**Pharmacokinetic/Pharmacodynamic (PK/PD) Report**

**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  
**Study Duration:** March 2, 2024 – September 22, 2024  
**Sponsor:** Novitor Pharmaceuticals Inc.  
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**1. Introduction**

This report summarizes the pharmacokinetic (PK) and pharmacodynamic (PD) findings from the Phase 2 trial of Novostatin (Novitor), a novel statin designed to lower LDL cholesterol with low dosage administration to minimize side effects. The PK assessments characterized the absorption, distribution, metabolism, and elimination profile of Novostatin, while the PD assessments evaluated its lipid-lowering effects and related biomarker changes. The positive outcomes support the decision to advance to Phase 3 clinical trials.

**2. Objectives**

**2.1 PK Objectives**

* To determine the plasma concentration-time profile of Novostatin.
* To assess key PK parameters including maximum plasma concentration (C\_max), time to reach maximum concentration (T\_max), area under the concentration-time curve (AUC), and elimination half-life (t\_1/2).

**2.2 PD Objectives**

* To evaluate the effect of Novostatin on lipid parameters, primarily the percentage change in LDL cholesterol from baseline.
* To assess secondary effects on total cholesterol, HDL cholesterol, and triglyceride levels.
* To explore changes in biomarkers of cardiovascular risk (e.g., high-sensitivity C-reactive protein [hs-CRP]).

**3. Methods**

**3.1 Study Design and Population**

* **Population:** A subset of 50 subjects from the Intent-to-Treat (ITT) population participated in the PK sampling schedule.
* **Dosing:** Subjects received Novostatin 10 mg once daily.
* **Sampling Schedule:** Blood samples for PK analysis were collected pre-dose and at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on Day 1 and at steady state (Week 12).
* **PD Assessments:** Lipid panels and biomarker analyses were performed at baseline, Week 12, and Week 24.

**3.2 Analytical Methods**

* **PK Analysis:** Plasma concentrations of Novostatin were quantified using a validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method. PK parameters were calculated using non-compartmental analysis.
* **PD Analysis:** Lipid parameters were measured using standard clinical laboratory methods. hs-CRP levels were measured by enzyme-linked immunosorbent assay (ELISA).

**4. Results**

**4.1 Pharmacokinetic Findings**

**Table 1: Key PK Parameters of Novostatin (n = 50)**

| **Parameter** | **Day 1** | **Week 12 (Steady State)** |
| --- | --- | --- |
| C\_max (ng/mL) | 14.8 ± 3.2 | 15.2 ± 3.0 |
| T\_max (hours) | 2.0 (median; range: 1.5–2.5) | 2.0 (median; range: 1.5–2.5) |
| AUC\_0–24 (ng·h/mL) | 180 ± 45 | 185 ± 40 |
| t\_1/2 (hours) | 11.5 ± 2.1 | 11.8 ± 2.0 |

**Text Summary:**  
Novostatin demonstrated rapid absorption with a median T\_max of 2 hours and dose-proportional increases in C\_max and AUC. The elimination half-life was approximately 11.5–11.8 hours, supporting once-daily dosing. The PK profile was consistent between Day 1 and steady state.

**4.2 Pharmacodynamic Findings**

**Table 2: Lipid Parameter Changes from Baseline to Week 24**

| **Parameter** | **Novostatin (n = 100)** | **Placebo (n = 100)** | **Between-Group Difference** | **p-value** |
| --- | --- | --- | --- | --- |
| LDL Cholesterol | -20.5% ± 6.0% | -4.8% ± 4.5% | -15.7% | < 0.001 |
| Total Cholesterol | -15.0% ± 5.5% | -3.5% ± 3.8% | -11.5% | < 0.001 |
| HDL Cholesterol | +5.0% ± 2.5% | +1.0% ± 1.8% | +4.0% | 0.002 |
| Triglycerides | -12.0% ± 4.0% | -2.0% ± 3.0% | -10.0% | < 0.001 |

**Figure 1: Mean Percentage Change in LDL Cholesterol Over Time**

*(A line graph illustrates a progressive reduction in LDL cholesterol levels in the Novostatin arm compared to the placebo arm from baseline through Week 24.)*

**Table 3: Biomarker (hs-CRP) Changes from Baseline to Week 24**

| **Parameter** | **Novostatin (n = 100)** | **Placebo (n = 100)** | **Between-Group Difference** | **p-value** |
| --- | --- | --- | --- | --- |
| hs-CRP (mg/L) | -25% ± 8% | -5% ± 6% | -20% | < 0.001 |

**Text Summary:**  
The PD assessments demonstrated a significant reduction in LDL cholesterol, with a mean decrease of 20.5% in the Novostatin group compared to 4.8% in the placebo group (p < 0.001). Total cholesterol and triglycerides were also significantly reduced, while HDL cholesterol increased modestly. Additionally, a significant reduction in hs-CRP levels (−25%) was observed in the Novostatin group, suggesting an improvement in systemic inflammation and cardiovascular risk profile.

**5. Discussion**

The PK data indicate that Novostatin is rapidly absorbed and exhibits a consistent, predictable pharmacokinetic profile that supports once-daily dosing. The PD outcomes confirm that the drug effectively lowers LDL cholesterol and improves other lipid parameters, with statistically significant differences compared to placebo. The reduction in hs-CRP further suggests potential benefits in reducing cardiovascular risk beyond lipid lowering.

**6. Conclusion**

The Phase 2 trial of Novostatin (Novitor) demonstrated a favorable PK profile and robust PD effects, including significant improvements in LDL cholesterol, total cholesterol, HDL cholesterol, triglycerides, and hs-CRP levels. These findings, coupled with the excellent safety profile observed, support the decision to advance Novostatin to Phase 3 clinical trials.

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