# A Phase II, Multi-center, Two-Part (Part 1: Randomized, Double-Blind, Placebo-Controlled with Leronlimab 700mg and placebo; and Part 2: Open-label, Single Arm with Leronlimab 350mg), Three-Arm, Dose-Ranging Study of the Safety and Efficacy of Leronlimab (PRO 140) in Adult Patients with Nonalcoholic Steatohepatitis (NASH)

| | |
|---|---|
| **Protocol Number:** | **CDI-NASH-01** |
| **Final Version:** | **7.0** |
| **Date:** | **14-Jun-2021** |


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**Confidentiality Statement**

## PROTOCOL APPROVAL PAGE

| | |
|---|---|
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We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

## PROTOCOL APPROVAL FOR USE

## INVESTIGATOR'S SIGNATURE PAGE

| | |
|---|---|
| **Protocol Number:** | **CDI-NASH-01** |
| **Final Version:** | **7.0** |
| **Date:** | **14-Jun-2021** |

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with US Food and Drug Administration (FDA) regulations and Investigational Review Board/Institutional Ethics (IRB/IEC) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Site Number _____

**SPONSOR INFORMATION**

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# PROTOCOL SYNOPSIS

| | |
|---|---|
| **Name of Sponsor/Company:**<br>CytoDyn, Inc. | |
| **Name of Study Product:**<br>Leronlimab (PRO 140)-Humanized monoclonal antibody to CCR5 | |
| **Protocol Number:**<br>CDI-NASH-01 | **Indication:**<br>Nonalcoholic Steatohepatitis (NASH) |
| **Title of Study:**<br>A Phase II, Multi-center, Two-Part (Part1: Randomized, Double-Blind, Placebo-Controlled with Leronlimab 700mg and placebo; and Part 2: Open-label, Single Arm with Leronlimab 350mg), Three-Arm, Dose-Ranging Study of the Safety and Efficacy of Leronlimab (PRO 140) in Adult Patients with Nonalcoholic Steatohepatitis (NASH) | |
| **Planned Number of Subjects:**<br>Part 1 (Randomized Phase): Up to 60 Subjects<br>Part 2 (Non-Randomized, Open-label Phase): Up to 30 Subjects | **Study Development Phase:**<br>Phase II |
| **Study Population:**<br>Adult patients with Nonalcoholic Steatohepatitis (NASH) | |

**Objectives:**

**Primary Objective:**

- The Primary objective of this study is to assess the efficacy of Leronlimab (PRO 140) in improving liver function in adult patients diagnosed with NASH compared to placebo

**Secondary Objective:**

- The Secondary objective of this study is to assess the safety and tolerability of Leronlimab (PRO 140) in adult patients diagnosed with NASH compared to placebo

**Study Outcome Measures**

**Primary Efficacy Outcome Measure:**

- Change from baseline in hepatic fat fraction assessed by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) at week 14

**Secondary Efficacy Outcome Measures:**

- Change from baseline in fibro-inflammatory activity as assessed by cT1 (corrected T1) assessed by multiparametric magnetic resonance imaging (MRI) of liver at week 14

  *Note: cT1 measured in milliseconds (ms) is a quantitative metric for assessing a composite of liver inflammation and fibrosis*

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- Change from baseline in liver fibrosis using FibroTest at week 14
- Change from baseline in hepatic inflammatory activity using FibroTest at week 14
- Change from baseline in serum pro-inflammatory biomarkers assessments
- Change from baseline in Gamma-glutamyltransferase (GGT) at week 14
- Change from baseline in Cytokeratin 18 (CK-18) level at week 14
- Change from baseline in Leronlimab (PRO 140) PK assessments

**Exploratory Outcome Measures:**

- Change from baseline in Alanine transaminase (ALT) at week 14
- Change from baseline in Aspartate transaminase (AST) at week 14
- Change from baseline in total bilirubin at week 14
- Change from baseline in triglycerides at week 14
- Change from baseline in Low Density Lipoprotein (LDL) at week 14
- To explore Monocyte/T cell CCR5 biomarkers that may predict activity of leronlimab.

**Safety Assessments**

Safety will be assessed by close monitoring and timely assessment of Adverse Events (AEs), laboratory parameters (blood tests, urinalysis), vital signs (blood pressure, heart rate), subject's medical condition (physical examination including weight). Each subject will be regularly assessed in each cycle for potential AEs and disease related signs and symptoms. The CTCAE v5.0 will be used to grade toxicities/AEs.

Tolerability of repeated subcutaneous administration of leronlimab (PRO 140) as assessed by study participants (using 11-point Numeric Pain Rating Scale) and by investigator-evaluation of injection site reactions.

**Trial Design:**

This is a phase II, multi-center, two-part study (Part 1: randomized, double-blind, placebo-controlled, two-arm with 60 patients; Part 2: non-randomized, single-arm, open-label with 30 patients) designed to evaluate the safety, tolerability, and efficacy of leronlimab (PRO 140) SC in patients with NASH for 13 weeks. In Part 1 of the study, leronlimab (PRO 140 700 mg dose) or placebo will be weekly administered subcutaneously (SC) by a licensed healthcare professional at the clinic sites.

A single arm, non-randomized, open-label phase (Part 2) is added to the protocol after completion of enrollment in the Randomized Phase (Part 1) of the study. In Part 2 of the study, leronlimab (PRO 140 350

mg dose) will be weekly administered subcutaneously (SC) by a licensed healthcare professional at the clinic sites.

- **Part 1**: randomized, double-blind, placebo-controlled, two-arm (up to 60 subjects)
  - Leronlimab (PRO 140 700 mg) or Placebo SC weekly injection for 13 weeks
- **Part 2**: non-randomized, open-label, single-arm (up to 30 subjects)
  - Leronlimab (PRO 140 350 mg) SC weekly injection for 13 weeks

This study consists of screening, treatment, and follow-up periods.

**Screening Period (Up to 4 weeks):**

Screening assessments will commence after obtaining signed Informed Consent Form (ICF), and review of medical history, demographic information, baseline disease characteristics, eligibility evaluation, physical examination, vital signs, height and weight, prior and concomitant medications, electrocardiogram (ECG), Liver MRI, FibroScan (or equivalent non-invasive imaging test), FibroTest, routine serum biochemistry including liver function test, hematology, HIV and hepatitis serology panel, urinalysis, serum pregnancy (if applicable). These assessments must be conducted within 28 days of the first treatment visit. Subjects who fail to meet eligibility criteria will be considered screen failures and exit the study without any further evaluations.

**Treatment Period (Up to 14 Weeks):**

In the Part 1 of the study, subjects who meet all eligibility criteria, as per data gathered from Screening Visit, will be randomized 1:1 to one of the two study arms to receive Leronlimab 700 mg (Group A), or placebo (Group B) during the treatment period.

- PRO 140 (700mg) SC weekly injection (Group A)
- Placebo (0 mg) SC weekly injection (Group B)

Study treatments for each group (Leronlimab 700 mg or placebo) will be subcutaneously administered every week by a licensed healthcare professional at the study site for 13 weeks. The End of Treatment (EOT) visit (or early withdrawal visit in case of patients withdrawn prematurely from the study) will happen 1 week after receiving the last study treatment.

In the non-randomized, single-arm, open-label phase (Part 2) of the study, leronlimab (PRO 140 350 mg dose) will be weekly administered subcutaneously (SC) by a licensed healthcare professional at the clinic sites for 13 weeks.

**Follow-Up Period:**

A Follow-Up visit will be conducted 28 (± 3) days after the End of Treatment (EOT) or Early Termination (ET) Visit.

**Duration of Treatment:**

- **Screening Period:** Up to 4 weeks
- **Treatment Period:** Up to 14 weeks
- **Follow-Up Period:** Up to 4 weeks after End of Treatment (EOT) or Early Termination (ET) Visit

| | |
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- **Total Study Duration:** Up to 22 weeks

**Inclusion Criteria:** Subjects are required to meet ALL of the following criteria for enrollment into the study:

1. Subject is a male or female between 18 to 75 years of age inclusive.
2. Evidence of nonalcoholic steatohepatitis (NASH) based on one of the following criteria:
   - Criteria 1: Histologically-confirmed diagnosis of NASH on a liver biopsy, or
   - Criteria 2: FibroScan or Shearwave US during screening (or within 6 months before screening) shows kPa ≥7 but <14 and CAP ≥260.
3. Subject shows presence of hepatic fat fraction as defined by ≥ 8% on MRI-PDFF and cT1 ≥ 800 ms at Screening.
4. Has had a stable body weight (±5%) within 6 months prior to Screening.
5. Body Mass Index (BMI) ≥ 28 kg/m$^2$ at Screening
6. Has clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator.
7. Laboratory Screening results as indicated below:
   a. AST:ALT Ratio ≤ 1, if AST or ALT value is > ULN
   b. Screening Liver enzymes (AST, ALT, and ALK PHOS) < 5 x ULN.
   c. Total Bilirubin ≤ 1.3 mg/dL (except if Gilbert's Disease)
   d. Platelet count ≥ 150,000/mm$^3$
   e. International normalized ratio (INR) < 1.3
   f. Estimated Glomerular Filtration Rate (eGFR) ≥ 60/mL/min
   g. Glycosylated hemoglobin (HbA1c) < 9%.
   h. Thyroid-Stimulating Hormone (TSH) within normal reference range.

   *Note: Any subject with a non-clinically significant TSH value outside of the normal range may be enrolled if their T3 and free T4 values are within the normal range.*
8. Subjects with pre-diabetes or type 2 diabetes will be allowed to participate if the following criteria is met:

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- Subjects who are taking anti-diabetic medications should be on a stable dose for a period of at least 3 months prior to Screening and do not anticipate clinically significant dose adjustments during the course of study.
- Subjects must be on a stable diet/lifestyle regimen for at least 3 months prior to screening and do not anticipate a clinically significant change during the course of study.

9. Subjects who are taking Vitamin E should be on a stable dose of Vitamin E (if ≥ 400 IU) for a period of at least 4 weeks prior to Screening and do not anticipate dose adjustments for the duration of the study.
10. Both male and female patients and their partners of childbearing potential must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, tubal sterilization or vasectomy) or must practice complete abstinence from intercourse of reproductive potential from study entry to 6 months after the last day of treatment (excluding women who are not of childbearing potential and men who have been sterilized).
11. Females of child-bearing potential must have a negative serum pregnancy test at Screening Visit and negative urine pregnancy test prior to receiving the first dose of study drug; and Male participants must agree to use contraception and refrain from donating sperm for at least 90 days after the last dose of study intervention.
12. Subject is willing and able to give informed consent prior to any study specific procedures being performed.
13. Subject is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures and study restrictions

**Exclusion Criteria:** Subjects meeting ANY of the following criteria will be excluded from enrollment:

1. Any concurrent clinically significant liver disease with an etiology other than NASH including autoimmune hepatitis, alcoholic hepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.
2. History of alcohol consumption greater than 21/units/week (for males) and 14/units/week (for females) within the last 2 years prior to screening.
   *Note: Use of online unit calculator for alcohol consumption is recommended (e.g., https://alcoholchange.org.uk/alcohol-facts/interactive-tools/unit-calculator)*
3. Any drug-induced steatohepatitis secondary to amiodarone, corticosteroids, estrogens, methotrexate,

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tetracycline, or other medications known to cause hepatic steatosis.

4. Undergone major surgery, including liver surgery, within 6 months prior to screening deemed clinically significant by the investigator.
5. Prior or pending liver transplantation.
6. History or presence of cirrhosis or stage 4 fibrosis in historical liver biopsy and/or hepatic decompensation including ascites, hepatic encephalopathy or variceal bleeding.
7. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test), hepatitis C (defined as having a positive Anti-HCV test with detectable reflex HCV RNA; Note: Subject with positive Anti-HCV test and with undetectable HCV RNA would not be excluded), acute hepatitis A (defined as subjects with serum positive for hepatitis A IgM (HAV) antibody) or acute hepatitis E (defined as having anti-HEV IgM antibody).
8. Any active infection requiring systemic therapy at the time of screening, which is considered clinically significant per the Investigator.
9. Positive test for human immunodeficiency virus (HIV) or HIV infection.
10. History of bleeding diathesis within 6 months of screening.
11. Any malignancy within the past 5 years, excluding successfully treated basal cell carcinoma or squamous cell carcinoma without evidence of metastases.
12. Seizure disorder requiring ongoing antiseizure therapy or with any condition that, in the judgment of the investigator, is likely to increase the risk of seizure (e.g. CNS malignancy)
13. Clinically significant active cardiac disease which would interfere with study conduct or study results interpretation per the PI.
14. Any known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. Prior therapy with Leronlimab or any other CCR5 antagonist (e.g. maraviroc) within 6 months prior to screening.
16. History of severe allergic, anaphylactic, or other hypersensitivity reactions to humanized monoclonal antibodies.
17. Any condition requiring continuous systemic treatment with immunosuppressive (such as corticosteroids) or immunomodulatory medications.

*Note: Inhaled or topical steroids of up to 5 mg daily prednisone equivalent dose are permitted in the*

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*absence of active autoimmune disease.*

18. History of administration of a live, attenuated vaccine within four weeks prior to start of PRO 140 treatment or anticipation that such a live attenuated vaccine will be required during the remainder of the study.

    *Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist ®) are live attenuated vaccines, and are not allowed.*

19. Currently participating in an investigational study or received an investigational drug within 28 days or 5 half-lives (whichever is longer) prior to study drug administration

**Statistical Considerations:**

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical variables.

Adverse events will be coded using the most recent version of MedDRA. Treatment Emergent Adverse Events (TEAS) will be summarized by System Organ Class (SOC), and preferred term (PT).

**Sample Size Determination and Rationale:**

The sample size of 90 total subjects [60 subjects (30 subjects per arm) for the Randomized Phase and up to 30 subjects for the non-randomized, open-label phase] is selected on the basis of clinical judgment and not based on statistical power calculation. The number of subjects is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

**Analysis Populations:**

The Intent-to-Treat (ITT) population is defined as the set of subjects who have received at least one dose of study treatment (Leronlimab (PRO 140) or placebo) and have at least one post-baseline efficacy assessment. The ITT population will be used as the primary analysis population.

The Per Protocol (PP) population is defined as the set of subjects who meet the ITT population requirements, were not associated with any major protocol violations and have at least 80% compliance with study treatment. This population will be identified before the database lock.

The Safety Population will include all subjects who have received at least one dose of study treatment (Leronlimab (PRO 140) or placebo). This population will be used for the analysis of safety parameters or measurements.

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## LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| ADA | Anti-Drug Antibodies |
| AE | Adverse Event |
| AASLD | American Association for the Study of Liver disease |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis of Covariance |
| ART | Antireteroviral therapy |
| AST | Aspartate Aminotransferase |
| BUN | Blood Urea Nitrogen |
| BMI | Body Mass Index |
| BLM | Baseline Measurement |
| CAP | Controlled Attenuation Parameter |
| CBC | Complete Blood Count |
| CBR | Clinical Benefit Rate |
| CCL5 | C-C Chemokine Ligand Type-5 (RANTES) |
| CCR5 | C-C Chemokine Receptor Type-5 |
| CFR | Code of Federal Regulations |
| CHO | Chinese Hamster Ovary |
| CK | Creatine Kinase |
| CK-18 | Cytokeratin 18 |
| $C_{max}$ | Maximal Concentration |
| CNS | Central Nervous System |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| cT1 | Corrected T1 |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CVD | Cardiovascular Disease |
| D/M | Dual/Mixed |
| DILI | Drug- Induced Liver Injury |
| ECG | Electrocardiogram |
| ECL2 | ExtraCellular Loop 2 |

| Abbreviation | Term |
|---|---|
| eCRF | Electronic Case Report Form |
| EASL | European Association for the Study of the Liver |
| eGFR | Estimated Glomerular Filtration Rate |
| EGFR | Epidermal Growth Factor Receptor |
| ELF Score | Enhanced Liver Fibrosis Score |
| EOT | End of Treatment |
| ET | Early Termination |
| F1-F4 | Fibrosis (Stage) |
| FDA | U.S. Food and Drug Administration |
| Flu-Mist | Influenza Vaccine |
| FOCBP | Females of Child-bearing Potential |
| GCP | Good Clinical Practice |
| GGT | Gamma-Glutamyltransferase |
| GMP | Good Manufacturing Practice |
| GVHD | Graft versus Host Disease |
| HAV | Hepatitis A Virus |
| HbA1c | Hemoglobin A1c |
| HBsAg | Hepatitis B Virus Surface Antigen |
| HCC | Hepatocellular Carcinoma |
| HCV | Hepatitis C Virus |
| HEENT | Head, Ears, Eyes, Nose, and Throat |
| HEV | Hepatitis E Virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV-1 | Human Immunodeficiency Virus Type 1 |
| HSC | Hepatic Stellate Cells |
| IA | Interim Analysis |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry assay |

| Abbreviation | Term |
|---|---|
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| ISR | Injection Site Reactions |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| KC | Kupffer cell |
| kPa | kilopascals |
| LDL | Low Density Lipoprotein |
| LTF | Lost to Follow-up |
| mAb | Monoclonal Antibody |
| mCRC | Metastatic Colorectal Cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| M/F | Male/Female |
| MRI | Magnetic Resonance Imaging |
| MSS | Microsatellite Stable |
| MTD | Maximum Tolerated Dose |
| mTNBC | Metastatic Triple-Negative Breast Cancer |
| NAFLD | Nonalcoholic Fatty Liver Disease |
| NASH | Nonalcoholic Steatohepatitis |
| NOAEL | No Observed Adverse Effect Level |
| NCS | Not Clinically Significant |
| Nt | N terminus |
| OBT | Optimized Background Therapy |
| OELF Score | Original European Liver Fibrosis Panel Score |
| ORR | Overall Response Rate |
| OTC | Over the Counter |
| PD | Pharmacodynamics |
| PDFF | Proton derived fat fraction |
| PI | Principal Investigator |
| PK | Pharmacokinetics |

| Abbreviation | Term |
|---|---|
| PP | Per Protocol |
| PT | Preferred Term |
| QTc | QT interval corrected for heart rate |
| RNA | Ribonucleic Acid |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SOC | System Organ Class |
| SOP | Standard Operating Measures |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| TBL | Total Bilirubin |
| T2DM | Type 2 Diabetes Mellitus |
| TEAE | Treatment Emergent Adverse Event |
| TSH | Thyroid-Stimulating Hormone |
| ULN | Upper Limit Normal |
| US | United States |
| USP | United States Pharmacopeia |
| VEGF | Vascular Endothelial Growth Factor |
| VL | Viral Load |

# 1 INTRODUCTION AND BACKGROUND

## 1.1 STATEMENT OF INTENT

The design, conduct and reporting of this study shall be conducted in compliance with the protocol, International Council for Harmonisation/Good Clinical Practice (ICH/GCP), and all appropriate regulatory requirements. Investigator(s) participating in this study will have documented training in GCP. Independent monitoring of the trial will be accomplished utilizing a Contract Research Organization (CRO).

## 1.2 BACKGROUND OF THE DISEASE

Nonalcoholic steatohepatitis (NASH) is a chronic liver disease characterized histologically by the presence of hepatic inflammation and cell injury (hepatocellular ballooning) due to hepatic fat accumulation (steatosis) equal or superior to 5% of hepatocytes. NASH develops in the absence of excessive alcohol consumption but is linked to unhealthy eating habits and lack of physical activity. It is often referred to as metabolic disease of the liver (Naga Chalasani, 2018). NASH can progress to high-burden conditions such as cirrhosis, end stage liver disease and Hepatocellular Carcinoma (HCC) (Manca Povsic, 2019). It is predicted that NASH will become the leading cause of liver transplantation by 2020 in the United States. It is the most common form of chronic liver disease, affecting about one-quarter of the population in the United States. An estimated 3-7% of the adult population develop NASH, of which approximately 15-20% progress to advanced fibrosis or cirrhosis (Zobair M. Younossi, 2018). Despite its very high burden, there are currently no approved pharmacological therapies for NASH. Available therapies focus solely on treating NASH comorbidities, such as obesity, Type 2 Diabetes Mellitus (T2DM) and Cardiovascular Disease (CVD), while NASH management options focus on lifestyle changes, based on diet and exercise, and control of the associated comorbidities. Lifestyle changes have demonstrated greatest benefit in improving steatosis and mild fibrosis; however, as patients with advanced fibrosis due to NASH are at a significantly higher risk of liver-related mortality, pharmacological treatments are urgently needed.

<u>Inflammatory response in nonalcoholic steatohepatitis (NASH)</u>

In NASH, liver homeostasis is impaired due to an accumulation of toxic lipids. Certain gut bacteria-derived products can also penetrate in the liver, where they activate immune responses. This contributes to local inflammation of hepatic tissue. This pathological environment provokes hepatocytes damage and leads to a state called ballooning. Steatosis, inflammation and ballooning are the three lesions that define NASH histologically.

The inflammatory response to hepatocyte injury plays a key role in hepatic fibrogenesis and involves recruitment of inflammatory cells to the site of injury. Recruitment of extra-hepatic inflammatory

cells to the site of hepatic injury is largely mediated by interactions between chemokines and their receptors. Monocytes, Kupffer cells (KCs) and Hepatic Stellate Cells (HSCs) can express C-C chemokine receptor types 5 (CCR5) on their surface. Evidence implicates CCR5 and their ligands including C-C chemokine ligand type 5 (CCL5) in the pathogenesis of liver fibrosis following liver injury.

It has also been shown that patients with chronic liver disease show high levels of CCR5 and CCL5, thus showing the role of CCR5 and its ligands in liver fibrosis. Numerous studies of NASH with other CCR5 agents have shown anti-inflammatory and anti-fibrotic effects (Lefebvre E, 2016). For that reason, CCR5 has become an attractive target for developing new antifibrotic therapies (Zobair M. Younossi, 2018).

### 1.3 STUDY TREATMENT

Leronlimab (PRO 140)

Leronlimab (PRO 140) is a humanized IgG4,κ Monoclonal Antibody (mAb) to the C-C chemokine receptor type 5 (CCR5), under development as a therapy for Human Immunodeficiency Virus (HIV) infection and other indications including triple negative breast cancer, colorectal cancer and Graft versus Host Disease (GVHD).

Leronlimab (PRO 140) has been administered intravenously or subcutaneously to more than 750 healthy and HIV-1 infected individuals in Phase I/II/III studies. The drug has been well tolerated following intravenous administration of single doses of 0.5 to 10 mg/kg or up to 700 mg weekly doses as Subcutaneous (SC) injection. Overall, more than 300 subjects have been exposed to Leronlimab (PRO 140) 350 mg SC weekly dose with the longest duration of exposure lasting more than 5 years. Similarly, more than 250 and 150 subjects have been exposed to Leronlimab (PRO 140) 525 mg and 700 mg SC weekly dose, respectively. To date, the longest exposure to PRO 140 525 mg and 700mg SC weekly dose is more than 2 years and 48 weeks, respectively. Considering its anti-CCR5 activity and per the pre-clinical studies conducted, Leronlimab (PRO 140) is being developed as a potential therapy for liver fibrosis and inflammation conditions, including NASH.

### 1.4 PRE-CLINICAL STUDIES OF LERONLIMAB (PRO 140)

*In vitro* and *in vivo* preclinical studies have been conducted to determine the pharmacokinetic, immunogenicity, and toxicity profiles of Leronlimab (PRO 140) following Intravenous (IV) and SC administration. Several acute and chronic toxicity studies have been conducted to support the clinical development plan.

Acute toxicity of Leronlimab (PRO 140) was evaluated in New Zealand rabbits, following IV administration of 5 or 15 mg/kg. Chronic toxicity was evaluated in cynomolgus monkeys following biweekly administration of IV doses up to 10 mg/kg for six months and biweekly administration of

various SC doses up to 50 mg/kg for 24 weeks. The drug was generally well tolerated. Biweekly administration of IV doses up to 10 mg/kg for six months resulted in minimum to mild lymphoid hyperplasia in assorted lymph nodes and spleen, which was considered an expected immune response to a foreign protein. Biweekly administration of SC doses up to 50 mg/kg for 24 weeks resulted in minimum injection-site reactions (minimal, multifocal, mononuclear cell infiltrates in the subcutis), which were considered due to an inflammatory response to the injected antigen. Monkeys tolerated treatment with Leronlimab (PRO 140) for 24 weeks without evidence of local or systemic toxicity. Leronlimab (PRO 140) caused no mortality, cageside observations, in-life injection-site observations, or gross pathologic findings. Chronic treatment with Leronlimab (PRO 140) did not affect body weight, food consumption, hematology, clinical chemistry or coagulation parameters.

Both IV and SC administration resulted in elimination half-lives of approximately 200 hours, and overall exposure increased with increasing doses. Following SC administration of Leronlimab (PRO 140) in monkeys, the maximal concentration ($C_{max}$) was achieved within 56 hours and bioavailability for Leronlimab (PRO 140) after SC dosing was approximately 70%.

Non-Clinical Studies with Leronlimab (PRO 140) on NASH

An *in vivo* study was conducted to determine the anti-fibrotic activity of PRO 140 humanized monoclonal antibody against CCR5 in mouse xenograft models of NASH (Study No.20127293). The objective of this study was to assess the effect of PRO 140 on NASH in mice when given by intraperitoneal injection bi-weekly for 4 weeks.

Reduction in liver fibrosis was observed when 2mg PRO 140 was administered via intraperitoneal injection twice weekly for 4 weeks

### 1.5 CLINICAL STUDIES WITH LERONLIMAB (PRO 140)

Current human experience with Leronlimab (PRO 140) consists of ten completed and six ongoing clinical trials, mostly on healthy subjects or HIV-1 positive subjects. These studies are summarized in Table 1-1 and Table 1-2. In all clinical trials, the majority of Adverse Events (AEs) have been mild or moderate. No dose-limiting toxicities or patterns of drug-related toxicities were observed.

PRO 140 1101 Study

For the first-in-human trial, PRO 140 1101, the drug was administered IV at 0.1, 0.5, 2.0, or 5.0 mg/kg to healthy subjects and was generally well tolerated, non-immunogenic, and without clinically relevant toxicity. Treatment Emergent Adverse Events (TEAEs) did not increase with rising PRO 140 dose levels. Seventy-five percent (75%) of subjects reported TEAEs, most of which were deemed unrelated to study treatment by the investigator.

PRO 140 1102 Study

For PRO 140 1102, the majority of AEs, other than injection-site reactions, were considered mild and possibly related to drug administration. The majority of injection-site reactions were considered mild, self-resolving, and definitely related to drug administration. PRO 140 derived from Chinese Hamster Ovary (CHO) cells and administered at 100 mg/mL was generally well tolerated in healthy, normal volunteers. Overall, PRO 140 administered SC using Autoject® 2 appeared better tolerated than manual injection.

PRO 140 1103 Study

In PRO 140-1103, administration of PRO 140 at 350 mg using Autoject® 2 appeared well tolerated. Manual injections, on the other hand, were associated with a greater number of AEs. There did not appear, however, to be any substantial difference in subject perception of pain or discomfort related to site of drug administration. No anti-PRO 140 antibodies were detected in any subjects in this study. There was a tendency of higher exposure associated with SC administration of PRO 140 at 350 mg in the abdomen and the thigh. A higher number of AEs was associated with injections in the arm. Based on these observations, thigh and abdominal administration of PRO 140 were preferred over arm injection.

PRO 140 1302 Study

The initial proof-of-concept study was a randomized, double-blind, placebo-controlled study in subjects with early-stage, asymptomatic HIV infection, only R5 HIV-1 detectable, and no antiretroviral therapy for 12 weeks [Jacobson, 2008]. Subjects (n=39) were randomized to receive a single IV injection of placebo or PRO 140 at doses of 0.5, 2, or 5 mg/kg. Subjects were monitored for antiviral effects, safety, and PRO 140 Pharmacokinetics (PK) for 58 days.

PRO 140 demonstrated potent, rapid, prolonged, and dose-dependent antiviral activity. Intravenous PRO 140 was generally well tolerated. No drug-related serious events or dose-limiting toxicity was observed [Jacobson, 2008]. The most common adverse events (headache, lymphadenopathy, diarrhea, and fatigue) were observed at similar frequencies across the placebo and PRO 140 dose groups. There was no significant effect on QTc intervals or other electrocardiographic parameters, and there were no remarkably laboratory findings.

PRO 140 2301 Study

PRO 140 2301 was a multi-center, randomized, double-blind, placebo-controlled, parallel group study in 30 male and female adult subjects infected with HIV-1 [Jacobson, 2010]. Subjects were randomized to one of three groups (N=10/group), each receiving one of three treatments: (i) a single IV dose of 5 mg/kg by 30-minute IV infusion; (ii) a single IV dose of 10 mg/kg by 30-minute IV infusion; (iii) a single placebo dose by 30-minute IV infusion. The objective of the study was to assess and characterize the Pharmacokinetics (PK) and Pharmacodynamics (PD) of PRO 140

administered by IV infusion, assess efficacy at a new dosage level, and safety and tolerability of single doses of PRO 140.

All PRO 140-treated subjects had more than 10-fold reduction in viral loads [Jacobson, 2010]. Both the 5 mg/kg and 10 mg/kg doses have shown favorable tolerability and no dose-limiting toxicity has been observed. High levels of receptor occupancy (>85% reduction in the number of cells detected) were observed for 29 days after treatment with both 5 and 10 mg/kg doses.

PRO 140 2101 Study

A subcutaneous (SC) form of PRO 140 was tested in HIV-infected subjects. The trial was a randomized, double-blind, placebo-controlled study in subjects (n=44) with early-stage, asymptomatic HIV infection, only R5 HIV-1 detectable, and no antiretroviral therapy for 12 weeks [Thompson, 2009]. Placebo (n=10) and three PRO 140 doses were examined: 162 mg weekly for three weeks (n=11), 324 mg weekly for three weeks (n=11), and 324 mg biweekly (every other week) for two doses (n=12). Subjects were followed for 44 days after the final dose.

Potent, dose-dependent and highly statistically significant antiviral activity was observed. The trial established the first antiviral proof of concept for a long-acting, self-administrable drug for HIV-1 infection [Thompson, 2009].

Subcutaneous PRO 140 was generally well tolerated both locally and systemically. There was no obvious dose-related pattern of toxicity. The most common adverse events (diarrhea, headache, lymphadenopathy and hypertension) were mild to moderate and self-resolving. These events are common in HIV infection and were reported with similar frequencies in the placebo and PRO 140 treatment groups. Administration-site reactions were mild, transient, and observed in a fraction of subjects.

PRO 140_CD01 Study

PRO 140_CD01 study (open-label, 43 subjects, multi-center) evaluated the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 12 weeks) for the maintenance of viral suppression following substitution of antiretroviral therapy in HIV-1 infected patients (with exclusive CCR5-tropic virus). Participants in this study were experienced HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy. Consenting patients were shifted from combination antiretroviral regimen to PRO 140 monotherapy for 12 weeks.

Forty-three (43) subjects (M/F: 37/3) with median age of 54.5 years (26-72) and median CD4 T-cell count of 604.5 cells/mm3 (365-1240) were enrolled in the CD01 study. Overall, twenty-two out of 40 (55%) enrolled subjects completed 12 weeks of PRO 140 monotherapy without experiencing virologic failure. Virologic failure was defined as two consecutive HIV-1 RNA levels of $\geq$ 400 copies/mL separated by at least 3 days. Of the 43 enrolled subjects, 3 subjects were found to have Dual/Mixed (D/M) tropism [1 at baseline and 2 at the time of virologic failure] and 37

subjects were found to have exclusive CCR5-tropic virus. A letter of amendment was filed to increase the planned number of subjects from 40 to 43 subjects to compensate for the 3 Dual/Mixed subjects enrolled in the study.

All virologic failure subjects who had available lab data in both studies achieved viral suppression to < 400 HIV-1 RNA copies/mL, as well as viral suppression to 'Non Detectable' or < 50 HIV-1 RNA copies/mL after re-initiation of Antiretroviral Therapy (ART).

The by-subject analysis of PhenoSense® Entry Assay data for PRO140, maraviroc, and AMD3100 shows no significant changes in the post-treatment IC50 and IC90 values were noted when compared with baseline values in virologic failure and non-virologic failure groups of subjects. As the aggregate analysis shows for initial 40 subjects, the subjects who experienced virologic failure had higher IC90 value for PRO 140 at baseline compared to subjects without virologic failure. The mean IC90 for subjects who experienced virologic failure was higher (10.84 µg/mL) than the IC90 for subjects without virologic failure (6.70 µg/mL) in the CD01 study (p=0.0115).

Anti-PRO 140 antibodies were not identified in any post-treatment sample and data derived from the CD01 study further supports the favorable PRO 140 PK profile data generated from both pre-clinical as well as prior Phase 1/2 clinical trials.

Safety data were analyzed for all 43 enrolled subjects. One (1) of 43 subjects experienced a Serious Adverse Event (SAE) that was deemed not related to the study drug by the Principal Investigator. Twenty-eight (28) of 43 subjects (67%) experienced one or more AEs after receiving at least one dose of PRO140. The most commonly occurring AEs were infections and infestation conditions which were reported by 14 of 43 (32.5%) subjects. The majority of the reported AEs (62/87; 71.2%) were deemed either unlikely or not related to study treatment by the Investigator. Similarly, the majority of the reported AEs (70/87; 80.4%) were deemed mild in nature.

PRO 140_CD01 Extension Study

PRO 140_CD01-Extension study (open-label, 28 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly) for the continued maintenance of viral suppression following substitution of antiretroviral therapy in HIV patients (with exclusive CCR5-tropic virus). Participants in this study were HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy and completed the first 12 weeks of CD01 study without experiencing virologic failure. As with the CD01 study, virologic failure was defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/mL separated by at least 3 days. Consenting patients may remain on PRO 140 monotherapy until PRO 140 receives marketing approval or Investigational New Drug (IND) application is withdrawn by Sponsor.

A total of 17 subjects participated in the CD01-Extension study of which one subject was considered not eligible as subject experienced virologic failure prior to first extension treatment.

Sixteen (16) eligible subjects (M/F: 14/2) with median age of 54.9 years (26-68) and median CD4 T-cell count of 593 cells/mm3 (365-1059) were enrolled in an extension study. One patient discontinued at week 37 (with viral load of <40 copies/mL) due to relocation. Two subjects were withdrawn due to non-treatment related SAEs at week 140 and 149, respectively. One subject was withdrawn due to re-starting their ART at week 99. Two subjects withdrew consent at week 81 and 139, respectively. Five (5) subjects experienced virologic failure (VF) (two consecutive viral load of ≥400 copies/mL). The mean time to virologic failure was 329 days (106-691).

Five (5) subjects are currently receiving weekly 350 mg PRO140 SC monotherapy and have completed more than three years of treatment (176 – 198 weeks). Overall, 12 subjects completed at least one year of treatment and 9 subjects completed at least two years of treatment in this study

PRO140 was generally well tolerated, and no drug-related SAEs were observed.

This clinical study is currently ongoing.

PRO 140_CD02 Study

PRO 140_CD02 study (double blind, placebo controlled, 52 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 in combination with either existing ART (failing regimen) or Optimized Background Therapy (OBT) in patients infected with HIV-1. The study population includes 52 adult patients with a documented history of genotypic or phenotypic resistance to ART drugs within two or more drug classes who demonstrate evidence of HIV-1 replication despite ongoing antiretroviral therapy and have limited treatment options. The options may be limited as a result of drug antiviral class cross-resistance, documented treatment intolerance, documented objective assessments such as renal or hepatic insufficiency (e.g. high creatinine at baseline, limiting treatment options due to potential for toxicity), past adverse reactions such as hypersensitivity reactions or neuropsychiatric issues that could limit use of currently approved drugs.

In Part 1 of double-blind treatment period, virally non-suppressed subjects will be randomized and treated with either PRO 140 or Placebo in combination with the failing ART regimen for 7 days until HIV-1 genotypic drug resistance assay results are available to construct an OBT. The primary efficacy endpoint is proportion of participants with ≥ 0.5 log10 reduction in HIV-1 RNA viral load from baseline at the end of the 7 day functional monotherapy period.

In Part 2 of double-blind treatment period, subjects will continue treatment with PRO 140 in combination with OBT within the 24-week open-label period.

Fifty-two subjects with a mean age of 52.4 years, 73.1% male, 48.1% non-white and mean duration of HIV-1 infection of 20.4 years were randomized 1:1 to the PRO 140 SC or placebo arm. Subjects had been previously exposed to an average of 11 ART drugs and had documented resistance to >9 ART drugs. Mean baseline Viral Load (VL) and CD4 cell count were 21,104 c/mL and 297.8 c/mm3, respectively. The primary efficacy endpoint- the proportion of patients with ≥0.5 log10

reduction in HIV-1 VL from baseline at the end of the 1-week double-blind, randomized, placebo-controlled treatment period- was met (16/25 vs 6/26 [p-value <0.0032, ITT population]). Forty seven (47) of 52 patients have completed the 25-week study. Approximately 81% of patients completing 25-weeks of PRO 140 SC treatment demonstrated HIV-1 VL <50 c/mL and 92% had HIV-1 VL <400 c/mL. Continued access to PRO 140 SC was provided through a rollover study and 40 patients entered the extension protocol after completing the CD02 study. PRO 140 SC was generally well tolerated. No drug-related SAEs or treatment discontinuations were reported in the study. This clinical study is completed.

PRO 140_CD06 Study

PRO 140_CD06 study (double-blind, 80 subjects, single-center) seeks to evaluate the comparability of PRO 140 formulation Batch Lot # 3-FIN-3143 versus formulation Batch Lot# 3-FIN-2618 as a one-time subcutaneous (SC) injection in healthy subjects under non-fasting conditions. This clinical study is completed.

PRO 140_CD02 Extension Study

PRO 140_CD02 Extension study (open label, 40 subjects, multi-center) seeks to evaluate the long term efficacy, safety and tolerability of PRO 140 weekly injection in combination with Optimized Background Therapy (OBT) in patients infected with HIV-1. The study population includes 40 treatment-experienced HIV-infected adult patients with CCR5-tropic virus who successfully completed PRO 140_CD02 study and continues to demonstrate HIV-1 viral suppression.

This clinical study is currently ongoing.

PRO 140_CD03 HIV Study

PRO 140_CD03 HIV (open-label, 566 subjects, multi-center) is a three part study enrolling virally suppressed HIV-1 patients with CCR5-tropic HIV-1 receiving combination antiretroviral (cART) therapy. Patients received weekly doses of PRO 140 on single-agent maintenance therapy following one week of overlap of the existing cART regimen that is then discontinued. In part 1, 156 participants received 350 mg PRO 140 SC in a single-arm design. In part 2, 147 participants received 350 or 525 mg PRO 140 SC in a 1:1 ratio as randomized controlled, two-arm study. In an ongoing part 3, 263 participants have been randomized to receive 525 or 700 mg PRO 140 SC in a 1:1 ratio.

Of the 566 patients enrolled, median age was 52 yrs (21-81) with the majority reported as male (78%) and 38% were non-white. A total of 132 subjects have been randomized to 700 mg dose. In addition, another 71 subjects have been exposed to 700mg dose after rescuing from the lower doses (350 mg or 525mg). On average, participants were diagnosed with HIV-1 infection for approximately 17 yrs and were on cART regimen for approximately15 yrs. The frequency and severity of injection site reactions were comparable between the three dose groups (350, 525 and

700mg) and the incidence or severity of injection site reactions was not increased in patients receiving higher doses. Overall, PRO 140 SC was generally well tolerated at all dose levels in this study.

This clinical study is currently ongoing.

PRO 140_CD03 HIV Extension Study

PRO 140_CD03 study (open-label, 350 subjects, multi-center) seeks to evaluate the long term efficacy, safety and tolerability of PRO 140 SC as long-acting single-agent maintenance therapy in virologically suppressed subjects with CCR5-tropic HIV-1 infection. The study population includes up to 300 treatment-experienced HIV-infected adult patients who successfully completed PRO 140_CD03 HIV study and continue to demonstrate HIV-1 viral suppression.

This clinical study is currently ongoing.

CD07_TNBC Study

CD07_TNBC study (open-label, two-part [Phase Ib: Up to 18 subjects; Phase II: 30 Subjects], multi-center) seeks to evaluate the efficacy, safety, tolerability and Maximum Tolerated Dose (MTD) of leronlimab (PRO 140) when combined with carboplatin in patients with CCR5+ metastatic triple-negative breast cancer (mTNBC).

The study population includes patients with CCR5-positive, locally advanced or metastatic triple-negative breast cancer (mTNBC) who are naïve to chemotherapy in metastatic setting but have been exposed to anthracyclines and taxane in neoadjuvant and adjuvant settings (first-line).

This clinical study is currently ongoing.

CD08_mCRC_Study

CD08_mCRC study (open-label, 30 Subjects, multi-center) seeks to evaluate the effect on Overall Response Rate (ORR) of Leronlimab (PRO 140) when combined with Regorafenib in patients with CCR5+, Microsatellite Stable (MSS), Metastatic Colorectal Cancer (mCRC).

The study population includes patients with CCR5+, MSS, mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-Vascular Endothelial Growth Factor (VEGF) therapy, and, if RAS wild type, an anti- Epidermal Growth Factor Receptor (EGFR) therapy.

**Table 1-1: List of Completed Clinical Studies with Leronlimab (PRO 140)**

| Protocol Number | Phase | No. of Subjects (Planned/ Analyzed) | Doses | Subject Population | Comments |
|---|---|---|---|---|---|
| PRO 140 1101 | 1 | 20/20 | Single 0.1, 0.5, 2.0, or 5.0 mg/kg | Healthy | Generally well tolerated; non-immunogenic; dose-dependent coating of CCR5; significant coating of CCR5 over placebo at 0.5, 2, and 5 mg/kg |
| PRO 140 1102 | 1 | 20/20 | Either two or three doses totaling 200 or 350 mg respectively | Healthy | Generally well tolerated; drug derived from CHO cells well tolerated also; SC administration by Autoject® 2 better tolerated than manual injection |
| PRO 140 1103 | 1 | 15/14 | Two doses, each of 350 mg | Healthy | More AEs associated with arm injection; trend of lower exposure in arm injections; thigh and abdominal administration preferred |
| PRO 140 1302 | 1b | 40/39 | Single 0.5, 2.0, or 5.0 mg/kg | HIV-1 positive | Generally well tolerated; antiviral suppression maintained for approximately 10 days with higher doses; favorable tolerability and potent, dose-dependent antiviral activity provide proof-of-concept |
| PRO 140 2301 | 2a | 30/31 | Single 5.0 or 10.0 mg/kg | HIV-1 positive | Generally well tolerated with no dose-limiting toxicities; potent antiviral suppression maintained for approximately 20 days when administered IV at 5 or 10 mg/kg. No dose-limiting toxicities at 10 mg/kg. |
| PRO 140 2101 | 2a | 40/44 | Three doses of 162 or 324 mg each | HIV-1 positive | Generally well tolerated, no drug-related SAEs or dose-limiting toxicity; antiviral activity was statistically significant; two-fold exposure at higher dose; single dose demonstrated favorable tolerability, and potent, long-acting, dose-dependent antiviral activity. |
| PRO 140 CD01 | 2b | 43/43 | 350 mg SC weekly dose for 12 weeks of monotherapy (total treatment duration 14 weeks) | HIV-1 positive | Generally well tolerated, no drug-related SAEs or dose-limiting toxicity; Open-label administration of PRO 140 demonstrated favorable tolerability, and potent, long-acting, antiviral activity. |
| PRO 140 CD02 | 2b/3 | 50/52 | 350 mg SC weekly dose of PRO 140 or placebo along with existing ART for 1 week then PRO 140 along with optimized background therapy for 24 | HIV-1 positive, treatment-experienced | This study is completed. |

| Protocol Number | Phase | No. of Subjects (Planned/ Analyzed) | Doses | Subject Population | Comments |
|---|---|---|---|---|---|
| | | | weeks (total treatment duration 25 weeks) | | |
| PRO 140 CD06 | PK | 80/79 | Single dose PK study with 350 mg SC dose | Healthy | This clinical study is completed. |
| CD10_COVID-19 | 2 | 75/86 | Two doses of leronlimab 700 mg or placebo | Mild-to-moderate COVID-19 | This clinical study is completed. |

**Table 1-2: List of Ongoing Clinical Studies with Leronlimab (PRO 140)**

| Protocol Number | Phase | No. of Subjects (Planned/ To be analyzed) | Doses | Subject Population | Comments |
|---|---|---|---|---|---|
| PRO 140 CD_01-Extension | 2b | 17/16 | 350 mg SC weekly dose (as monotherapy) | HIV-1 positive, treatment experienced | This clinical study is currently ongoing. |
| PRO 140 CD02 Extension | 2b/3 | 50/40 | 350 mg SC weekly dose in combination with Optimized Background Therapy (OBT) | HIV-1 positive, treatment experienced | This clinical study is currently ongoing. |
| PRO 140 CD03 | 2 | 500/566 | 350 or 525 or 700 mg SC weekly dose for 46 weeks of monotherapy (total treatment duration 48 weeks) | HIV-1 positive, treatment-experienced | This clinical study is currently ongoing. |
| PRO 140 CD03 Extension | 2 | 350/TBD | 350 or 525 or 700 mg SC weekly dose (as monotherapy) | HIV-1 positive, treatment experienced | This clinical study is currently ongoing. |
| CD07_TNBC | 1a/2b | Phase Ib: Up to 18 subjects Phase II: 30 Subjects | 350 or 525 or 700 mg SC weekly dose (as monotherapy) | Triple negative breast cancer | This clinical study is currently ongoing. |

| Protocol Number | Phase | No. of Subjects (Planned/ To be analyzed) | Doses | Subject Population | Comments |
|---|---|---|---|---|---|
| CD08_mCRC | 2 | Phase II: Up to 30 Subject | 700 mg SC weekly dose (as monotherapy) in combination with Regorafenib | CCR5+ Metastatic Colorectal Cancer (mCRC), Microsatellite Stable (MSS), treated with chemotherapy | This clinical study is pending start-up. |
| CD12_COVID-19 | 2b/3 | 390/238 | Two doses of leronlimab 700 mg or placebo | Severe and Critical COVID-19 | This clinical study is currently ongoing. |

### 1.6 Dose Section Rationale

Leronlimab (PRO 140) is currently under development for the indication of HIV in combination with other antiretroviral agents or as single agent maintenance therapy for the treatment of only CCR5-tropic HIV type 1 (HIV-1) infection.

In vitro and in vivo preclinical studies have been conducted to determine the pharmacokinetic, immunogenicity, and toxicity profiles of PRO 140 following IV and SC administration. Several acute and chronic toxicity studies have been conducted to support the clinical development plan. Chronic administration of PRO 140 in monkeys for 6 months via an IV or SC route have demonstrated robust safety and tolerability profile and generated No Observed Adverse Effect Levels (NOAELs). Exposure data were derived that adequately support the planned clinical trials. An immunogenic response to PRO 140 was evident in monkeys 2-3 weeks following dosing. Both IV and SC administration resulted in elimination half-lives of approximately 200 hours, and overall exposure increased with increasing doses. Following SC administration of PRO 140 in monkeys, the maximal concentration ($C_{max}$) was achieved within 56 hours and bioavailability for PRO 140 after SC dosing was approximately 70%.

**Leronlimab 700mg Exposure Summary in Clinical Trials**

| | Duration of Treatment | Approximate Number of Subjects Received 700mg dose of Leronlimab |
|---|---|---|
| **CD10_COVID-19**<br>A Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate Coronavirus Disease 2019 (COVID-19) | 2 Weeks | 56 |
| **CD12_COVID-19**<br>A Phase 2b/3, Randomized, Double Blind, Placebo Controlled, Adaptive Design Study to Evaluate the Efficacy and Safety of Leronlimab for Patients with Severe or Critical Coronavirus Disease 2019 (COVID-19) | 2 Weeks | 130 |
| **PRO 140_CD03**<br>A Multicenter Study to Assess the Clinical Safety and Treatment Strategy of Using PRO 140 SC as Long-Acting Single-Agent Maintenance Therapy for 48 Weeks in Virologically Suppressed Subjects with CCR5-tropic HIV-1 infection | Up to 48 Weeks | 132<br>+<br>79 (Rescue dose) |
| **PRO 140_CD03 extension**<br>An Extension Protocol for Virologically Suppressed Subjects Who Successfully Completed PRO140_CD03 Study | Up to 100+ Weeks | 29 |
| **Total Number of Subjects receiving Leronlimab 700mg dose:** | | **426** |

The safety profile of Leronlimab (PRO 140) has been extensively evaluated in clinical trials of HIV-positive patients. Data accumulated for PRO 140 suggest a favorable profile in terms of safety in humans and efficacy against HIV-1 infection. PRO 140 has been administered intravenously or subcutaneously to more than 750 healthy and HIV-1 infected individuals in Phase I/II/III studies. The drug has been well tolerated following intravenous administration of single doses of 0.5 to 10 mg/kg or up to 700 mg weekly doses as SC injection. Overall, more than 250 subjects have been exposed to PRO 140 525 mg SC weekly dose with the longest duration of exposure lasting >2 years. Similarly, more than 150 subjects have been exposed to PRO 140 700 mg SC weekly dose, respectively. To date, the longest exposure to PRO 140 700 mg SC weekly dose is 48 weeks.

Subjects treated with 525 mg and 700 mg Leronlimab (PRO 140) have not experienced any SAEs related to Leronlimab (PRO 140). The majority of AEs have been mild in severity. In addition, there have been no presented patterns of drug-related toxicities observed during treatment with 525 mg and 700 mg Leronlimab (PRO 140). The most common AEs have been injection site reactions, the majority which have been mild and considered as self-resolving. Considering the favorable safety profile of PRO 140 to date, this study is meant to further evaluate safety and potential efficacy of Leronlimab (PRO 140 at 700 mg) compared to placebo in adult patients with NASH.

We anticipate a manageable safety profile with Leronlimab (PRO 140) therapy since: 1) Leronlimab (PRO 140) is not metabolized by the liver, and therefore may have the potential for a better tolerability profile than many of the existing small-molecule therapies; 2) Unlike small molecules, monoclonal antibodies are too large to be filtered by the kidneys and are not eliminated in the urine, except in pathologic conditions. If low molecular weight antibody fragments are filtered, they are usually reabsorbed and metabolized in the proximal tubule of the nephron.

Considering the results of studies on CCR5 blocker we believe, CCR5 inhibition may provide us with a new strategy for the treatment of NASH.

### 1.7 RISKS / BENEFITS ASSESSMENT

Risks/Discomfort to Subjects and Precautions to Minimize Risk

**Allergic Reaction**

Leronlimab (PRO 140) belongs to the monoclonal antibody class of drugs. Monoclonal antibodies are sometimes associated with allergic reactions or flu-like reactions (such as fever, chills, and aches) or injection-site reactions. These events are usually of short duration if they occur at all. Severe allergic reactions, however, can be life-threatening. Although anaphylaxis has not been observed in prior trials of Leronlimab (PRO 140), infusion of proteins always carries with it the theoretical risk for anaphylactic shock. Accordingly, whenever Leronlimab (PRO 140) is administered to subjects, there should be available and in place the procedures required to manage anaphylactic shock.

**Immune Response**

People who take Leronlimab (PRO 140) or other monoclonal antibodies can also develop an immune response to Leronlimab (PRO 140) that may affect their ability to receive monoclonal antibodies, or to benefit from diagnosis or therapy with a monoclonal antibody in the future.

**Pregnancy**

Risks to unborn babies are unknown at this time; pregnant females will be excluded from this study. Females of childbearing potential must have a negative pregnancy test prior to enrollment. Both male and female patients and their partners of childbearing potential must agree to use appropriate birth control methods throughout the study duration (excluding women who are not of childbearing potential and men who have been sterilized).

**Venipuncture**

Blood sampling is required as part of the study protocol. Blood sampling carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture and, rarely, the possibility of infection at the needle puncture site.

**Unknown Risks**

As with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

**Theoretical risk for increased severity of West Nile virus infection**

Individuals who lack a functional CCR5 gene are at increased risk for severe infection by West Nile virus [Thompson, 2009]. Because of this, treatment with CCR5 co-receptor antagonists poses a theoretical risk for increased severity of West Nile virus infection. However, this concern is mitigated by several factors. First, no increased risk was observed for individuals who possess one functional and one non-functional CCR5 gene, indicating that an intermediate amount of CCR5 is sufficient for defense against West Nile virus [Thompson, 2009]. Second, use of CCR5 co-receptor antagonists is unlikely to completely abrogate CCR5 function, and there has been no association reported to date between CCR5 co-receptor use and severe West Nile virus. Additionally, Leronlimab (PRO 140) weakly antagonizes the natural activity of CCR5 and thus is less likely to adversely affect immune function. However, patients enrolled in this study may have immune suppression from chemotherapy and therefore, the investigators will be alerted to risks of West Nile infections. Furthermore, this has not been established to be a risk with maraviroc, the other FDA-approved anti-CCR5 drug already.

Collectively, the experience with both IV and SC, simulation modeling and the recent confirmation that a higher concentration of Leronlimab (PRO 140) synthesized using a highly efficient CHO cell line can be conveniently and safely administered has resulted in the design of the current study.

Intended Benefit for Subjects

This study provides an opportunity for subjects with NASH to have once weekly SC treatment with Leronlimab (PRO 140). Subjects participating in the present study will contribute to the development of a drug which has the potential to become a treatment option for them and others in the future.

# 2 STUDY OBJECTIVES

## 2.1 PRIMARY OBJECTIVE:

- The Primary objective of this study is to assess the efficacy of Leronlimab (PRO 140) in improving liver function in adult patients diagnosed with NASH compared to placebo

## 2.2 SECONDARY OBJECTIVE:

- The Secondary objective of this study is to assess the safety and tolerability of Leronlimab (PRO 140) in adult patients diagnosed with NASH compared to placebo

# 3 STUDY DESIGN

This is a phase II, multi-center, two-part study (Part 1: randomized, double-blind, placebo-controlled, two-arm with 60 patients; Part 2: non-randomized, single-arm, open-label with 30 patients) designed to evaluate the safety and efficacy of leronlimab (PRO 140) SC in patients with NASH for 13 weeks. In Part 1 of the study, leronlimab (PRO 140 at 700 mg dose) or placebo will be weekly administered subcutaneously by a licensed healthcare professional at the clinic sites.

A single arm, non-randomized, open-label phase (Part 2) is added to the protocol after completion of enrollment in the Randomized Phase (Part 1) of the study. In Part 2 of the study, leronlimab (PRO 140 350 mg dose) will be weekly administered subcutaneously (SC) by a licensed healthcare professional at the clinic sites.

- **Part 1**: randomized, double-blind, placebo-controlled, two-arm (up to 60 subjects)
  - Leronlimab (PRO 140 700 mg) or Placebo SC weekly injection for 13 weeks
- **Part 2**: non-randomized, open-label, single-arm (up to 30 subjects)
  - Leronlimab (PRO 140 350 mg) SC weekly injection for 13 weeks

This study consists of screening, treatment, and follow-up periods.

The study flow diagram is presented in Figure 3-1.

## 3.1 STUDY CENTERS

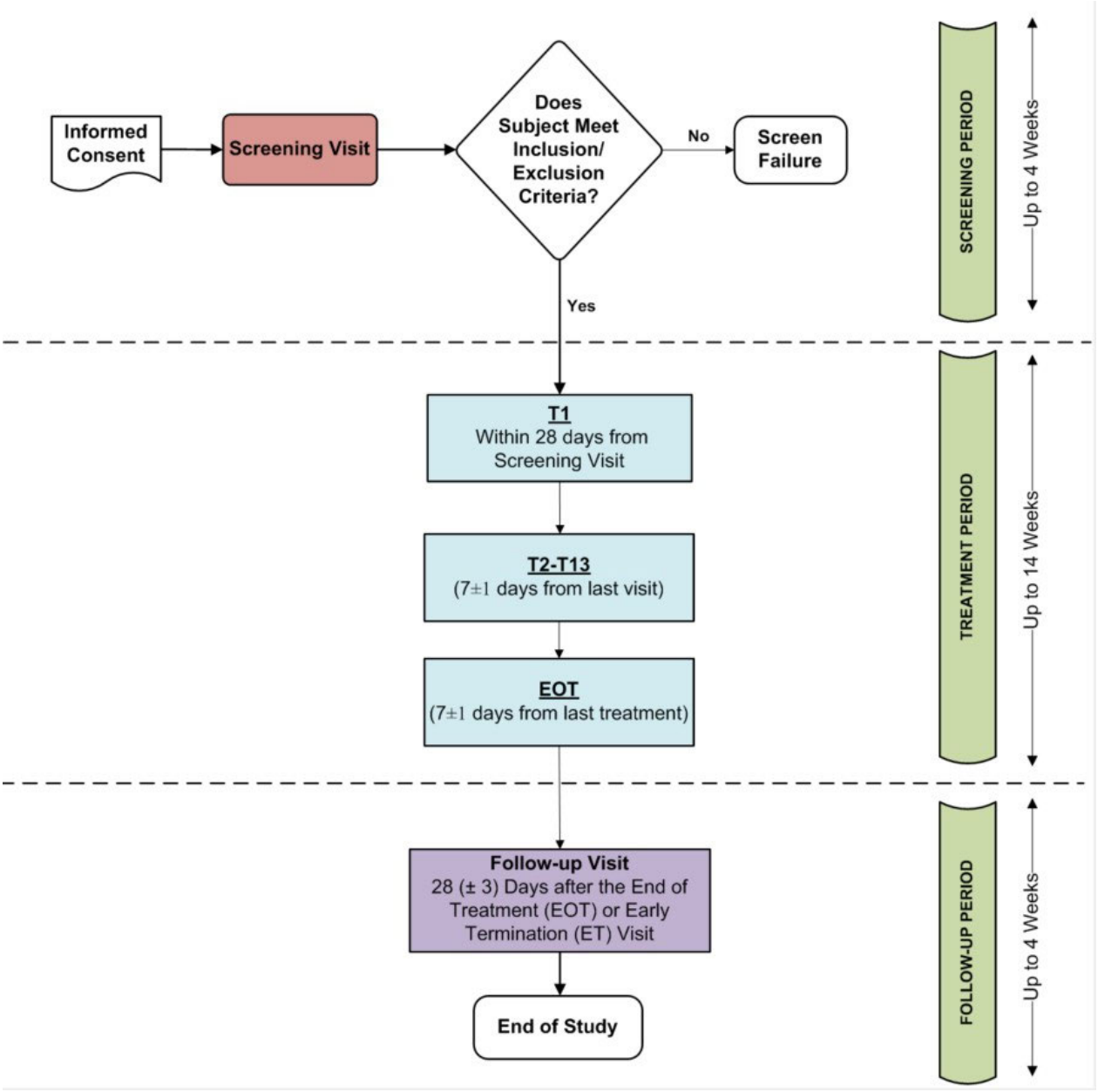
Up to 20 centers in the United States (US).

## 3.2 STUDY POPULATION

For this study, adult patients with NASH will be enrolled. This will be a multicenter trial with up to 90 subjects.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be enrolled in the study.

**Figure 3-1: Study Design Schematic**



### 3.3 ELIGIBILITY CRITERIA

Inclusion Criteria

Subjects are required to meet ALL of the following criteria for enrollment into the study:

1. Subject is a male or female between 18 to 75 years of age inclusive.
2. Evidence of nonalcoholic steatohepatitis (NASH) based on one of the following criteria:
   - Criteria 1: Histologically-confirmed diagnosis of NASH on a liver biopsy, or
   - Criteria 2: FibroScan or Shearwave US during screening (or within 6 months before screening) shows kPa ≥7 but <14 and CAP ≥260.
3. Subject shows presence of hepatic fat fraction as defined by ≥ 8% on MRI-PDFF and cT1 ≥ 800 ms at Screening.
4. Has had a stable body weight (±5%) within 6 months prior to Screening.
5. Body Mass Index (BMI) ≥ 28 kg/$m^2$ at Screening
6. Has clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator.
7. Laboratory Screening results as indicated below:
   a. AST:ALT Ratio ≤ 1, if AST or ALT value is > ULN
   b. Screening Liver enzymes (AST, ALT, and ALK PHOS) < 5 x ULN.
   c. Total Bilirubin ≤ 1.3 mg/dL (except if Gilbert's Disease)
   d. Platelet count ≥ 150,000/$mm^3$
   e. International normalized ratio (INR) < 1.3
   f. Estimated Glomerular Filtration Rate (eGFR) ≥ 60/mL/min
   g. Glycosylated hemoglobin (HbA1c) < 9%.
   h. TSH within normal reference range.

   *Note: Any subject with a non-clinically significant TSH value outside of the normal range may be enrolled if their T3 and free T4 values are within the normal range.*
8. Subjects with pre-diabetes or type 2 diabetes will be allowed to participate if the following criteria is met:
   - Subjects who are taking anti-diabetic medications should be on a stable dose for a period of at least 3 months prior to Screening and do not anticipate clinically significant dose adjustments during the course of study.

- Subjects must be on a stable diet/lifestyle regimen for at least 3 months prior to screening and do not anticipate a clinically significant change during the course of study.

9. Subjects who are taking Vitamin E should be on a stable dose of Vitamin E (if ≥ 400 IU) for a period of at least 4 weeks prior to Screening and do not anticipate dose adjustments for the duration of the study.
10. Both male and female patients and their partners of childbearing potential must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, tubal sterilization or vasectomy) or must practice complete abstinence from intercourse of reproductive potential from study entry to 6 months after the last day of treatment (excluding women who are not of childbearing potential and men who have been sterilized).
11. Females of child-bearing potential must have a negative serum pregnancy test at Screening Visit and negative urine pregnancy test prior to receiving the first dose of study drug; and Male participants must agree to use contraception and refrain from donating sperm for at least 90 days after the last dose of study intervention.
12. Subject is willing and able to give informed consent prior to any study specific procedures being performed.
13. Subject is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures and study restrictions.

Exclusion Criteria

Subjects meeting ANY of the following criteria will be excluded from enrollment:

1. Any concurrent clinically significant liver disease with an etiology other than NASH including autoimmune hepatitis, alcoholic hepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.
2. History of alcohol consumption greater than 21/units/week (for males) and 14/units/week (for females) within the last 2 years prior to screening.

   *Note: Use of online unit calculator for alcohol consumption is recommended (e.g., https://alcoholchange.org.uk/alcohol-facts/interactive-tools/unit-calculator)*
3. Any drug-induced steatohepatitis secondary to amiodarone, corticosteroids, estrogens, methotrexate, tetracycline, or other medications known to cause hepatic steatosis.
4. Undergone major surgery, including liver surgery, within 6 months prior to screening.

5. Prior or pending liver transplantation.
6. History or presence of cirrhosis or stage 4 fibrosis in historical liver biopsy and/or hepatic decompensation including ascites, hepatic encephalopathy or variceal bleeding.
7. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test), hepatitis C (defined as having a positive Anti-HCV test with detectable reflex HCV RNA; Note: Subject with positive Anti-HCV test and with undetectable HCV RNA would not be excluded), acute hepatitis A (defined as subjects with serum positive for hepatitis A IgM (HAV) antibody) or acute hepatitis E (defined as having anti-HEV IgM antibody).
8. Any active infection requiring systemic therapy at the time of screening, which is considered clinically significant per the Investigator.
9. Positive test for human immunodeficiency virus (HIV) or HIV infection.
10. History of bleeding diathesis within 6 months of screening.
11. Any malignancy within the past 5 years, excluding successfully treated basal cell carcinoma or squamous cell carcinoma without evidence of metastases.
12. Seizure disorder requiring ongoing antiseizure therapy or with any condition that, in the judgment of the investigator, is likely to increase the risk of seizure (e.g. CNS malignancy)
13. Clinically significant active cardiac disease which would interfere with study conduct or study results interpretation per the PI.
14. Any known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. Prior therapy with Leronlimab or any other CCR5 antagonist (e.g. maraviroc) within 6 months prior to screening.
16. History of severe allergic, anaphylactic, or other hypersensitivity reactions to humanized monoclonal antibodies.
17. Any condition requiring continuous systemic treatment with immunosuppressive (such as corticosteroids) or immunomodulatory medications.

    *Note: Inhaled or topical steroids of up to 5 mg daily prednisone equivalent dose are permitted in the absence of active autoimmune disease.*
18. History of administration of a live, attenuated vaccine within four weeks prior to start of PRO 140 treatment or anticipation that such a live attenuated vaccine will be required during the remainder of the study.

    *Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist ®) are live attenuated*

*vaccines, and are not allowed.*

19. Currently participating in an investigational study or received an investigational drug within 28 days or 5 half-lives (whichever is longer) prior to study drug administration.

# 4 STUDY SCHEDULE

The total study duration for each subject consists of screening, treatment, and follow-up periods. The study flow diagram is presented in Figure 3-1 and study Schedule of Assessments is presented in Table 4-2.

Screening assessments will commence after obtaining signed informed consent, and review of medication history, demographic information, baseline disease characteristics, eligibility evaluation, physical examination, vital signs, height and weight, prior and concomitant medications, Electrocardiogram (ECG), Liver MRI, FibroScan (or equivalent non-invasive imaging test), FibroTest, routine serum biochemistry including liver function test, hematology, HIV and hepatitis serology panel, urinalysis, serum pregnancy (if applicable). These assessments must be conducted within 28 days of the first treatment visit. Subjects who fail to meet eligibility criteria will be considered screen failures and exit the study without any further evaluations.

**Treatment Period:**

In the Part 1 of the study, subjects who meet the eligibility criteria, as per data gathered from the Screening Visit, will be blindly randomized to 1:1 to one of two treatment arms per Table 4-1 below:

**Table 4-1: Treatment Groups**

**Part 1:**

| Study Group | Study Drug | Dose | Route | Schedule |
|---|---|---|---|---|
| A | Leronlimab (PRO 140) | 700 mg | SC | Start on Day 1 and every week thereafter |
| B | Placebo | N/A | SC | Start on Day 1 and every week thereafter |

**Part 2:**

| Study Group | Study Drug | Dose | Route | Schedule |
|---|---|---|---|---|
| C | Leronlimab (PRO 140) | 350 mg | SC | Start on Day 1 and every week thereafter |

The study treatment (Leronlimab 700 mg or placebo) will be subcutaneously administered every week by a licensed healthcare professional at the study site for 13 weeks.

Up to 30 subjects will be enrolled in the Non-Randomized, open-label phase (Part 2) of the study. In Part 2 of the study, eligible subjects will be enrolled to receive leronlimab (PRO 140) 350 mg as one subcutaneous injection every week by a licensed healthcare professional at the study site for 13 weeks.

**End of Treatment (EOT)**

Subjects who complete the treatment period will continue to End of Treatment (EOT) Visit assessments at week 14 and enter the Follow-up Phase of the study. Subjects who meet any criteria for discontinuation of study treatment as specified in Section 5.1 of the protocol, will undergo Early Termination (ET) Visit assessments 7 days after the last injection and enter the Follow-up Phase of the study.

**Follow-Up Period:** Follow-up visit will be conducted 28 (± 3) days after the End of Treatment (EOT) or Early Termination (ET) Visit.

## Table 4-2: Schedule of Assessments

| Tests and Assessments | Screening Period | Treatment period | | | | | | | | | | | | | | | | Follow up Period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | Screening Visit 1 | T1 | | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 | T13 | EOT | (ET)[20] | Follow-up Visit |
| | | Pre-Rx | Post-Rx | | | | | | | | | | | | | | | |
| Day(s) | Day -28 | Day 1 | | Day 8 | Day 15 | Day 22 | Day 29 | Day 36 | Day 43 | Day 50 | Day 57 | Day 64 | Day 71 | Day 78 | Day 85 | Day 92 | | 28 Days (±3) after EOT or ET Visit |
| Week(s) | | 1 | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | | |
| Window period | | Within 28 Days from Screening visit | | 7 (±1) Days since last Treatment | | | | | | | | | | | | | | |
| Informed Consent [1] | X | | | | | | | | | | | | | | | | | |
| Demographics and Baseline Disease Char. | X | | | | | | | | | | | | | | | | | |
| Medical and Medication History [2] | X | X | | | | | | | | | | | | | | | | |
| Vital Signs [3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height, Weight, BMI | X | X[4] | | X[4] | | | | X[4] | | | | X[4] | | | | X[4] | X[4] | |
| Physical Exam | X | X | | X[5] | | | | X[5] | | | | X[5] | | | | X | X[5] | X[5] |
| 12-lead ECG [6] | X | X | | X | | | | X | | | | X | | | | X | X | |
| FibroTest [7] | X | X | | X | | | | X | | | | X | | | | X | X | |
| FibroScan [8] | X | | | | | | | | | | | | | | | | | |
| Liver MRI [9] | X | | | | | | | | | | | | | | | X | X | |
| Complete Blood Count [10] | X | X | | X | | | | X | | | | X | | | | X | X | |
| Biochemistry [11] | X | X | | X | | | | X | | | | X | | | | X | X | X |
| Urinalysis [12] | X | X | | X | | | | X | | | | X | | | | X | X | |
| Serum Pregnancy test [13] | X | | | | | | | | | | | | | | | | | |
| Urine Pregnancy test [13] | | X | | | | | | X | | | | X | | | | X | X | |
| HBS Ag, HCV Ab and HCV RNA (if required), HIV Ab, HA IgM antibody, HEV Ab | X | | | | | | | | | | | | | | | | | |
| Anti-drug antibodies (ADA) to PRO 140 [14] | | X | | X | | | | X | | | | X | | | | X | X | X |
| Serum PK Assessments [14] | | X | | X | | | | X | | | | X | | | | X | X | X |
| Serum pro-inflammatory Assessments [14] | | X | | X | | | | X | | | | X | | | | X | X | X |
| Monocyte/T cell CCR5 biomarker assay [14] | | X | | X | | | | X | | | | X | | | | X[21] | X | X |

| Tests and Assessments | Screening Period | Treatment period | | | | | | | | | | | | | | | | Follow up Period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | Screening Visit 1 | T1 | | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 | T13 | EOT | (ET)[20] | Follow-up Visit |
| | | Pre-Rx | Post-Rx | | | | | | | | | | | | | | | |
| Day(s) | Day -28 | Day 1 | | Day 8 | Day 15 | Day 22 | Day 29 | Day 36 | Day 43 | Day 50 | Day 57 | Day 64 | Day 71 | Day 78 | Day 85 | Day 92 | | 28 Days (±3) after EOT or ET Visit |
| Week(s) | | 1 | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | | |
| Window period | | Within 28 Days from Screening visit | | 7 (±1) Days since last Treatment | | | | | | | | | | | | | | |
| Eligibility Assessment | X | X | | | | | | | | | | | | | | | | |
| Randomization[15]<br>– Group A (700mg SC)<br>– Group B (Placebo) | | X | | | | | | | | | | | | | | | | |
| Leronlimab (PRO 140) or placebo administration [16] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Post Injection Site Evaluation by Investigator [17] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Injection Site Pain Assessment [18] | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Concomitant medications [19] | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events [19] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

[1] Informed consent must be obtained prior to patient participation in any protocol-related activities that are not part of routine care.

[2] A complete review of the subject's past medical history (liver disease ), history of prior symptoms or concurrent diseases (including liver disease), past surgeries, and current therapies (medications and non-medications) will be undertaken

[3] Vital signs including blood pressure, heart rate, respiration rate, and temperature will be measured at each clinic visit.

[4] Weight only on visits T1 (Pre-Treatment), T2, T6, T10 and EOT/ET

[5] Symptom-directed physical examination at clinic visits

[6] A 12-lead ECG will be repeated during the study

[7] FibroTest (requires fasting for 12 hours or more) combines 5 standard biomarkers (gamma-glutamyltransferase, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1, and haptoglobin). The Acti-Test adds a marker for inflammatory activity (alanine aminotransferase: ALT). These markers are weighted depending on the patient's age and gender.

[8] Fibroscan or equivalent non-invasive imaging test is acceptable

[9] Liver MRI will be performed to evaluate MRI-derived biomarkers such as proton density fat fraction (PDFF) and corrected T1 (cT1).

[10] Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, absolute lymphocyte count, absolute neutrophil count (ANC) and platelets.

[11] Serum Biochemistry will include:
Hepatic function/NASH indicators: Total bilirubin, Direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST)/SGOT, alanine aminotransferase (ALT)/SGPT, Prothrombin Time (PT), International Normalized Ratio (INR), albumin, total protein, Triglyserides, Cholesterol (Low density lipoprotein), creatine kinase, Gamma-glutamyltransferase (GGT), and serum CK-18
Renal function indicators: blood urea nitrogen (BUN), creatinine, eGFR
Electrolytes: sodium, potassium, chloride, calcium and bicarbonate

Other: Fasting blood Glucose , Serum HbA1C, Thyroid profile
Note: Screening laboratory testing can be repeated once during the 28-day screening window based on the Investigator's clinical judgement).

[12] Urine samples will be tested for pH, appearance, color, specific gravity, turbidity, ketones, bilirubin, occult blood, glucose, protein, nitrites, urobilinogen, and leukocyte esterases. Microscopic examination of urine sediment will be performed if there are abnormalities in macroscopic urinalysis results. Microscopic urine tests include bacteria, cast, crystals, epithelial cells, RBC and WBC.

[13] Only performed on women of childbearing potential

[14] Blood sample collected at T1 (prior to first dose of PRO 140), pre-dose at T2, T6, T10, and at EOT (or ET) and Follow-up visit

[15] Randomization via WebView CTMS system only applicable for Part 1 of the study

[16] Leronlimab (PRO 140) or placebo is administered as subcutaneous injection in the abdomen weekly. In Part 1 of the study, a total of 700 mg dose of leronlimab (PRO 140) or placebo will be delivered as two injections of 2 mL. In the Part 2 of the study, a total dose of 350 mg dose of leronlimab (PRO 140) will be delivered as one injection of 2 mL.

[17] Injection Site Reaction Assessment as assessed by Investigator (or designee) at the clinic .

[18] Subject-perceived injection site pain (average pain since last treatment) will be assessed using 11-point Numeric Rating Scale from 0 to 10 prior to each study treatment administration. "0" meaning "no pain" and "10" meaning "worst possible" pain.

[19] AE and CM evaluations to be conducted at each clinic visit applicable

[20] Subjects discontinuing the study at any time for any reason (early termination-ET) should complete the procedures listed AND the follow-up visit

[21] In case subjects have already completed their EOT/ET and FU visits, site should use the Unscheduled Visit option to collect blood sample for Monocyte/T Cell CCR5 analysis.

### 4.1 SCREENING PERIOD

Screening Visit

The subject will sign and date the Informed Consent Form (ICF) and Health Insurance Portability and Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures. A unique identification number (screening number) will be assigned to each subject who has provided written informed consent. The screening number will incorporate a three-digit Study Center number (101, 102, etc.) and a three-digit numeric ID assigned in successive order of consenting to screening procedures after signing the ICF at each center, beginning with 001 at each site (e.g. 101-001 or 102-001, etc.).

**Subject Screening #:** **XXX - YYY**

XXX=Study Center YYY=Subject Numeric ID

All study centers will be instructed to maintain the study-specific screening and enrollment logs at their sites. If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled if they are found to meet all inclusion and no exclusion criteria when re-screened.

Once the Screening ICF has been signed, screening procedures and information will be obtained to confirm subject eligibility including:

- Demographic information and baseline disease characteristics (see Section 7.3),
- Medical history (see Section 7.4),
- Prior and concomitant medications assessment (see Section 7.5),
- Vital Signs (see Section 7.6),
- Body Weight & Height measurements (see Section 7.6),
- Physical examination (see Section 7.7),
- 12-lead Electrocardiogram (see Section 7.8)
- FibroScan (or equivalent non-invasive imaging test) (see Section 7.13)
- Collection of lab specimens (see Section 7.9) for
    - Complete blood count
    - Biochemistry

- Serum pregnancy test, for female subjects of childbearing potential
- Urine sample for urinalysis parameters
- FibroTest
- HBS Ag, HCV Ab and HCV RNA (if required), HIV Ab, HAV IgM antibody, and HEV Ab

- Liver MRI (see section 7.14)

All screening information will be fully documented in the subject's medical records (i.e., source documents).

- For consented subjects who do not meet eligibility criteria, a Screen Failure Case Report Form (CRF) will be completed. The Screen Failure CRF will contain the following details: the subject identification number, the date of ICF signature, demographic information (see Section 7.3), and the reason for screen failure. No additional information will be required for subjects who fail screening.
- For consented subjects who meet eligibility criteria, all required screening information will be transcribed onto the appropriate page of the CRF.

### 4.2 TREATMENT PERIOD

Subjects who meet all eligibility criteria, as per data gathered from Screening Period are to be treated. All subjects who fail to meet eligibility criteria will be considered screen failure and exit the study without further evaluation

The maximum sample size for this study is 90 subjects that will be followed by treatment according to the schedule described above.

In Part 1 of the study, eligible subjects will be randomized to 1:1 to one of the two study arms to receive Leronlimab (PRO 140) 700 mg (Group A), or placebo (Group B) as two subcutaneous injections, given once per week (± 1 day) for up to 13 weeks during the treatment period.

- PRO 140 700mg SC weekly injection (Group A)
- Placebo 0 mg SC weekly injection (Group B)

The study treatment (PRO 140 700 mg or placebo SC injections) will be administered by a licensed healthcare professional once a week at the study site.

In Part 2 of the study, eligible subjects will be enrolled to receive leronlimab (PRO 140) 350 mg as one injection, given once per week (± 1 day) for up to 13 weeks during the treatment period.

- PRO 140 350mg SC weekly injection

The study treatment (PRO 140 350 mg SC injection) will be administered by a licensed healthcare professional once a week at the study site.

Treatment Visit 1 (T1)

The following assessments will be performed at the first treatment visit, unless otherwise specified:

***Pre-Treatment***

- Confirmation of eligibility criteria by reviewing test results and other criteria assessments performed at Screening Visit (see Section 7.2)
- Vital Signs and body weight measurement (see Section 7.6),
- Physical examination (see section 7.7),
- 12-lead Electrocardiogram (see Section 7.8)
- Change in concomitant medications (see Section 7.5),
- Any changes in medical history since Screening Visit (see Section 7.4),
- Randomization only applicable for Part 1 of the study (see Section 8.4)
- Collection of lab specimens (see Section 7.9) for
    - Complete blood count
    - Biochemistry
    - Urine pregnancy test, for female subjects of childbearing potential
    - Urine sample for urinalysis parameters
    - FibroTest
    - Anti-Drug Antibodies (ADA) to PRO 140
    - PK evaluations
    - Serum pro-inflammatory cytokine/chemokine evaluations
    - Monocyte/T cell CCR5 biomarker assay

***Administration of study treatment [PRO 140 or placebo]***

PRO 140 or placebo is administered as subcutaneous injection in the abdomen weekly. In part 1 of the study, a total of 700 mg (175 mg/mL) or placebo is delivered as two injections of 2 mL on opposite sides of the abdomen. In Part 2 of the study, a dose of 350 mg of leronlimab (PRO 140) (175 mg/mL) will be delivered as one injection of 2 mL and administered subcutaneously in the abdomen.

**Note:** All study treatments (PRO 140 or placebo) must be administered by a licensed healthcare professional.

***Post-Treatment***

- Injection Site Reaction Assessment (see Section 7.11)
- Assessment of Adverse Events (AE) ( see Section 9.1)
- Vital Signs (see Section 7.6) will be assessed within 15 minutes of study treatment administration.

After treatment administration, subjects who meet any criteria for discontinuation of study treatment as specified in Section 5.1 of the protocol, will undergo End of Treatment (EOT) Visit assessments and enter the Follow-up Phase of the study.

Treatment Visit 2 (T2) to Treatment Visit 13 (T13)

The following assessments will be performed at each visit, unless otherwise specified:

- Assess for any AEs (see Section 9.1)
- Concomitant medications assessment (see Section 7.5)
- Vital Signs and body weight measurement (see Section 7.6) (weight only on visits T2, T6, T10 )
- Symptom-directed physical examination at clinic visits (see Section 7.7) (only on visits T2, T6, T10)
- 12-lead Electrocardiogram (see Section 7.8) (only on visits T2, T6, T10)
- Collection of lab specimens at T2 , T6, T10 (see Section 7.9 ) for:
    - Complete blood count
    - Biochemistry
    - Urine sample for urinalysis parameters
    - Urine pregnancy test, for female subjects of childbearing potential (T6 and T10 only)
    - FibroTest
    - Anti-Drug Antibodies (ADA) to PRO 140
    - PK assessment
    - Serum pro-inflammatory cytokine/chemokine evaluations
    - Monocyte/T cell CCR5 biomarker assay

- Leronlimab (PRO 140) Administration (see Section 6.4)
- Injection Site Reaction Assessment (see Section 7.11)
- Subject-perceived Injection Site Pain Assessment (see Section 7.12)

**Note:** Subject-perceived injection site pain will be assessed using 11-point Numeric Pain Rating Scale from 0 to 10 prior to study treatment administration assessing average pain at injection site since last treatment. "0" meaning "no pain" and "10" meaning "worst possible pain".

End of Treatment (EOT) Visit

Subjects who complete the treatment period will undergo End of Treatment (EOT) Visit. The following assessments will be performed for the subjects:

- Assess for any Adverse Events (see Section 9.1)
- Changes in Concomitant medications (see Section 7.5),
- Physical examination (see Section 7.7),
- Vital Signs and body weight measurement (see Section 7.6),
- Subject-perceived Injection Site Pain Assessment (see Section 7.12),
- 12-lead Electrocardiogram (see section 7.8),
- Liver MRI (see section 7.14)
- Collection of Blood Specimens (see section 0) for:
    - Complete Blood Count
    - Biochemistry
    - FibroTest
    - Anti-Drug Antibodies (ADA) to PRO 140
    - PK assessment
    - Serum pro-inflammatory cytokine/chemokine evaluations
    - Monocyte/T cell CCR5 biomarker assay

    ***Note:*** *In case subjects have already completed their EOT/ET and FU visits, site should use the Unscheduled Visit option to collect blood sample for Monocyte/T Cell CCR5 analysis.*

- Urine pregnancy test, for female subjects of childbearing potential.
- Urine sample for urinalysis parameters

Early Termination (ET) Visit

Subjects who meet any criteria for discontinuation of study treatment as specified in Section 5.1 of the protocol, will undergo Early Termination (ET) Visit.

The following assessments will be performed:

- Assess for any Adverse Events (see Section 9.1)
- Changes in Concomitant medications (see Section 7.5),
- Symptom-directed physical examination (see Section 7.7),
- Vital Signs and body weight measurement (see Section 7.6),
- 12-lead Electrocardiogram (see section 7.8),
- Liver MRI (see section 7.14)
- Collection of Blood Specimens (see section 0) for:
    - Complete Blood Count
    - Biochemistry
    - FibroTest
    - Anti-Drug Antibodies (ADA) to PRO 140
    - PK assessment
    - Serum pro-inflammatory cytokine/chemokine evaluations
    - Monocyte/T cell CCR5 biomarker assay
- Urine pregnancy test, for female subjects of childbearing potential.
- Urine sample for urinalysis parameters

### 4.3 FOLLOW-UP PERIOD

Follow- up visit will be conducted 28 (± 3) days after the End of Treatment (EOT) or Early Termination (ET) Visit. All subjects will be followed for biochemistry lab assessment, anti-drug antibodies (ADA) to PRO 140, PK assessment, serum pro-inflammatory assessment, blood sample for Monocyte/T cell CCR5 biomarker assay vital signs, symptom-directed physical exam, adverse events, and concomitant medications assessment.

Subjects who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event (i.e. the grade is not changing).

### 4.4 UNSCHEDULED VISITS

In the event that the subject will return to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications, will be noted in the eCRF.

Any hospitalization or ER visits in between the scheduled visits should be promptly notified to the site staff.

# 5 SUBJECT COMPLETION, WITHDRAWAL AND CRITERIA FOR STOPPING THE STUDY

A subject who has completed the 14-week treatment period and 4-week follow-up period will be considered as having completed the study.

## 5.1 SUBJECT WITHDRAWAL

A subject who enters the Treatment Phase but does not complete the study, as defined in this section, is considered to have prematurely withdrawn (early terminated) from the Study.

All subjects have the right to withdraw at any point during treatment without prejudice to future care. It will be documented whether or not each subject completed the clinical study. If for any subject, study treatment or observations were discontinued, the reason(s) will be recorded.

Subjects WILL be withdrawn from the study, in consultation with the Medical Monitor and the Investigator, if any of the following are met:

- A subject is significantly non-compliant with the requirements of the protocol.
- The Investigator determines that it is in the best interest of the subject.
- Subject chooses to withdraw or is withdrawn due to an adverse event
- A subject becomes pregnant

Note: The pregnancy will be followed to term for safety follow-up. Relevant safety information collected after the study has completed will be reported as supplemental information.

- Discontinuation of study by Sponsor
- Subject becomes lost to follow-up (LTF)
- Subject experiences unacceptable toxicity
- Subject voluntarily withdraws from treatment (follow-up permitted)
- Subject withdraws consent (no follow-up permitted)

Discontinuation of study treatment for the individual subject MAY occur if, in consultation with the Medical Monitor and the Investigator, any of the following are met:

- A subject is treated with a prohibited medication.
- Diabetic subjects with an increased $HbA1_C$ results of >9% or experiencing significant changes in glucose control requiring modification to the dosage or regimen of antidiabetic medication
- Major protocol violation (Section 0)

- Subjects who have two occurrences of a Grade 2 or higher allergic/hypersensitivity reaction directly related to the study drug that lead to permanent discontinuation of study drug.
- Subjects experiencing grade 3 or higher AE (per CTCAE v5.0) that is possibly or probably related to the study drug OR grade 4 or higher AE regardless of attribution to the study drug.
- Subjects considered to potentially have Drug-Induced Liver Injury (DILI) as described below.

**Drug- induced liver Injury (DILI)**

If subjects with abnormal baseline liver indices develop elevations of AST or ALT >2x baseline or Total Bilirubin (TBL) >1.5x baseline values during the study, the tests will be repeated within 48-72 hours. If there are persistent elevations (AST or ALT>2x baseline or TBL >1.5 baseline values) upon repeat testing, then close observation of the subjects per below should be implemented and discontinuation of the study treatment will be considered as per Section 5.1. During the close observation period, liver enzyme and serum bilirubin tests will need to be repeated two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study treatment has been discontinued and the subject is asymptomatic.

Additionally, further gastroenterology or hepatology consultations and/or liver biopsy can be considered per Investigator's discretion.

If patient is unable to come to clinic for blood draw during the close observation period, laboratory testing can be performed locally, and the results should be promptly communicated to the investigator site. A decision to discontinue or temporarily interrupt the study drug will be considered based on factors that include how much higher than baseline the ALT and AST are relative to the upper limit of normal (ULN) and how much the AST and ALT levels have increased relative to baseline, in addition to whether there is a concomitant elevation of bilirubin or INR. The study treatment will be discontinued or temporarily interrupted under the following conditions:

- If Baseline Measurements (BLM) were <2x ULN, The study treatment should be discontinued if ALT or AST increases to >5x BLM
- If BLM was 2x ULN but <5x ULN, The study treatment will be discontinued if ALT or AST increases to 3x BLM
- If BLM was 5x ULN, The study treatment will be discontinued if ALT or AST increases to >2x BLM
- If ALT or AST increases >2x BLM and the increase is accompanied by a concomitant increase in TB to >2x BLM or the INR concomitantly increases by 0.2, The study treatment will be discontinued

- If any subject presents with signs or symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and or eosinophilia (>5%), the study treatment should be discontinued

Note: For the purpose of the assessment of drug-induced liver injury (DILI), Baseline Measurements (BLM) for lab values (such as AST, ALT, total Bilirubin) refers to the average (mean) value of Screening Visit (SV) and T1 Visit. If liver function tests are repeated during Screening Phase, the average (mean) value of all Screening Visit tests and T1 Visit will be used to calculate the Baseline Measurements.

All data normally collected at the scheduled EOT Visit should be recorded at the time of premature discontinuation.

If a subject fails to return for the scheduled study visit or is discontinued from the study, an attempt will be made to determine the reason(s). If the subject is unreachable by telephone, a registered letter will be sent to the subject requesting that he/she contact the clinic.

All patients with an ongoing SAE at the Post-Study (Follow-up) Visit (scheduled or premature) must be followed until the event is resolved (with or without sequelae) or deemed stable.

### 5.2 SUBJECT REPLACEMENT

Subject replacement is not applicable in this study.

### 5.3 DATA COLLECTED FROM WITHDRAWN SUBJECTS

Every attempt should be made to collect follow-up information. The reason for withdrawal from the study will be recorded in the source documents and on the appropriate page of the CRF.

Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one certified letter.

In the event that a subject is withdrawn from the study at any time due to an adverse event or SAE, the procedures stated in Sections 9.2 and 9.4 must be followed.

### 5.4 SCREEN FAILURES

A subject who signed a consent form, but did not meet the inclusion/exclusion criteria is classified as a screen failure. Subject number, demographics and reason for screen failure will be recorded.

In the event that a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened again (i.e., up to two

screenings) and may be enrolled if they are found to meet all inclusion and no exclusion criteria at the subsequent screening visit.

### 5.5 CLINICAL TRIAL STOPPING CRITERIA

The clinical trial should be halted if any of the following occurs:

- Three patients develop the same Grade 3 AE attributed to the study drug per CTCAE v5.0

  OR

- Two patients develop any Grade 4 AE attributed to study drug per CTCAE v5.0

  OR

- One patient develops a grade 5 AE attributed to study drug per CTCAE v5.0

# 6 STUDY TREATMENT

## 6.1 INVESTIGATIONAL PRODUCT

In Part 1 of the study, Leronlimab (PRO 140) or placebo will be administered subcutaneously (SC) at a weekly dose for 13 weeks. In Part 2 of the study, Leronlimab (PRO 140) will be administered as a 350 mg, weekly dose for 13 weeks.

**Table 6-1: Treatment Administration Summary**

**Part 1:**

| Study Group | Study Drug | Dose | Route | Schedule |
|---|---|---|---|---|
| A | Leronlimab (PRO 140) | 700 mg | SC | Start on Day 1 and every week thereafter |
| B | Placebo | N/A | SC | Start on Day 1 and every week thereafter |

**Part 2:**

| Study Group | Study Drug | Dose | Route | Schedule |
|---|---|---|---|---|
| C | Leronlimab (PRO 140) | 350 mg | SC | Start on Day 1 and every week thereafter |

Leronlimab (PRO 140)

Leronlimab (PRO 140) is a humanized IgG4,κ Monoclonal Antibody (mAb) to the chemokine receptor CCR5. Leronlimab (PRO 140) is provided at a concentration of 175 mg/mL and is intended for SC route of administration.

**Part 1:**

In Part 1 of the study, for Group A (Leronlimab 700 mg), one study injection kit will be assigned per subject per treatment visit. Leronlimab kits will be labeled with a unique identification number. Each kit used during the Treatment Period will contain two vials of Leronlimab (PRO 140) for SC injection.

Each vial of the Leronlimab (PRO 140) product contains ~2.4 mL antibody at 175mg/mL in a buffer containing [redacted] L-histidine, [redacted] glycine, [redacted] sodium chloride, [redacted] sorbitol, [redacted] polysorbate 20 (Tween 20®), and sterile water for injection, at pH of [redacted].

**Note:** *For Group A (Leronlimab (PRO 140 at 700 mg), 2 mL will be drawn from 2.4 mL solution filled vial. Remaining 0.4 mL medication will be discarded appropriately from each vial.*

Placebo

For Group B, Isotonic 0.9% Sodium Chloride Injection, USP will be used as placebo.

A dose of 700 mg of Leronlimab (PRO 140) (175 mg/mL) or placebo will be delivered as two injections of 2 mL each and administered subcutaneously on opposite sides of the abdomen.

**Note:** *The IP preparations mentioned above will be conducted by the unblinded pharmacist or qualified designated unblinded site staff. The IP administrations will be conducted by blinded designated site staff.*

**Table 6-2: Part 1: Investigational Product - Leronlimab (PRO 140) or Placebo**

| Study Group | IP Dosage | Dosage Form | IP concentration | Dosing Frequency and Amount | Route of Administration |
|---|---|---|---|---|---|
| A | PRO 140 700 mg | Parenteral solution | 175 mg/mL | 2 injections of PRO 140 (2 mL/inj.) per week on opposite sides of abdomen | SC injection |
| B | Placebo | Parenteral solution | 0 mg/mL | 2 injections of Placebo (2 mL/inj) per week on opposite sides of abdomen | SC injection |

***Note**: Patients with low body fat percentages may find subcutaneous injections uncomfortable. In such cases, Leronlimab (PRO 140) or placebo can be injected at different areas other than abdomen as per discretion of the Investigator.*

**Part 2:**

In Part 2 of the study, (Leronlimab 350 mg), one study injection kit will be assigned per subject for two treatment visits. Leronlimab kits will be labeled with a unique identification number. Each kit used during the Treatment Period will contain two vials of Leronlimab (PRO 140) for SC injection.

**Table 6-3: Part 2: Investigational Product - Leronlimab (PRO 140)**

| Study Group | IP Dosage | Dosage Form | IP concentration | Dosing Frequency and Amount | Route of Administration |
|---|---|---|---|---|---|
| C | PRO 140 350 mg | Parenteral solution | 175 mg/mL | 1 injection of PRO 140 (2 mL/inj.) per week in the abdomen area | SC injection |

**Note:** For group C *(Leronlimab (PRO 140 at 350 mg), 2 mL will be drawn from 2.4 mL solution filled vial. Remaining 0.4 mL medication will be discarded appropriately from each vial.*

A dose of 350 mg of Leronlimab (PRO 140) (175 mg/mL) will be delivered as one injection of 2 mL and administered subcutaneously in the abdomen.

## 6.2 LERONLIMAB (PRO 140) - PACKAGING AND LABELING

Study drug will be packaged, labeled, and shipped by PCI Pharma services

The contents of each vial are described in Section 0. Leronlimab (PRO 140) kits will be labeled with information such as: study protocol #; fill volume; concentration; storage condition; a "use as per study protocol" statement; a cautionary statement; sponsor's name and address; and the kit number.

Below are representative samples of the Investigational Product, FDP individual vial (Figure 6-1), and kit label (

Figure 6-2) designated for use in this clinical protocol. Each kit contains two labeled vials.

**Figure 6-1: Investigational Product - Vial Label**

| | |
|---|---|
| Protocol: CDI-NASH-01 Kit No. N01-XXXX<br>Subject No. _____<br>Single use vial of PRO 140 2 mL at 175 mg/mL solution for subcutaneous injection<br>Store at 2ºC to 8ºC<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA | Protocol: CDI-NASH-01 Kit No. N01-XXXX<br>Subject No. _____<br>Single use vial of PRO 140 2 mL at 175 mg/mL solution for subcutaneous injection<br>Store at 2ºC to 8ºC<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA |

**Figure 6-2: Investigational Product - Kit Label**

| |
|---|
| Protocol: CDI-NASH-01 Kit No. N01-XXXX<br>Site No. _____ Subject No. _____<br>Kit contains 2 single-use vials of PRO 140 2mL at 175 mg/mL solution for subcutaneous injection<br>USE AS PER STUDY PROTOCOL Store at 2ºC to 8ºC<br>Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use<br>CytoDyn Inc., Vancouver, WA, USA |

The pharmacy manual provides the criteria regarding vial acceptance or rejection, as well as instructions for the preparation of the IP syringes to be used to administer drug.

### 6.3 LERONLIMAB (PRO 140) - STORAGE AND HANDLING

Study drug will be shipped at 2°C to 8°C (refrigerated [36°F to 46°F]) to the investigator's site. Upon receipt at the site, the responsible site staff or pharmacist should verify the integrity of the vials. Study drug should be stored at 2°C to 8°C (refrigerated [36°F to 46°F]). The contents of the vial should appear as a clear to opalescent, colorless to yellow solution; fine translucent particles may be present. This is normal.

The investigator must maintain an accurate record of the shipment, storage, and dispensing of the study drug in a drug accountability log. An accurate record including the date and amount of study drug dispensed to each subject must be available for inspection at any time. An unblinded study Clinical Research Associate (CRA) assigned to monitor the investigational site will review these documents once study drug has been received by the investigational site. Study drug will be accounted for on an ongoing basis during the study.

### 6.4 INVESTIGATIONAL PRODUCT ADMINISTRATION

Guidelines for dose preparation can be found in the pharmacy manual.

Leronlimab (PRO 140) will be provided to the administering personnel in single-use syringes prepared from vials of study drug stored at 2-8°C at the site pharmacy prior to use. In Part 1 of the study, each of two syringes is filled to deliver 2.0 mL of study drug. Equivalent volumes of PRO 140 or placebo will be administered subcutaneously on opposite sides of the abdomen.

In Part 2 of the study, one syringe is filled to deliver 2.0 mL of study drug. Leronlimab (PRO 140) will be administered subcutaneously in the abdomen.

A 20-guage needle should be used to remove PRO 140 or placebo from vial and a 25-guage needle is used for administration to subjects.

Note: After the leronlimab or placebo solution is drawn into the syringe, it can be stored at

- room temperature (20°C to 25°C, 68°F to 77°F) for up to 2 hours, or
- refrigerated (2°C to 8°C, 36°F to 46°F) for up to 4 hours.

IP should be administered slowly over 15 seconds per mL.

Following each SC delivery of drug, careful examination will be made to assess the appearance of any study drug Injection Site Reactions (ISRs) as per CTCAE v5.0.

In Part 1 of the study, all doses of study drug will be prepared by either the unblinded credentialed pharmacist or qualified medical professional and will be provided to a blinded licensed healthcare professional at clinic site to be administered as SC injection. The blinding aspect is not applicable for the Part 2 of the study.

All Leronlimab (PRO 140) SC weekly injections must be administered at clinic by a healthcare professional.

**Note:** It is preferred that the same injection site be used throughout the study. At the same time, it is not recommended to inject the study drug into areas where skin shows signs of a previous injection site reaction. It is advised to change the injection site if any previous injection site reaction remains unresolved.

Post Injection Monitoring

Subject will be observed at approximately 30 minutes post-injection or longer, if necessary, for injection site reaction as per CTCAE v5.0.

In addition, the tolerability of repeated subcutaneous administration of PRO 140 is evaluated based on assessment of subject-perceived injection site pain using 11-point Numeric Pain Rating Scale.

Dose Modifications

The dose interruption, reduction, and permanent discontinuation for any toxicity are described below.

**Dose interruption:** Refer to Table 6-4 below. Recovery to acceptable levels must occur to allow Leronlimab (PRO 140) continuation.

**Table 6-4: Leronlimab (PRO 140) Dose Modification and Management for Injection Site Reactions**

| CTCAE Grade | Treatment Modifications |
|---|---|
| Grade 1 | No dose adjustment is required. |
| Grade 2 | First Occurrence: No dose adjustment is required.<br>Second Occurrence of the same event: Closely follow-up for resolution of the AE to Grade ≤ 1 |
| Grade 3 | Withhold treatment until symptoms resolve to:<br>• Grade 1 or less |
| Grade 4 | Study treatment will be permanently discontinued |

### 6.5 Investigational Product Disposition

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any drug labels or any partially used or unused drug supply until instructed by the Sponsor. At the conclusion of the study and as appropriate during the course of the study, the investigator will return all unused drug containers and drug labels to the drug distributor as directed by the Sponsor. A copy of the completed drug disposition form will be sent to CytoDyn, Inc. or to its designee.

### 6.6 Investigational Product Accountability

Study drug must be used in accordance with this protocol and only under the direction of the responsible investigator. The investigational site must maintain complete and accurate records showing receipt and disposition of all study drug, including master records listing the date of receipt, the number and nature of medication units received, and a dispensing record which includes each quantity dispensed, identification of the staff member/subject to whom dispensed, the date of dispensing, the intended study participant, and the identification of the preparer. All used and unused study kits will be retained by the investigational site until drug accountability can be confirmed by study CRA (unblinded CRA, for Part 1 of the study) during the monitoring visits. Instructions will be provided by Sponsor regarding final disposition of all study drug in compliance with applicable regulations.

# 7 DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

## 7.1 INFORMED CONSENT

A written informed consent will be obtained for this study for pre-screening and screening by the Investigator or designee from all subjects prior to performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

The Investigator must comply with applicable regulatory requirements and must adhere to the GCP in the process of obtaining and documenting the informed consent. The Investigator, or designee, must also inform subjects of all pertinent aspects of the study. Before written informed consent is obtained from the subject, the Investigator or a person designated by the Investigator, must provide the subject enough time and opportunity to inquire about the details of the study and to decide whether or not to participate in the trial. All questions addressed by the subject about the study must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

## 7.2 ASSESSMENT OF ELIGIBILITY

The Investigator must assess subject' continued eligibility for the study as per the Inclusion and Exclusion criteria, during the Screening Period. The eligibility criteria are described in Section 0 (Inclusion Criteria) and Section 0 (Exclusion Criteria). In the event that the subject is not suitable or eligible for the study, the subject will be considered "screen failure".

Re-screening

If a subject fails initially to meet the eligibility criteria, and is later reconsidered for participation, the subject will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled in the study only if they meet all Inclusion and no Exclusion criteria when re-screened.

## 7.3 DEMOGRAPHIC INFORMATION AND BASELINE DISEASE CHARACTERISTICS

In this study the demographic information will include:

- Dates of ICF signature
- Date of birth
- Gender

- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other)
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino)

In addition, the following baseline disease characteristics will be collected:

- Disease diagnosis date
- Medications used for the indication
- Previous histological procedures, if available for the indication:
    - Date of the most recent procedure
    - Stage of liver fibrosis per the most recent procedure
    - Any indication for cirrhosis per the most recent procedure
    - Stage of steatosis per the most recent procedure

### 7.4 MEDICAL HISTORY

A complete review of the subject's past medical history (including prior and concurrent liver disease and cirrhosis), past surgeries, current therapies (medications and non-medications), and history of exposure to environmental chemical agents will be undertaken by the Investigator to check that all inclusion and no exclusion criteria have been met.

Events that emerge prior to the first treatment (T1) will be recorded in the medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration and severity of any ongoing baseline medical conditions prior to the subject's receiving investigational product treatment.

Medical histories will be recorded using the body system categories outlined below:

- Cardiovascular
- Respiratory
- Gastrointestinal
- Renal
- Hepatic
- Neurological
- Endocrine
- Lymphatic
- Hematologic
- Immunologic
- Dermatologic
- Psychiatric
- Genitourinary
- Other

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of diagnosis
- History status (resolved or ongoing).

### 7.5 CONCOMITANT MEDICATION

All concomitant medication administered or taken by the subject beginning 6 month prior to Screening Visit and throughout the study will be recorded in the source documents and on the appropriate page of the Case Report Form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication and topical medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).

**Note:** *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*

- Route of dosing
- Indication for use
- The start date
- The stop dates (if medication/therapy is not ongoing).

Permitted Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Prohibited Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Period of this trial:

- Use of radiation or cytotoxic chemotherapy, immunosuppressants and immunomodulating agents (e.g., interleukins, interferons)
- Use of any non-FDA approved/investigational therapy

- Use of hepatotoxic medications such as antiarrhythmic drugs e.g., Amiodarone, Dronedarone
- Clinically significant dose adjustments of the existing T2DM medication regimen or initiation of new anti-diabetic medications for the duration of the study.

### 7.6 VITAL SIGNS, HEIGHT AND WEIGHT

The following will be collected:

- Vital signs:
  - Seated blood pressure (taken after the subject has been seated for at least 5 minutes)
  - Pulse
  - Temperature (oral or tympanic)
  - Respiratory Rate
- Height (only at the Screening Visit)
- Weight
- BMI (derived from the height and weight measurements).

### 7.7 PHYSICAL EXAMINATION

The physical examination will include routine examinations for the following:

- Head, Ears, Eyes, Nose, Throat (HEENT)
- Abnormalities of the extremities
- Neurologic abnormalities
- Heart/cardiovascular abnormalities
- Musculoskeletal abnormalities
- Dermatologic abnormalities
- Any other body system for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety or efficacy results for the subject; i.e., the abnormality is clinically significant.

Each abnormality will be recorded and the Investigator will record an assessment of its clinical significance.

The complete physical examination will be conducted at the Screening Visit (SV), T1 (Pre-treatment) and End of Treatment (EOT) Visit. Only symptom-directed physical examination will

be performed at treatment visits T2, T6, T10 and at unscheduled visits within the Treatment period and also at Early Termination (ET) Visit and Follow-up Visit.

### 7.8 ELECTROCARDIOGRAM (ECG)

A resting supine 12-lead ECG will be conducted at Screening Visit (SV), T1 (Pre-treatment), T2, T6, T10, EOT/ET visits. A 12-lead ECG will be repeated during the study only if clinically indicated and at the discretion of the treating physician. The results will be evaluated by the Investigator. The following parameters will be recorded: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). Additionally, the Investigator will record the overall results of the ECG reading as either normal or abnormal, and as either not clinically significant or clinically significant. If abnormalities are observed, each will be recorded.

### 7.9 CLINICAL LABORATORY ASSESSMENTS

Blood samples will be collected for analysis of the following parameters:

- Hematology (Complete Blood Count) will be performed at SV, T1 (prior to first dose), T2, T6, T10, EOT/ET visits.
- Biochemistry will be performed at SV, T1 (prior to first dose), T2, T6, T10, EOT/ET and FU visits.

  Note: Screening laboratory test can be repeated once during the 28-day screening window based on the Investigator's clinical judgement).
- Serum pro-inflammatory biomarkers including IL-1 alpha, IL-1 beta, IL-6, RANTES (CCL5), TNF-alpha, TNF-beta, CRP will be performed at T1 (prior to first dose), T2 (pre-dose), T6 (pre-dose), T10 (pre-dose), EOT/ET and FU visits.
- FibroTest (requires fasting for 12 hours or more) combines 5 standard biomarkers (gamma-glutamyltransferase, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1, and haptoglobin). The Acti-Test adds a marker for inflammatory activity (alanine aminotransferase: ALT). FibroTest will be performed at SV, T1 (prior to first dose), T2, T6, T10, EOT/ET visits.
- Serology tests including HBs Ag, HCV Ab and HCV RNA (only performed if HCV Ab is positive), HIV Ab, Hepatitis A and Hepatitis E Abs will be performed at SV.
- Anti-Drug antibodies (ADA) to PRO 140 at T1 (prior to first dose), T2 (pre-dose), T6 (pre-dose), T10 (pre-dose), EOT/ET and FU visits.
- PK assessment at T1 (prior to first dose), T2 (pre-dose), T6 (pre-dose), T10 (pre-dose), EOT/ET and FU visits.

- Serum pregnancy test (for female subjects of childbearing potential) at SV.
- Monocyte/T cell CCR5 biomarker assay at T1 (prior to first dose), T2 (pre-dose), T6 (pre-dose), T10 (pre-dose), EOT/ET and FU visits.

  *Note: In case subjects have already completed their EOT/ET and FU visits, site should use the Unscheduled Visit option to collect blood sample for Monocyte/T Cell CCR5 analysis.*

Urine samples will be collected for analysis of the following parameters:

- Urine pregnancy at T1 (prior to first dose), T6, T10, EOT/ET visits.

  *Note: A urine sample will be collected from female subjects of childbearing potential. This test will be performed at the study site using a commercially available kit.*
- Urine analysis testing at SV, T1 (prior to first dose), T2, T6, T10, EOT/ET visits.

Urine samples will be tested for color, appearance, specific gravity, pH, protein, glucose, occult blood, ketones, leukocyte esterases, nitrites, bilirubin, urobilinogen. Microscopic examination of urine sediment will be performed if there are abnormalities in macroscopic urinalysis results. Microscopic urine tests include bacteria, cast, crystals, epithelial cells, RBC and WBC.

All laboratory reports will be reviewed by the Investigator. Abnormal results that are considered by the Investigator to be clinically significant will be recorded as adverse events. In order to make the determination of clinical significance the testing may be needed to be repeated as per Investigator's judgement. Validated, quality-controlled laboratory data will be transferred to the main database for analyses.

**Table 7-1: Central Lab Parameters**

| CBC Parameters | Biochemistry Parameters | Urinalysis |
|---|---|---|
| Hemoglobin | **Liver Function Tests / NASH Markers** | pH |
| Hematocrit | Total Bilirubin | Appearance |
| RBC count | Direct Bilirubin | Color |
| WBC count | Alkaline Phosphatase (ALP) | Specific gravity |
| WBC Differential | Alanine Aminotransferase (ALT) (or SGPT) | Turbidity |
| Absolute lymphocyte count | Aspartate Aminotransferase (AST) (or SGOT) | Ketones |
| Absolute neutrophil count | Prothrombin Time (PT) | Bilirubin |
| Platelet count | International Normalized Ratio (INR) | Blood |
| **Serology** | Albumin | Glucose |
| HBs Ag, HCV Ab and HCV RNA (if required), HAV Ab, HEV Ab, HIV Ag | Total Protein | Protein |
| | Triglycerides | Nitrites |
| **Miscellaneous** | Cholesterol (Low density lipoprotein) | Urobilinogen |
| Serum pregnancy test | Creatine Kinase | Leukocyte esterases |
| Urine pregnancy test *(for female subjects of childbearing potential)* | Gamma-glutamyltransferase (GGT) | Note: Microscopic examination of urine sediment will be performed if there are abnormalities in macroscopic urinalysis results. Microscopic urine tests include bacteria, cast, crystals, epithelial cells, RBC and WBC. |
| Anti-Drug Antibodies (ADA) to PRO 140 | Serum CK-18 | |
| PK evaluations | **Renal Function Tests** | |
| Monocyte/T cell CCR5 biomarker assay | blood urea nitrogen (BUN) | |
| **Pro-inflammatory Biomarkers** | Creatinine | |
| IL-1 alpha, IL-1 beta, IL-6, RANTES (CCL5), TNF-alpha, TNF-beta, CRP | eGFR | |
| | **Electrolytes** | |
| **FibroTest** | Sodium | |
| Gamma-glutamyltransferase* | Potassium | |
| Total bilirubin* | Chloride | |
| Alpha-2-macroglobulin | Calcium | |
| Apolipoprotein A1 | Bicarbonate | |
| Haptoglobin. | **Other:** | |
| ALT* | Fasting Blood Glucose | |
| **Part of Liver Function Tests Panel* | Serum HbA1c | |
| | Thyroid profile | |

For the purpose of this study, the below baseline (normal) values/reference range for the liver function panel will be used:

| | |
|---|---|
| Total Bilirubin | 0.2-0.9 mg/dl |
| Direct Bilirubin | 0.0 – 0.2 mg/dl |
| SGOT (AST) | 15-41 IU/L |
| SGPT (ALT) | M: 17-63 IU/L; F: 14-54 IU/L |
| Alkaline Phosphatase (ALP) | 34-104 IU/L |

Sample Collection Guidelines

Please refer to laboratory manual for more details

Sample Processing, Storage, and Shipment

Please refer to laboratory manual for more details

### 7.10 Study Treatment Application

Refer to Section 0 for details.

### 7.11 Post-Injection Evaluation and Injection Site Reaction Assessment

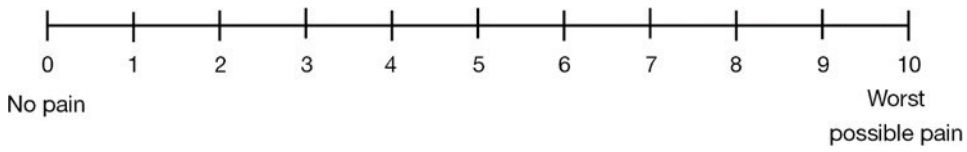
At each treatment visit, an injection site reaction assessment will be made for the current and previous injection sites. Injection site reaction assessments are recorded by the Investigator starting after the first injection is given. Subject will be observed at approximately 30 minutes post-injection or longer if necessary for injection site reaction as per CTCAE v5.0. Refer to Sections 0 for more details.

### 7.12 Pain Severity Assessment

Tolerability of repeated subcutaneous administration of Leronlimab (PRO 140) is evaluated based on assessment of subject-perceived injection site pain using 11-point Numeric Pain Rating Scale.

Before each study treatment administration (T2 to T13, and at EOT), subjects will be asked to evaluate the pain intensity **over the past week** at the site of injection administration based on 11-point Numeric Rating Scale from 0 to 10. “0” meaning “no pain” and “10” meaning “worst possible pain”.

**Figure 7-1: 11-Point Numeric Pain Rating Scale**



### 7.13 FIBROSCAN

Fibroscan ultrasound measures both liver fibrosis (scarring) and steatosis (fatty change). FibroScan steatosis (Controlled Attenuation Parameter (CAP)) score and fibrosis score will be evaluated for eligibility in this study.

### 7.14 LIVER MRI (MULTISCAN)

Liver MRI (MultiScan) is a non-invasive diagnostic technology for evaluating liver diseases using multiparametric MRI to non-invasively quantify liver tissue. Combining the information from multiple parametric maps provides a comprehensive analysis of liver tissue, which can be used to aid the diagnosis of liver disorders.

The Magnetic Resonance Imaging–derived Proton Density Fat Fraction (MRI-PDFF) is a novel imaging-based biomarker that allows fat mapping of the entire liver.

Corrected T1 (cT1) is also an MRI-based diagnostic imaging biomarker of the liver. cT1 is intended to be used as a proxy for inflammation and fibrosis.

In this study, Liver MRI will be performed to evaluate MRI-derived biomarkers such as PDFF and cT1 at SV and EOT/ET visits.

# 8 STATISTICAL ANALYSIS

This section presents general information about statistical considerations and concepts and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be in a separate document; i.e., the Statistical Analysis Plan (SAP).

## 8.1 TREATMENT GROUPS

In Part 1 of the study, all eligible subjects will be randomized to receive PRO 140 as a 700mg subcutaneous injection or placebo weekly for up to 13 weeks.

In Part 2 of the study, all eligible subjects will receive PRO 140 as a 350 mg subcutaneous injection weekly for up to 13 weeks.

## 8.2 STUDY OUTCOME MEASURES

Primary Efficacy Outcome Measure:

- Change from baseline in hepatic fat fraction assessed by magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) at week 14

Secondary Efficacy Outcome Measures:

- Change from baseline in fibro-inflammatory activity as assessed by cT1 (corrected T1) assessed by multiparametric magnetic resonance imaging (MRI) of liver at week 14

  *Note: cT1 measured in milliseconds (ms) is a quantitative metric for assessing a composite of liver inflammation and fibrosis*

- Change from baseline in liver fibrosis using FibroTest at week 14
- Change from baseline in hepatic inflammatory activity using FibroTest at week 14
- Change from baseline in serum pro-inflammatory biomarkers assessments
- Change from baseline in Gamma-glutamyltransferase (GGT) at week 14
- Change from baseline in CK-18 level at week 14
- Change from baseline in Leronlimab (PRO 140) PK assessments

Exploratory Outcome Measures:

- Change from baseline in Alanine transaminase (ALT) at week 14
- Change from baseline in Aspartate transaminase (AST) at week 14

- Change from baseline in total bilirubin at week 14
- Change from baseline in triglycerides at week 14
- Change from baseline in Low Density Lipoprotein (LDL) at week 14
- To explore Monocyte/T cell CCR5 biomarkers that may predict activity of leronlimab.

### 8.3 SAMPLE SIZE DETERMINATION AND RATIONALE

The sample size of 90 total subjects [60 subjects (30 subjects per arm) for the Randomized Phase and up to 30 subjects for the non-randomized, open-label phase] is selected on the basis of clinical judgment and not based on statistical power calculation. The number of subjects is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

### 8.4 RANDOMIZATION

Subjects who are eligible to participate in the trial will be randomized to one of the treatment groups via IWRS (Interactive Web Based Randomization System) at the T1 Visit prior to IP administration. The randomization will be central and will use 1:1 ratio of Treatment groups A and B:

- PRO 140 700mg SC weekly injection (Group A)
- Placebo 0 mg SC weekly injection (Group B)

Note: Randomization is not applicable for the open-label, single-arm portion (Part 2) of the study.

### 8.5 BLINDING

All subjects, Investigators and their staff, and all Sponsor/CRO personnel involved in the management of the study will be blinded to treatment assignments.

The [redacted] Information Technology department will be unblinded to treatment. As noted above, the [redacted] Technology department is not otherwise involved with the study.

Treatment unblinding for the study will occur after all clinical data have been received, data inconsistencies have been resolved, and the database is locked, except for safety reasons on a case-by-case basis (i.e., emergency unblinding).

Note: Blinding is not applicable for the open-label, single-arm portion (Part 2) of the study.

### 8.6 INTERIM ANALYSIS

No interim analysis (IA) will be performed for efficacy.

### 8.7 GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

Analysis Populations

**Intent-to-Treat Population**

The **Intent-to-Treat (ITT) population** is defined as the set of subjects who have received at least one dose of study treatment (Leronlimab (PRO 140) or placebo) and have at least one post-baseline efficacy assessment. The ITT population will be used as the primary analysis population.

**Per Protocol Population**

The **Per Protocol (PP) population** is defined as the set of subjects who meet the ITT population requirements, were not associated with any major protocol violations and have at least 80% of compliance with study treatment. This population will be identified before the database lock.

The PP analysis of primary and secondary endpoints will be considered supportive.

**Safety Population**

The **Safety Population** will include all subjects who have received one dose of study treatment (Leronlimab (PRO 140) or placebo). This population will be used for the analysis of safety parameters.

Covariates

For efficacy analyses, the baseline values will be used as covariates in the analysis models. Other important prognostic factors will be specified in the SAP for the study.

Missing Data

All data will be used as observed, and no imputations will be made for any missing data point for early phase study.

### 8.8 ANALYSIS METHODS

A SAP will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the data from this trial. All inferential statistical analysis will be based on a two-sided test with a Type I error rate of 0.05.

All the efficacy analyses presented here will be conducted using both the ITT and PP populations. All safety analyses will be conducted using the Safety population. Continuous data summaries will

include number of observations, mean, standard deviation, median, and minimum and maximum values. Categorical data summaries will include frequency counts and percentages.

Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, received treatment, completed, and discontinued during the study, as well as the reasons for all post-enrollment discontinuations will be listed and/or summarized by treatment group.

Demographic and Baseline Disease Characteristics

Demographics and baseline disease characteristics including medical history, prior and concomitant medications/therapies will be listed and/or summarized by treatment group using appropriate descriptive statistics.

Study Analyses

**Efficacy Analysis**

Analysis of the efficacy endpoints will be conducted according to below methods:

- If the Normality assumption is met, Analysis of Covariance (ANCOVA) or Mixed Model using the covariates in the model.
- If the Normality assumption is not met, a non-parametric method or a rank – ANCOVA analysis will be used.

**Safety Analyses**

Safety will be assessed by close monitoring and timely assessment of adverse events (AEs), laboratory parameters (blood tests, urinalysis), vital signs (blood pressure, heart rate), subject's medical condition (physical examination including weight). Tolerability of repeated subcutaneous administration of Leronlimab (PRO 140) as assessed by study participants (using 11-point Numeric Pain Rating Scale) and by investigator-evaluation of injection site reactions.

**Adverse Events**

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- by PT in descending order of frequency
- by SOC and PT
- by SOC, PT, and severity

- by SOC, PT, and relationship to study drug

**Clinical Laboratory Data**

All laboratory values will be listed. Laboratory measurements will also be summarized as continuous variable and presented by treatment group and time point.

**Physical Examination**

All physical examination findings will be listed and/or summarized.

**Vital Signs**

All vital sign findings will be listed and summarized.

**Electrocardiograms (ECGs)**

All ECG findings will be listed and summarized.

**Tolerability**

Pain severity assessment (using 11-point Numeric Pain Rating Scale) and injection site reactions will be listed and summarized.

# 9 ADVERSE EVENTS (DEFINITIONS AND REPORTING)

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs as detailed in this Section of the protocol.

## 9.1 ADVERSE EVENT (AE)

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the subject to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormalities in visit evaluations, physical examination findings or laboratory results that the investigator believes are clinically significant to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should be not be recorded as an AE.

## 9.2 REPORTING AND FOLLOW-UP OF ADVERSE EVENTS

Report initiation for all AEs and serious adverse events (SAEs), (see Section 9.3), will begin at the time of the first treatment and continue up to the final study visit. All events will be followed to resolution or until 30 days after the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see Section 9.3), the impact the event had on study treatment (see Section 0), the CTCAE grade (intensity) of the event (see Section 0), the causality of the event (see Section 0), whether treatment was given as a result of the event (see Section 0), and the outcome of the event (see Section 0).

Impact on Study Treatment

The impact the event had on the study treatment will be assessed as either: dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, unknown, and not applicable. The "not applicable" assessment will be used only when the subject is no longer in the treatment period of the protocol or died.

CTCAE Grade (Intensity) Assessment

The guidelines outlined in CTCAE v5.0 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

**Table 9-1: CTCAE v5.0 General Guidelines**

| Grade | Description |
|---|---|
| Grade 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*. |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL†. |
| Grade 4 | Life-threatening consequences; urgent intervention indicated. |
| Grade 5 | Death related to AE.‡ |

*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.
‡Unlike the AE outcome assessment (see Section 0), a subject may have more than one Grade 5 event.

-Common Terminology Criteria for Adverse Events (CTCAE), v5.0: Nov 27, 2017

Causality Assessment

Adverse events will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Unrelated** – The event is definitely not associated with the study biologic or control. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication explain the reported AE.
2. **Unlikely** – The temporal association, patient history and/or circumstances are such that the study biologic or control is not likely to have had an association with the observed event. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication, appear to explain the reported AE.
3. **Possibly** – The event follows a reasonable temporal sequence from study biologic or control but could have been produced by the patient's clinical state or other therapies administered to the patient.

4. **Probably** – The event follows a reasonable temporal sequence from the study biologic or control, abates upon discontinuation of the study drug or control, or cannot be reasonably explained by known characteristics of the patient's clinical state.
5. **Definitely** – The event follows a reasonable temporal sequence from the study biologic or control, abates upon discontinuation and cannot be explained by known characteristics of the patient's clinical state.

Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

Outcome Assessment

The outcome of the event will be assessed as either: fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequalae, recovering/resolving, and unknown. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death

Injection-site reactions

Injection-site reactions thought to be directly related to the injection are considered to be AEs of special interest, and will be assessed as per CTCAE v5.0.

For subjects who develop Grade 1 or Grade 2 events, therapy will be continued as per protocol. If a subject chooses to discontinue study treatment, the site should notify the protocol team leadership, and encourage the subject to complete any remaining study visits until the toxicity resolves.

For subjects who develop Grade 3 events following study drug injection, the subject should be reevaluated closely until the AE returns to Grade 1 or less, at which time study treatment may be reintroduced at the discretion of the site investigator. If the same Grade 3 AE recurs following the next administration of study drug, study treatment must be permanently discontinued. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of study treatment should be followed closely for resolution of the AE to Grade 1 or less and the team leadership must be notified.

For Grade 4 events permanently discontinue therapy.

### 9.3 SERIOUS ADVERSE EVENTS

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the adverse experience)

- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device effect when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

### 9.4 REPORTING OF SERIOUS ADVERSE EVENTS

The Investigator is required to report all SAEs that occur during the time period specified in Section 9.2. Once the Investigator becomes aware of an SAE, he/she must report the SAE to [redacted] Safety and Pharmacovigilance Department within 24 hours:

[redacted]

A written SAE report must include a full description of the event as described in Section 9.2 and must follow within 24 hours from the time the Investigator first learned of the event. The [redacted] Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, electrocardiogram (ECG) reports, discharge summary, hospital notes, etc, if applicable.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

### 9.5 SAE FOLLOW-UP

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further

improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

#### 9.5.1. Regulatory Reporting Requirements for SAEs

The investigator, or responsible person per local requirements, must comply with the applicable local regulatory requirements related to the reports of SAEs to regulatory authorities and the Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC).

The Sponsor is responsible for the ongoing evaluation of the study drug. Any adverse experience associated with the use of the study drug that is both serious and unexpected must be reported. In accordance with the US Code of Federal Regulations, Title 21 CFR Part 312.32, and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the Sponsor must submit written documentation in the form of an Investigational New Drug (IND) Safety Report or suspected unexpected serious adverse reaction (SUSAR) reports, respectively. All events qualifying as IND Safety Reports/SUSARs will be reported to the IRB/IECs, and Investigators will be provided by the drug safety group for regulatory authorities. IND Safety Reports/SUSARs are required to be reported within 7 calendar days for life-threatening events and those resulting in death or 15 calendar days for all others. These timeframes begin with the first notification of the IND Safety Reports/SUSARs to the drug safety group from the Investigator.

The Sponsor should submit to the regulatory authority all safety updates and periodic reports, as required by applicable regulatory requirements.

### 9.6 PREGNANCY REPORTING

Pregnancies detected during the study must be reported to Medical Monitor within the same timelines as an SAE using the appropriate form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother and/or child should be reported. The investigator must report any pregnancy that occurs in a study subject. Any female subject who becomes pregnant during the study will be discontinued from investigational product and will be followed for pregnancy outcome.

# 10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The local IRB, FDA, the monitors, auditors and personnel authorized by the Sponsor are eligible to review the medical and research records related to this study as part of their responsibility to protect human subjects in clinical research. They will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy and each site will be required to ensure access while remaining compliant with institutional requirements.

# 11 QUALITY CONTROL AND QUALITY ASSURANCE

## 11.1 MONITORING REQUIREMENTS

The specific obligations outlined in 21 Code of Federal Regulations (CFR) and ICH guidelines require the Sponsor to maintain current personal knowledge of the progress of a study. Therefore, the Sponsor's designated monitor will visit the site during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

As delineated above, the Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the eCRF. In addition to the original medical records, these data may include but are not limited to study, laboratory reports, etc.

In accordance with federal regulations, site inspections will serve to verify strict adherence to the protocol and the accuracy of the data that is being entered on the case report forms. A Monitoring Log will be maintained at each study site. The Monitoring Log will be signed by the monitor, dated and stated the type of visit. The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

## 11.2 ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

For each subject who has signed an informed consent form, a CRF must be completed. For subjects who are screen failures, this would be limited to the screen failure CRF page. All source documents and CRFs will be completed as soon as possible after the subject's visit and corrections to data on the CRFs will be documented, if applicable. The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

## 11.3 MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator’s IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or

2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be provided in writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

### 11.4 REPORTING PROTOCOL DEVIATIONS

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well being and/or the completeness, accuracy and reliability of the study data. Examples of this include:

- Failure to obtain informed consent prior to initiation of study-related procedures
- A research subject does not meet the protocol's eligibility criteria but was enrolled without prior approval from the sponsor.
- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received a prohibited concomitant medication.
- Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes.
- Changing the protocol without prior sponsor and IRB approval.
- Multiple minor violations of the same nature after multiple warnings.

Minor Protocol Deviation or Violation

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT

have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples of this include:

- Follow-up visits that occurred outside the protocol required time frame because of the participant’s schedule.
- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

# 12 ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, the study product used in this study is manufactured, handled and stored in accordance with applicable GMP. The study product provided for this study will be used only in accordance with this protocol.

## 12.1 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The Principal Investigator (PI) at the site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC, and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

## 12.2 INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations.

Information regarding to the study center participating in this study that cannot comply with these standards will be documented.

### 12.3 SUBJECT INFORMED CONSENT REQUIREMENTS

All subjects participating in this study will be given to by the Investigator and/or designee, written and oral information about the study in a language understandable by the subject. Written informed consent will be obtained from each subject prior any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form ICF will be in compliance with CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. The study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject’s medical record, if allowed by institutional policy.

# 13 DATA HANDLING AND RECORD KEEPING

## 13.1 RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approve case report forms (CRF). The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with the Lead Investigator.

The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

## 13.2 CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan.

### 13.3 ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two (2) years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two (2) years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Completed CRFs
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- IP and accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Subject screening
- SAE reports
- IRB approval and re-approval letters
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator. Study records are subject to inspection by applicable health and regulatory agencies at any time.

# 14 PUBLICATION PLAN

All information supplied by CytoDyn in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of CytoDyn, shall not be disclosed to others without the written consent of CytoDyn, and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical trial in connection with the development of CytoDyn. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

**Publication and Disclosure**: The site and Investigator agree to submit any proposed manuscript, presentation or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities prior to completion of the trial, even if the multi-center trial or the study is terminated before its completion and the final clinical study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

# 15 REFERENCES

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# 16 APPENDIX

## 16.1 APPENDIX 1: ACCEPTABLE METHODS OF CONTRACEPTION

| Barrier Methods | Intrauterine Device Methods | Hormonal Methods |
|---|---|---|
| • Male condom plus spermicide<br>• Cap plus spermicide<br>• Diaphragm plus spermicide | • Copper T<br>• Progesterone T<br>• Levonorgestrel-releasing | • Implants<br>• Hormone shot or injection<br>• Combined pill<br>• Minipill<br>• Patch |

**NOTE**: choice of contraception should be discussed with primary treating physician to discuss the risks and benefits of different modalities of contraception.

## 16.2 APPENDIX 2: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0

For complete detailed information please refer to the link below:

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