected adverse reaction). The FDA Form 3500A can be found on the FDA website, www.fda.gov. All other AEs will be reported to the FDA in the IND Annual Report.

In addition to the above-mentioned reporting responsibilities, after discontinuation of the study, all SAEs considered to be drug related will be reported to Op-T LLC, by the Principal Investigator.

8.3 Adverse Event by Severity or Intensity

AE severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0) available at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

The grading scale is illustrated in Table 8.1. The severity of the AE should be recorded in the appropriate section of the AE page of the eCRF.

Table 8.1: Definitions of Adverse Events Severity

Grade 1 (Mild)	Mild; asymptomatic observed or mild symptoms (such as an asymptomatic self-limited rash); clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate)	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4 (Life-Threatening)	Life-threatening consequences: urgent intervention indicated.
Grade 5 (Death)	Death related to AE

Based on the Common Terminology Criteria for Adverse Events v5.0 (CTCAE).

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

ADL=activities of daily living

8.4 Relationship between Adverse Events and Investigational Product

The Investigator should assess and classify the causality of each AE. The determination of the relationship (if any) between the AE and the IP will be made using the guidelines in [Table 8.2](#).

Table 8.2: Guidelines for Determining the Relationship (if any) Between Adverse Event and the Investigational product

Definite:	This causal relationship is assigned if the AE starts a reasonable time after the administration of investigational product, stops/improves when the investigational product is stopped, and could reasonably be explained by known characteristics of the investigational product.
Probable:	This causal relationship is assigned when the AE starts a reasonable time after the administration of investigational product, stops/improves when the investigational product is stopped, and could not be reasonably explained by known characteristics of the subject's clinical state.
Possible:	This causal relationship is assigned when the AE starts a reasonable time after the administration of investigational product but could be produced by the subject's clinical state or other modes of therapy administered to the subject.
Not Related:	This causal relationship is assigned when the time association or the subject's clinical state is such that the investigational product was not likely to have had an association with the observed AE.

8.5 Tolerability

Tolerability assessment will be based on the incidence of DLTs after IP administration, on the day of dosing through to 15-days post-dosing. The definition of DLTs in this study is provided in [Section 5.5.1](#).

8.6 Physical Examination

A complete physical examination, assessing the subject's overall health and physical condition, will be performed at the time points indicated in the [Schedule of Procedures and Assessments, Phase 1b](#). The physical examination will consist of the following body systems: eyes, ears, nose, throat, lymph nodes, dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and nervous systems. Subsequent physical examinations performed at the indicated time points/days will be targeted and should also include previous abnormal physical exam findings and adverse events associated with new physical findings. Body height, weight (without shoes) will be recorded at screening and at the time points indicated in the [Schedule of Procedures and Assessments, Phase 1b](#). The Investigator will review all physical examination findings for clinical significance. Except for the screening examination, only changes from the previous physical examination need to be recorded on the eCRF.

8.7 Vital Signs

Vital signs will be performed by the Investigator or his/her qualified designees at the time points indicated in the [Schedule of Procedures and Assessments, Phase 1b](#). Routine vital sign assessment will be taken in the supine or seated position after at least 5 minutes of rest and will include heart rate, systolic and diastolic blood pressure, respiratory rate and pulse oximetry level. Oral body temperature will be collected pre-infusion, q15 minutes during infusion, q30 minutes until 60 minutes EOI. Blood pressure may be taken off of both arms (i.e. the blood pressure cuff can be moved from one arm to the other) during vital sign collection. However, a

baseline reading for blood pressure from both arms must be taken prior to vital signs collection.

Continuous cardiac monitoring will be completed for 8 hours (day 1) and thereafter at all infusions for up to 1 hour post-infusion.

The Investigator will review all vital sign values for clinical significance. Additional vital signs will be obtained when clinically indicated.

8.8 Clinical Laboratory Evaluations (including Coagulation Tests)

Blood samples will be collected, processed, and shipped according to the instructions from the site's safety laboratory at the time points indicated in the [Schedule of Procedures and Assessments, Phase 1b](#). The hematology, clinical chemistry, and coagulation tests will be performed in the local laboratory.

A list of testing to be performed on the blood samples is provided as follows:

Table 8.3 Clinical Laboratory Evaluations

Hematology:	Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Mean platelet volume (MPV) Lymphocytes Monocytes Eosinophils Basophils White blood cell (WBC) count (total and differential) Red blood cell width (RDW) Absolute neutrophil count
Coagulation:	International normalized ratio (INR) Prothrombin time (PT) Activated Partial Thromboplastin Time (aPTT) Fibrinogen D-Dimer Factor VIII Ferritin Von Willebrand Factor
Clinical Chemistry:	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Anti-drug antibodies Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) C-peptide Calcium Chloride Creatinine

	Cytokine Gamma-glutamyl transferase (GGT) Glucose Hemoglobin A1c Histamine Lipid panel (low- and high-density lipids, cholesterol, triglycerides; total cholesterol) Magnesium Potassium Sodium Total bilirubin Total Iron and total Iron Binding Capacity Total protein Tryptase Urea Nitrogen
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Reference ranges will be supplied by the local laboratory and used by the Investigator to assess the laboratory data for clinical significance and pathological changes.

8.9 Serology

Blood samples will be collected at screening to test for HIV, hepatitis B surface antigen, and hepatitis C antibody. A positive result in these serological tests would exclude the subject from study participation.

8.10 Electrocardiograms (ECG)

A 12-lead ECG recording will be conducted at the time points indicated in the [Schedule of Procedures and Assessments, Phase 1b](#) and interpreted according to the site's SOPs. The subject should rest in a supine position for at least 5 minutes before the recording is conducted. The ECG will record the electrical signal of the heart and provide insight toward cardiac risk. ECG data is captured on the ECG CRF in the EDC.

If the scheduled time for an ECG coincides with a blood collection, the blood draw should be performed as scheduled, with the ECG being performed at the nearest/closest to the time point indicated. If the unconfirmed ECG report from the instrument indicates QT prolongation with $QTc \geq 450$ msec, the Investigator should repeat the ECG within 1 hour. If the initial findings are confirmed, the Investigator should exclude/withdraw the subject from study participation. With regard to other ECG findings, the Investigator should employ his/her clinical judgment to determine whether the subject should continue in the study. The Investigator will review all ECG results for clinical significance.

8.11 Medical History

Information on prior illnesses will be collected as part of medical history. Concomitant illnesses are those recorded at Visit 1 and after. Medical histories will be obtained at screening and will include histories of acute, chronic, and infectious disease; surgical and oncologic histories; abnormalities in vital signs, 12-lead ECG, and clinical laboratory assessments; any known drug allergies; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance and subject's eligibility for study participation.

8.12 Medication History/Concomitant Medications

All medications (including prescription and non-prescription, herbal medications/natural health products, and investigational drugs) taken by the subjects 90 days prior to screening will be recorded in the source documentation as medication history. All medications taken from the time of screening through the end-of-study visit will be recorded in the source documentation as concomitant medications.

8.13 Urine Dipstick Analysis

Urine dipstick analysis will include glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrate and leukocytes. This test will be performed at all study visits and recorded. Urine samples will also be used to test for presence of the following drugs at screening; a positive result would exclude the subject from study participation. Drugs to be screened include; Amphetamines, secobarbital (short-acting barbiturate), oxazepam (benzodiazepine), benzoylecgonine (main metabolite of cocaine), methamphetamine, methadone, morphine (opiate), phencyclidine and nortriptyline.

8.14 Pregnancy

Blood sample will be collected at screening for serum pregnancy test. Serum pregnancy test will test for the presence of β -human chorionic gonadotropin in the serum of all female subjects. Results of pregnancy tests will be reported and determined to be negative prior to study participation. Urine pregnancy test will be performed on Day 1 and must be negative prior to IP administration. Urine pregnancy test will be repeated at the end-of-study visit to confirm absence of pregnancy in female subjects.

8.15 Handling of Pregnancy

The Investigator will collect pregnancy information on any subject or female partners of male subject who becomes pregnant while participating in this study. The Investigator will record pregnancy information on the appropriate Pregnancy report form and submit it to the Sponsor or its designee immediately (i.e., within 24 hours after acknowledgment of a subject's pregnancy). Any female subject who becomes pregnant while participating in the study will be withdrawn from the study. Full details of the pregnancy will be recorded on the withdrawal page of the eCRF. The subject's state of health will also be followed until delivery to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Any premature termination of the pregnancy will be reported.

Pregnancy, in and of itself, is not regarded as an AE or SAE unless the birth results in a congenital anomaly or birth defect or there is suspicion that the IP may have interfered with the effectiveness of a contraceptive medication or method. If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Any pregnancy that occurs in a female partner of a male study participant should be reported. Information on this pregnancy will be collected on the Pregnancy Report Form. In order for the study team to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

8.16 Periodic Reporting of Adverse Events by Sponsor

The Sponsor or its designee will provide annual safety reports to the Regulatory Authorities and the IRB/IEC responsible for the clinical study, as applicable. These updates will include information on unexpected SAE's and other relevant safety findings. Reporting of unexpected SAE's will follow all applicable local safety reporting requirements.

The Sponsor or their designee will notify the Investigators of relevant information about unexpected SAE's that could adversely affect the safety of subjects in a timely fashion. Follow-up information may be submitted if necessary.

9 DISCONTINUATION AND WITHDRAWALS

9.1 Withdrawal of Individual Subjects

Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The treatment of individual subject(s) may be discontinued under the defined circumstances as outlined below:

- The subject withdraws consent
- Use of prohibited concurrent therapy
- Non-compliance with the IP or study schedule
- Lost to follow-up
- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the Investigator's opinion, or unacceptable to the subject to continue
- If, in the opinion of the Investigator/Sponsor, it is in the best interest of the subject
- Intercurrent illness warranting removal by the Investigator
- Positive COVID diagnosis
- Pregnancy
- Termination of the study

The reason(s) for withdrawal (by the subject or Investigator) and date will be documented in the eCRF. All subjects who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. Any subject who withdraws consent as a result of an AE, regardless of severity or Investigator's opinion, must be reported as a discontinuation due to AE. Subjects withdrawing from the study will be encouraged to complete the final evaluations as detailed for end-of-study in the [Schedule of Procedures and Assessments, Phase 1b](#), particularly the safety evaluations. If a subject refuses to complete any early termination procedures, this information will be recorded in the source documentation. A subject who prematurely discontinues from the study for any reason will not be allowed to re-enter the study. The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning OPT101 making further treatment of subjects impossible. In this event, the Investigator(s) will be informed of the reason for study termination.

9.2 Replacement of Subjects

In all cohorts, any subject who drops out prior to the DLT evaluation before Day 15 due to unrelated (including unlikely related) AE will be replaced; any subject who withdraws consent or is withdrawn after Day 15 will not be replaced.

9.3 Withdrawal of Samples

No new information will be collected and added to existing data from subjects who requested to withdraw their consent from participation in this study. Subjects who discontinue the study will be instructed to contact the Investigator in writing should they wish to withdraw their laboratory samples from the study. The Investigator will then contact the Sponsor to remove the sample from storage and destroy it. As analyses may have already been performed prior

to the subject requesting their sample be withdrawn, the data generated may continue to be used

for analysis.

10 STATISTICAL METHODS

10.1 General Statistical Considerations

A complete description of the statistical methods will be provided in the statistical analysis plan (SAP), which will be prepared and finalized prior to data analysis. Unless otherwise stated tabulation of summary statistics and data analysis will be performed using SAS® Version 9.3 or later. Statistical analysis will be performed only after the database lock.

The statistical analyses will generally be descriptive in nature. Data collected will be presented using summary tables, data listings, and figures. For categorical variables, the number and percentage of each category within a parameter will be calculated. For continuous variables, the sample size (n), arithmetic mean, median, standard deviation (SD), and the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated.

10.2 Determination of Sample Size

The sample size for the dose escalation design is based on the dose escalation rules of the standard 3+3 design.

10.3 Analysis Sets

The study analysis populations will consist of the following:

1. Safety population: All subjects who receive any IP
2. PK population: All subjects in the safety population who have at least 1 evaluable PK profile and have no protocol deviations or other circumstances that would exclude them from analysis. Protocol deviations may include the following:
 - Incomplete OPT101 administration
 - Intake of prohibited previous and concomitant medication
 - Any deviation from inclusion/exclusion criteria

All safety and immunogenicity variables will be summarized on the Safety population. The PK analysis will be performed on all subjects with an adequate number of PK timepoints.

10.4 Demographics and Background Characteristics

10.4.1 Disposition

Subject disposition will be summarized on all enrolled subjects completing informed consent. The number and percentage of subjects dosed and who completed the study or withdrew early, the reasons for withdrawal, and subjects included in each study population will be summarized.

10.4.2 Demographics

Demographic information including date of birth, height, weight, race, and ethnicity will be collected during the screening period (Day -28 to Day -1) and will be summarized for the Safety population. Continuous variables will be summarized with descriptive statistics: n, arithmetic mean, SD, median, minimum and maximum values. The number and percentage of each race and ethnicity category will be tabulated.

10.4.3 Medical History

Medical history will be coded into the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA, version 21.0 or higher) and summarized by system organ class (SOC) and preferred term (PT). The number and percentage of subjects will be summarized by study part and cohort for the Safety population.

10.4.4 Exposure and Compliance

Exposure to the IP and compliance with the dosing schedule will be summarized for the Safety Population in terms of dose level received. The number and percentage of subjects will be presented for each study part and dose level. Accidental or intentional overdoses should be reported to the Sponsor/CRO promptly.

10.4.5 Medication History/Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug and summarized by Anatomical Therapeutic Chemical (ATC) and preferred term. A concomitant medication prescribed and over the counter, that a subject has taken before screening, or a subject is taking after screening will be summarized and presented for the safety population. The number and percentage of subjects taking concomitant medications, by medication name or class will be displayed by study part and cohort.

10.5 Analyses of Safety Assessments

Verbatim AE terms will be coded using the MedDRA (version 21.0 or higher). The number and percentage of subjects who report AEs will be summarized descriptively for each study part, cohort, as well as overall at the SOC and PT levels. These descriptive summaries of AEs will also be presented by relationship to the IP and severity. Laboratory test variables will be summarized by dose group and study visit using descriptive statistics. Laboratory data collected from baseline and up to 14 days after a subject's last dose of the study drug will be included in the analysis. Descriptive statistics will be used to summarize vital signs by dose group and study visit. Vital sign data collected from baseline and up to 14 days after a subject's last dose of the study drug will be included in the analysis.

10.6 Analyses of Pharmacokinetic

Individual and mean serum OPT101 concentration will be listed and summarized by study cohort. Serum OPT101 versus time profiles will be plotted for each subject by each cohort, similar

summary plots will also be constructed.

PK parameters will be calculated using non-compartmental techniques from serum OPT101 concentrations. PK parameters will be listed for each subject and summary statistics will be presented by study part and cohort.

10.7 Analyses for Detecting Trends of Special Interest

Any thromboembolic events/bleeding events, hepatic function abnormality (meeting definition for Hy's Law), acute and delayed hypersensitivity reactions (including anaphylaxis, immune complex disease, and infusion-related reactions), and infections including serious and opportunistic infections will be collected and summarized for each assessment time point by study part and cohort.

Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3- fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) placebo.
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

10.8 Cytokine Measurements

Serum levels of TNF- α , IL-1 β , IL-6, and MCP-1, will be summarized descriptively for each assessment time point by study part and cohort

10.9 Analyses of Immunogenicity

The number and percentage of subjects with presence of anti-OPT101 antibodies will be summarized descriptively for each assessment time point by study part and cohort.

10.10 Immunological Assessment

The percent and number of peripheral blood will be summarized descriptively for each assessment time point by study part and cohort.

10.11 Interim Analyses and Data Monitoring

No formal interim analyses will be performed. The SRC will meet periodically to review and discuss relevant safety data and make recommendations as stated in Section 10.11.

10.12 Changes in the Conduct of the Study or Planned Analysis

Any changes that affect the conduct of the study will necessitate amendment to the protocol. Any amendments to the study protocol will be communicated to the Investigators by the Sponsor/CRO. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days. (See [Section 11.6](#)).

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

11 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

11.1 Good Clinical Practice

The study will be conducted according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) for Good Clinical Practice in Clinical Studies ([ICH E6 R2](#)) guideline, and applicable national and local laws.

11.2 Institutional Review Board/Independent Ethics Committee

The Investigator at the site is responsible for obtaining IRB/IEC approval. The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the IRB for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the IRB. All subsequent protocol amendments and changes to the informed consent form will be required to be approved by the IRB.

11.3 Regulatory Authority Approval

The Sponsor or its designee will make the appropriate applications to the Regulatory Authority as needed for regulatory approval of the study and, if necessary, approval to import IP. The study will not start until the required regulatory approvals have been obtained in the appropriate jurisdiction.

11.4 Delegation of Investigator Duties

The Investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task. Delegation of study related tasks should be documented in a delegation of authority log. Delegation of tasks is primarily a concern when it involves tasks that are clinical in nature. In all cases, a qualified physician should be responsible for all study- related medical decisions and care. Examples of such tasks include, but are not limited to:

1. Screening evaluations
2. Physical examinations
3. Evaluation of AEs
4. Assessments of study endpoints
5. Obtaining informed consent

11.5 Informed Consent

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with potential subjects the

purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions and will be given as much time as needed to make an informed decision about participation in the study.

The signed original informed consent form will be stored in subjects' study files, and subjects will be provided with copies of their signed informed consent forms. The Principal Investigator and the study team are responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

11.6 Protocol Amendment and Study Termination

Protocol modifications must be made only after discussion between the Sponsor and the Principal Investigator/s. Any change to the protocol can only be made in the form of a written amendment to the study protocol. Such amendments must be signed by all persons who signed the previous protocol version prior to implementation.

Substantial amendments which affect the safety of the subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated or the subject selection criteria will also be submitted for written approval to the respective regulatory bodies according to current legislation prior to their implementation. Non-substantial amendments such as administrative changes, correction of spelling and grammar mistakes only should be recorded and contained in the documentation when it is subsequently submitted, e.g., within the subsequent notification of a substantial amendment.

Amendments which might have an impact on the subjects, such as the use of additional examinations or study visits, have effects on the informed consent procedure and require the signature of the revised ICF by all subjects enrolled in the study that are affected by the amendment. Both Sponsor and the Investigator reserve the right to suspend or terminate the study at any time, according to the study contract. The Investigator should notify the IRB/IEC in writing of the study's completion, suspension or early termination and send a copy of the notification to the Sponsor and/or its designee.

11.7 Ongoing Information for Institutional Review Board or Independent Ethics Committee

Unless otherwise instructed by the IRB/IEC or local law, the Sponsor or the Investigator must submit to the IRB/IEC:

1. Information on AEs that are serious AND unexpected AND associated with IP from the Investigator's site, in accordance with applicable legal requirements
2. Expedited safety reports from the Sponsor, as soon as possible

3. Periodic reports on the progress of the study

11.8 Subject Confidentiality and Disclosure

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP, Health Insurance Portability and Accountability Act (HIPAA), and local policies and regulations.

In compliance with the GCP guidelines, it is required that the Investigator and institution permit authorized monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IRB/IEC approving this research, and the regulatory authorities, as well as that of any other applicable agency or agencies direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject. By consenting to participate in the study, the subject also gives his/her agreement to the documentation of clinical data in the scope of the clinical study, to their transmission to the Sponsor for review, to the responsible regulatory authorities and, in case of person-related data, to their perusal by representatives of the Sponsor or of the authorities.

The Investigator must ensure that each subject's anonymity will be strictly maintained. On CRFs or other documents submitted to the Sponsor, subjects must not be identified by their name, but by an identification code consisting of the ID. If subjects' names are included on copies of documents submitted to the Sponsor, the names must be obliterated, and the assigned ID must be added to the documents instead. The Investigator will keep a separate Subject Identification Code

List of these codes, along with the full names and dates of birth of the subjects. Documents which contain the names associated with these codes are not for submission to the Sponsor. They will, together with completed consent forms, be maintained by the Investigator in strict confidence. All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with HIPAA, applicable to national and/or local laws and regulations on personal data protection.

11.9 Data Management and Record Retention

Data management

Sponsor/CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of Sponsor/CRO.

Record retention

According to ICH guidelines, source documentation and other essential documents must be archived. Essential documents include those documents which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced. This may include observations and source data contained in medical records (certified copies or originals are acceptable for archiving purposes), data collection forms or eCRFs and research related records held in support departments. All hard copies of source documents must be retained. If electronic records of documents exist these must be backed up and retained with the hard copies.

Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements and/or written agreements with the Sponsor (i.e., Master Service Agreement).

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the study and make them available upon request from the regulatory authority(ies).

11.10 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.11 Safety Review Committee

An SRC consisting of medical professionals, the medical monitor and the Sponsor will be established to review safety and tolerability data. An SRC Charter will be developed to reflect the conduct of the review, and composition, responsibilities and logistics of the SRC members.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified Principal Investigators and appropriate study centers, review of protocol procedures with the Principal Investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or its designee. Significant and/or repeated non-compliance will be investigated, and remedial action instituted when appropriate. Failure to comply with remedial actions may result in study site termination and regulatory authority notification.

12.1 Data Collection, Study Monitoring, and Source Data Verification

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at study sites for Quality Assurance. The Principal Investigator at each clinical center should be available to the clinical trial monitor during monitoring visits and ensure that access to all documents and records is provided. The Principal Investigator agrees to cooperate with the clinical trial monitor to ensure that any problems detected in the course of these monitoring visits are resolved. All study documents must be made available upon request to the clinical trial monitor and other authorized regulatory authorities, including but not limited to the National Institute of Health and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

12.2 On-Site Audits

The study may be audited by an audit team originating from the sponsor or its designee. The investigator agrees to cooperate with the auditor to ensure than any problems detected in the course of the audit visits are resolved.

13 DOCUMENTATION AND USE OF STUDY FINDINGS

13.1 Documentation of Study Findings

An eCRF form will be provided for each subject enrolled into the study. Study sites are required to submit clinical data for each enrolled subject via an electronic data capture (EDC) system. Site personnel will be trained on the EDC system before receiving access to the system. The Sponsor or its designee is responsible for maintaining a record of all system users. The subjects of the study will not be identified by name on any study documents to be collected by the Sponsor.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for any missing data. The Principal Investigator is responsible for reviewing all eCRFs, verifying them for accuracy, and approving them via an electronic signature. Copies of the completed eCRFs, saved to disk in Portable Document Format (PDF), will be sent to the Investigator's site at the completion of the study.

13.2 Availability and Retention of Records

The Investigator must make study data accessible to the study monitor, other authorized representatives of the Sponsor, and Regulatory Agency inspectors upon request. A file for each subject must be maintained that includes the signed ICF and the Investigator's copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

After completion of the study and when all collected data are validated, the database will be locked, pursuant to the prior approval by the Sponsor (or its designee). Final data will be extracted from the EDC system and delivered in the form of SAS® datasets. A PDF copy of the eCRF will be produced for each study subject and included in the final delivery.

All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with the Sponsor/CRO security standards. Each subject will have identifiers that will be kept at the study sites. If study site/the Sponsor becomes aware of loss or destruction of data due to a major breach occurrence that has jeopardized subject confidentiality and study data, the IRB/IEC will be notified. The Investigator must not discard any records unless given written authorization by the Sponsor.

13.3 Use of Study Findings/Study Report and Publication Policy

The Sponsor has full ownership of the eCRF completed as part of the study. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained. By signing the clinical study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

For clinical interventional studies in subjects, the Sponsor will post study results on websites such as <https://clinicaltrials.gov/> in accordance with FDA reporting rules. When the study is completed or prematurely terminated, the Sponsor or designee will ensure a Clinical Study Report is written in compliance with ICH E3 (Structure and Content of Clinical Study Reports) and submitted to the regulatory authorities, as required by the applicable regulatory requirement(s). Where required by applicable regulatory requirements, an Investigator/responsible medical officer signatory will be identified for the approval of the Clinical Study Report. The Investigator/responsible medical officer will be provided reasonable access to statistical tables, listings, and figures, as well as relevant reports, and will have the opportunity to review the complete study results. The Clinical Study Report may be published in part or in its entirety.

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