**Clinical Study Protocol (CSP)**

**Protocol Title:**  
A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Novostatin (Novitor) in Patients with Hypercholesterolemia

**Protocol Number:** NSP-002-2024  
**Version:** 1.0  
**Date:** February 15, 2024

**Sponsor:**  
Novitor Pharmaceuticals Inc.  
1234 Innovation Drive  
Biotech City, State, Country

**Investigational Drug:**  
Novostatin (Trade Name: Novitor)  
A novel statin designed for low-dosage administration to reduce high cholesterol while minimizing severe side effects.

**Study Duration:**  
March 2, 2024 – September 22, 2024

**Table of Contents**

1. **Background and Rationale**
2. **Study Objectives and Endpoints**
3. **Study Design and Methodology**
   * 3.1 Study Population
   * 3.2 Inclusion/Exclusion Criteria
   * 3.3 Treatment Regimens and Randomization
   * 3.4 Study Procedures and Schedule of Assessments
4. **Statistical Considerations**
5. **Safety and Efficacy Assessments**
6. **Ethical Considerations**
7. **Study Organization and Responsibilities**
8. **Data Management and Quality Assurance**
9. **Trial Timeline and Milestones**
10. **Conclusion and Next Steps**

**1. Background and Rationale**

Hypercholesterolemia remains a significant risk factor for cardiovascular diseases. Statins have proven effective in lowering low-density lipoprotein (LDL) cholesterol; however, higher dosages are frequently associated with adverse effects such as myopathy and liver enzyme elevations. Novostatin (Novitor) is a novel statin formulated to be effective at low dosages, potentially reducing the severity and incidence of side effects. Preclinical studies and early-phase trials have demonstrated promising lipid-lowering effects with an improved safety profile. This Phase 2 trial aims to further evaluate the efficacy and safety of Novostatin compared to placebo in patients with moderate to severe hypercholesterolemia.

**2. Study Objectives and Endpoints**

**Primary Objective**

* **Efficacy:** To assess the percentage change in LDL cholesterol from baseline to Week 24 in patients treated with Novostatin versus placebo.

**Secondary Objectives**

* To evaluate the effect of Novostatin on total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides.
* To assess the safety and tolerability of Novostatin, with particular attention to muscle and liver-related adverse events.
* To evaluate the pharmacokinetic (PK) profile of Novostatin.

**Exploratory Objectives**

* To assess biomarkers of inflammation and endothelial function.
* To evaluate quality-of-life changes as measured by validated questionnaires.

**Endpoints**

* **Primary Endpoint:**
  + Mean percentage reduction in LDL cholesterol at Week 24 compared to baseline.
* **Secondary Endpoints:**
  + Changes in total cholesterol, HDL, and triglyceride levels.
  + Incidence and severity of adverse events (AEs) and serious adverse events (SAEs).
  + PK parameters including C\_max, T\_max, and AUC.
* **Exploratory Endpoints:**
  + Changes in inflammatory biomarkers (e.g., C-reactive protein).
  + Quality-of-life assessment scores.

**3. Study Design and Methodology**

**3.1 Study Population**

This trial will enroll approximately 200 adult patients (aged 18–75 years) with a documented diagnosis of hypercholesterolemia who have not achieved target LDL levels with diet and lifestyle modifications alone. Subjects must provide written informed consent.

**3.2 Inclusion Criteria**

* Diagnosed with hypercholesterolemia (LDL ≥ 130 mg/dL).
* Body Mass Index (BMI) between 18 and 35 kg/m².
* Able to provide informed consent and comply with study procedures.
* Stable concomitant medications for at least 30 days prior to screening.

**3.3 Exclusion Criteria**

* History of statin intolerance or hypersensitivity to statins.
* Active liver disease or ALT/AST >3× upper limit of normal.
* Severe renal impairment (eGFR <30 mL/min/1.73 m²).
* Recent history of myocardial infarction or stroke (within the last 6 months).
* Participation in another clinical trial within 30 days prior to screening.

**3.4 Treatment Regimens and Randomization**

* **Randomization:**  
  Eligible patients will be randomized in a 1:1 ratio to receive either Novostatin or matching placebo.
* **Treatment Arms:**
  + **Arm A:** Novostatin 10 mg orally once daily.
  + **Arm B:** Placebo orally once daily.
* **Blinding:**  
  The study is double-blinded; both investigators and subjects will be unaware of the treatment assignments.

**3.5 Study Procedures and Schedule of Assessments**

* **Screening Phase (up to 4 weeks):**  
  Baseline evaluations including medical history, physical examination, laboratory assessments (lipid profile, liver enzymes, CK levels), and ECG.
* **Treatment Phase (24 weeks):**
  + **Baseline (Day 1):** Randomization and first dose administration.
  + **Follow-up Visits:**
    - Week 4, Week 8, Week 12, Week 16, Week 20: Safety labs, vital signs, adverse event assessments, and compliance checks.
    - Week 24: Final efficacy assessment including lipid panel, PK sampling (subset of 50 patients), and final safety evaluations.
* **End-of-Study Visit:**  
  Conducted 4 weeks after the last dose to assess any lingering effects and collect final laboratory data.

**4. Statistical Considerations**

**Sample Size Calculation**

Based on prior data, a sample size of 200 patients (100 per arm) will provide 80% power to detect a clinically significant difference of 15% reduction in LDL cholesterol (α = 0.05, two-sided test).

**Statistical Analysis Plan**

* **Primary Analysis:**  
  The primary endpoint will be analyzed using an ANCOVA model adjusting for baseline LDL levels and stratification factors.
* **Secondary Analyses:**  
  Secondary endpoints will be evaluated using mixed-effects models and descriptive statistics. Safety data will be summarized by treatment group.
* **Interim Analysis:**  
  An independent data monitoring committee (IDMC) will conduct an interim analysis at Week 12 to ensure safety and trial integrity without unblinding efficacy outcomes.

**5. Safety and Efficacy Assessments**

* **Efficacy Assessments:**  
  Lipid profiles (LDL, HDL, total cholesterol, triglycerides) measured at scheduled visits.
* **Safety Assessments:**  
  Monitoring of adverse events, vital signs, clinical laboratory tests (including liver function tests, creatine kinase), and ECG evaluations.
* **PK Assessments:**  
  In a subset of patients, blood samples will be collected at specified time points to determine the pharmacokinetic profile of Novostatin.

**6. Ethical Considerations**

* The study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and local regulatory requirements.
* An independent Ethics Committee/Institutional Review Board (IRB) has approved the protocol.
* Informed consent will be obtained from all participants before any study-related procedures are performed.
* Patient confidentiality will be maintained throughout the study.

**7. Study Organization and Responsibilities**

* **Sponsor (Novitor Pharmaceuticals Inc.):**  
  Overall study oversight, funding, and regulatory submissions.
* **Clinical Research Organization (CRO):**  
  Management of day-to-day trial operations, site management, and data collection.
* **Principal Investigators and Study Sites:**  
  Responsible for patient recruitment, conduct of study procedures, and reporting of adverse events.
* **Data Monitoring Committee (DMC):**  
  Oversight of safety data and interim analysis.

**8. Data Management and Quality Assurance**

* **Data Collection:**  
  Data will be captured electronically using validated electronic Case Report Forms (eCRFs).
* **Quality Control:**  
  Regular monitoring visits and audits will be conducted to ensure protocol compliance and data accuracy.
* **Confidentiality:**  
  All data will be de-identified and stored securely in compliance with data protection regulations.

**9. Trial Timeline and Milestones**

* **Study Start Date:** March 2, 2024
* **Last Patient Last Visit (LPLV):** September 22, 2024
* **Interim Analysis:** Planned at Week 12 (approximately mid-study)
* **Database Lock and Final Analysis:** Within 4 weeks post-study completion
* **Study Report Preparation:** Within 8 weeks after database lock

**10. Conclusion and Next Steps**

Based on the pre-specified primary and secondary endpoints, the Phase 2 study of Novostatin (Novitor) is designed to rigorously assess both the efficacy and safety profile of the drug in lowering LDL cholesterol levels in hypercholesterolemic patients. Preliminary preclinical and early-phase data suggest that Novostatin can achieve significant lipid reductions at low dosages, thereby reducing the incidence of high-severity side effects commonly associated with traditional statin therapies.

Given that the trial results are positive—demonstrating a statistically and clinically significant reduction in LDL cholesterol with an acceptable safety profile—the sponsor recommends advancing Novostatin into Phase 3 trials. Phase 3 studies will focus on confirming efficacy in a larger patient population, further exploring long-term safety, and assessing the drug’s impact on cardiovascular outcomes.