**Protocol Amendment Document**

**Amendment Title:**  
Amendment 1 – Update to Inclusion Criteria and Dose Adjustment Rationale

**Protocol Number:** NSP-002-2024  
**Amendment Number:** 1  
**Date of Amendment:** April 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 lower LDL cholesterol while reducing the incidence of high-severity side effects.

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

**1. Background and Rationale for Amendment**

During the initial phase of patient enrollment and early data monitoring, the Data Monitoring Committee (DMC) noted a subset of patients with a body mass index (BMI) at the higher end of the eligibility spectrum appeared to require a slightly adjusted dose to achieve optimal lipid-lowering effects. In addition, feedback from investigators indicated that the original inclusion criteria could be refined to better identify the patient population most likely to benefit from Novostatin. Therefore, this amendment aims to:

* Refine the inclusion criteria to ensure a more homogeneous study population.
* Introduce a protocol-specified dose adjustment for patients with BMI > 30 kg/m², allowing for an increase from 10 mg to 15 mg after Week 8 if LDL reduction is less than 10% and the patient demonstrates no safety concerns.

**2. Summary of Changes**

**2.1. Inclusion Criteria Modifications**

* **Previous Criterion:**  
  “Subjects must have a Body Mass Index (BMI) between 18 and 35 kg/m².”
* **Revised Criterion:**  
  “Subjects must have a Body Mass Index (BMI) between 18 and 35 kg/m² with a recommendation for additional dosing evaluation for subjects with a BMI > 30 kg/m². These subjects will undergo a review at Week 8 for potential dose escalation based on efficacy and safety outcomes.”

**2.2. Dose Adjustment Schedule**

* **New Dose Adjustment Rule:**  
  Subjects in the active treatment arm with a BMI > 30 kg/m² who exhibit less than a 10% reduction in LDL cholesterol at Week 8 and no safety concerns (e.g., normal liver enzymes, CK levels within acceptable range) will be eligible to have their dose increased from 10 mg to 15 mg once daily.

**2.3. Revised Study Procedures**

* **Monitoring Adjustments:**  
  Additional laboratory assessments (including liver enzymes, CK levels, and LDL cholesterol) will be conducted at Week 8 for patients with BMI > 30 kg/m² to determine eligibility for dose escalation.
* **Documentation:**  
  Updated Case Report Forms (CRFs) now include fields to capture BMI-specific data and decision criteria for dose adjustments.

**3. Rationale for Changes**

**3.1. Inclusion Criteria Refinement**

* **Rationale:**  
  Early enrollment data suggested that patients with a BMI > 30 kg/m² may metabolize Novostatin differently, potentially requiring a modified approach to achieve the desired lipid-lowering effect. Refining the inclusion criteria ensures that the study population more accurately reflects the target patient demographic for whom Novostatin is intended.

**3.2. Dose Adjustment Rationale**

* **Rationale:**  
  Adjusting the dose for patients with higher BMI is intended to enhance the efficacy of Novostatin without compromising safety. The interim data demonstrated that a subset of patients did not meet the desired LDL reduction threshold, suggesting a need for dose optimization. This approach is designed to maintain the drug's favorable safety profile by applying the dose increase only after a thorough assessment of efficacy and safety markers.

**4. Impact on Study Design and Operations**

**4.1. Patient Safety and Efficacy**

* **Efficacy Impact:**  
  The dose adjustment is expected to improve LDL cholesterol reduction in patients with higher BMI, thereby strengthening the overall efficacy findings of the study.
* **Safety Impact:**  
  Close monitoring and pre-defined safety criteria for dose escalation ensure that patient safety is not compromised. No additional risk is anticipated as the decision to increase the dose is based on comprehensive safety evaluations.

**4.2. Study Procedures**

* **Operational Impact:**
  + Updated CRFs and electronic data capture (EDC) systems to include BMI-based assessments.
  + Training sessions for site staff will be conducted to ensure proper implementation of the new criteria and dosing schedule.
  + Additional monitoring visits at Week 8 for patients with BMI > 30 kg/m² are scheduled.

**4.3. Regulatory and Documentation Updates**

* **Regulatory Impact:**  
  This amendment has been submitted to the Ethics Committee/Institutional Review Board (IRB) and relevant regulatory authorities for review and approval. All changes will be documented in the updated protocol and communicated to all participating sites.
* **Documentation Impact:**  
  All protocol-related documents, including the Investigator’s Brochure and the Statistical Analysis Plan (SAP), will be updated to reflect these changes.

**5. Approval and Implementation**

**5.1. Approval Signatures**

The following signatures indicate that the amendment has been reviewed and approved by the appropriate parties:

| **Role** | **Name** | **Signature** | **Date** |
| --- | --- | --- | --- |
| Principal Investigator | Dr. Jane Doe | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | April 16, 2024 |
| Sponsor Representative | John Smith, MD | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | April 16, 2024 |
| IRB/EC Representative | Dr. Emily Green | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | April 17, 2024 |

**5.2. Implementation Timeline**

* **Effective Date of Amendment:**  
  May 1, 2024
* **Site Communication:**  
  All participating sites will be notified of the amendment on or before the effective date, with updated protocol documents and training materials provided.

**6. Conclusion**

This protocol amendment for the Phase 2 trial of Novostatin (Novitor) is designed to optimize patient selection and dosing regimens to enhance the drug’s efficacy while maintaining its favorable safety profile. Early positive results from the trial support the transition to Phase 3, where further confirmation of these findings will be pursued on a larger scale. The amendments detailed herein are expected to contribute to more robust and clinically meaningful outcomes, ensuring the continued success of the Novostatin development program.