**Statistical Analysis Plan (SAP)**

**Study 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  
**SAP Version:** 1.0  
**Date:** April 25, 2024  
**Sponsor:** Novitor Pharmaceuticals Inc.

**Investigational Product:** Novostatin (Trade Name: Novitor)  
**Study Duration:** March 2, 2024 – September 22, 2024

**Table of Contents**

1. Introduction
2. Study Objectives and Endpoints
3. Analysis Populations
4. Sample Size and Power Considerations
5. Statistical Methods
   * 5.1 General Statistical Considerations
   * 5.2 Analysis of Primary Endpoint
   * 5.3 Analysis of Secondary Endpoints
   * 5.4 Pharmacokinetic/Pharmacodynamic Analyses
6. Handling of Missing Data
7. Interim Analysis
8. Data Presentation and Tables
9. Statistical Software
10. Appendices

**1. Introduction**

This Statistical Analysis Plan (SAP) outlines the planned methods for statistical analysis for the Phase 2 clinical trial of Novostatin (Novitor). The trial is designed to evaluate the efficacy and safety of Novostatin in reducing LDL cholesterol levels in patients with hypercholesterolemia, while maintaining a favorable safety profile at low dosages. The results from this study will inform the decision to progress to Phase 3 trials.

**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 compared to placebo.

**Secondary Objectives**

* To evaluate the effects of Novostatin on total cholesterol, HDL cholesterol, and triglyceride levels.
* To assess the safety and tolerability of Novostatin, focusing on adverse events related to liver and muscle toxicity.
* To describe the pharmacokinetic (PK) profile of Novostatin in a subset of patients.

**Endpoints**

**Primary Endpoint**

* **Mean Percentage Change in LDL Cholesterol:**  
  The primary efficacy endpoint is the mean percentage reduction in LDL cholesterol from baseline to Week 24.

**Secondary Endpoints**

* **Lipid Parameters:**  
  Change from baseline to Week 24 in total cholesterol, HDL cholesterol, and triglycerides.
* **Safety Endpoints:**  
  Incidence, severity, and relationship of adverse events (AEs) and serious adverse events (SAEs).
* **Pharmacokinetic Parameters:**  
  Key PK measures include maximum plasma concentration (C\_max), time to maximum concentration (T\_max), and area under the concentration-time curve (AUC).

**Exploratory Endpoints**

* Changes in inflammatory biomarkers (e.g., C-reactive protein) and quality-of-life scores.

**3. Analysis Populations**

**Intent-to-Treat (ITT) Population**

* **Definition:**  
  All randomized patients who received at least one dose of study medication and have at least one post-baseline efficacy assessment.

**Per-Protocol (PP) Population**

* **Definition:**  
  Subset of the ITT population that adheres to the protocol without major deviations and has completed the primary efficacy assessments.

**Safety Population**

* **Definition:**  
  All patients who received at least one dose of study medication. Safety analyses will include all available safety data from these patients.

**Pharmacokinetic (PK) Population**

* **Definition:**  
  All patients included in the PK sampling subset with sufficient concentration-time data to compute PK parameters.

**4. Sample Size and Power Considerations**

Based on historical data and Phase 1 findings, 200 patients (100 per treatment arm) will be enrolled to provide 80% power to detect a 15% difference in LDL cholesterol reduction between Novostatin and placebo, assuming a standard deviation of 25% and using a two-sided α of 0.05. The sample size calculation also accounts for an anticipated 10% dropout rate.

**5. Statistical Methods**

**5.1 General Statistical Considerations**

* **Analysis Approach:**  
  All statistical tests will be two-sided, with a significance level of 0.05.
* **Baseline Definition:**  
  Baseline is defined as the most recent measurement prior to the first dose of study medication.
* **Handling of Multiplicity:**  
  Secondary endpoints will be tested in a hierarchical order to control for type I error.
* **Data Transformation:**  
  Non-normally distributed variables may be log-transformed prior to analysis.

**5.2 Analysis of Primary Endpoint**

* **Primary Efficacy Analysis:**  
  The primary analysis will use an analysis of covariance (ANCOVA) model with the percentage change in LDL cholesterol at Week 24 as the dependent variable. Treatment group (Novostatin vs. placebo) will be the fixed factor, and baseline LDL cholesterol will be included as a covariate.
* **Missing Data:**  
  A last observation carried forward (LOCF) method will be applied for missing Week 24 values in the ITT population. Sensitivity analyses using multiple imputation will also be conducted.

**5.3 Analysis of Secondary Endpoints**

* **Lipid Parameters:**  
  Changes in total cholesterol, HDL, and triglycerides will be analyzed similarly using ANCOVA, adjusting for baseline values.
* **Safety Analyses:**  
  AE and SAE rates will be summarized descriptively by treatment group. The incidence of predefined laboratory abnormalities (e.g., liver enzymes, creatine kinase) will be presented as counts and percentages.
* **Pharmacokinetic Analyses:**  
  Descriptive statistics (mean, standard deviation, median, range) will be provided for PK parameters (C\_max, T\_max, AUC) calculated using non-compartmental methods.

**5.4 Pharmacodynamic and Exploratory Analyses**

* **Exploratory Biomarkers:**  
  Changes in inflammatory markers (e.g., C-reactive protein) will be summarized using descriptive statistics and exploratory ANCOVA models.
* **Quality-of-Life Assessments:**  
  Changes from baseline in validated questionnaire scores will be analyzed using repeated-measures analysis.

**6. Handling of Missing Data**

Missing data will be handled as follows:

* **Primary Endpoint:**  
  Use of LOCF for the primary efficacy endpoint, with sensitivity analyses using multiple imputation.
* **Secondary Endpoints:**  
  Missing continuous outcomes will be imputed based on mixed-model repeated measures (MMRM) if applicable.
* **Safety Data:**  
  All available data will be included; missing values will be clearly documented and summarized.

**7. Interim Analysis**

An interim analysis for safety will be conducted by an independent Data Monitoring Committee (DMC) at Week 12. The interim analysis will be descriptive in nature and will not involve any unblinding of the efficacy data. Decisions regarding trial continuation or modifications will be made based on pre-specified safety criteria.

**8. Data Presentation and Tables**

Results will be presented in the final clinical study report and include:

* **Tables:**  
  Summaries of baseline characteristics, primary and secondary endpoints, PK parameters, and safety data.
* **Figures:**  
  Graphical representations including box plots, line graphs of LDL cholesterol trends, and Kaplan–Meier curves for time-to-event analyses (if applicable).
* **Listings:**  
  Individual subject data listings for key safety parameters and protocol deviations.

**9. Statistical Software**

Analyses will be performed using validated statistical software. The primary analyses will be conducted using SAS (version 9.4 or later). Additional analyses may be performed using R (version 4.0 or later) as needed.

**10. Appendices**

* **Appendix A:** Detailed Statistical Tables Format
* **Appendix B:** Example CRF Pages and Data Collection Templates
* **Appendix C:** Statistical Code Examples for Primary Endpoint Analysis
* **Appendix D:** List of Abbreviations and Definitions