**Investigator’s Brochure (IB)**

**Investigational Product:** Novostatin  
**Trade Name:** Novitor  
**Indication:** Treatment of Hypercholesterolemia  
**Study Phase:** Phase 2 (Trial Period: March 2, 2024 – September 22, 2024)  
**Sponsor:** Novitor Pharmaceuticals Inc.  
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**1. Introduction and Product Overview**

**Novostatin (Novitor)** is a novel statin agent developed by Novitor Pharmaceuticals Inc. designed for the management of high cholesterol. The unique formulation of Novostatin allows for effective lipid-lowering activity at low dosages, minimizing the risk of severe side effects typically observed with conventional statins. Preclinical investigations and Phase 1 clinical data have supported its favorable safety profile and promising efficacy, justifying progression to Phase 2 trials.

**2. Preclinical Studies**

**2.1 Pharmacology**

* **Mechanism of Action:**  
  Novostatin selectively inhibits HMG-CoA reductase, resulting in reduced hepatic cholesterol synthesis and increased uptake of circulating LDL. In vitro studies demonstrated that even at low concentrations (0.1–1.0 µM), Novostatin achieved over 70% inhibition of HMG-CoA reductase activity compared to control.
* **In Vivo Efficacy:**  
  In animal models (rodents and primates), daily dosing with Novostatin at 1 mg/kg resulted in a significant reduction (up to 55%) in plasma LDL cholesterol levels within two weeks. These reductions were maintained over a 28-day treatment period.

**2.2 Toxicology**

* **Acute and Chronic Toxicity Studies:**  
  Preclinical toxicity studies conducted in rats and dogs established a No Observed Adverse Effect Level (NOAEL) at doses up to 20 mg/kg. No significant organ toxicity was observed during 90-day chronic dosing studies.
* **Safety Pharmacology:**  
  Cardiovascular, respiratory, and neurological safety assessments in animal models indicated no adverse effects at doses exceeding the anticipated therapeutic range. Particular attention was given to muscle and liver tissues, where typical statin-induced toxicity is observed; Novostatin demonstrated a markedly lower incidence of such toxicities.
* **Genotoxicity and Carcinogenicity:**  
  Standard battery tests (Ames test, in vivo micronucleus test) were negative for genotoxicity. Long-term carcinogenicity studies are ongoing, but preliminary data have not indicated any increased risk.

**3. Phase 1 Clinical Data**

**3.1 Study Design and Objectives**

* **Study Design:**  
  A randomized, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study was conducted in healthy volunteers.
* **Objectives:**  
  To evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of Novostatin administered at low doses.

**3.2 Safety and Tolerability**

* **Findings:**  
  A total of 80 healthy volunteers were enrolled. Novostatin was generally well tolerated with no serious adverse events (SAEs) reported. The most common adverse events were mild gastrointestinal discomfort and transient headache, which resolved without intervention.
* **Dose Range:**  
  Doses ranged from 5 mg to 15 mg daily. The low dosage was associated with fewer muscular and hepatic adverse events compared to historical data on other statins.

**3.3 Pharmacokinetics and Pharmacodynamics**

* **PK Profile:**  
  Novostatin exhibited dose-proportional increases in plasma concentration with a median time to peak concentration (T\_max) of 2 hours and an elimination half-life (T\_1/2) of approximately 12 hours.
* **PD Outcomes:**  
  Statistically significant reductions in LDL cholesterol (up to 20% from baseline) were observed in the higher dose cohorts within 7 days of dosing. These effects persisted throughout the dosing period, supporting the drug’s potential efficacy at low dosages.

**4. Rationale for Phase 2 Trials**

The transition to Phase 2 trials is supported by:

* **Efficacy Signals:**  
  Demonstrated LDL cholesterol reduction in Phase 1, with a promising trend toward improved lipid profiles.
* **Safety Profile:**  
  Low incidence of adverse events, especially at doses significantly lower than those used in conventional statin therapy.
* **Preclinical Data Corroboration:**  
  Robust preclinical efficacy and safety data that align with early clinical findings.

**5. Phase 2 Study Overview**

* **Objective:**  
  To further evaluate the efficacy and safety of Novostatin in patients with hypercholesterolemia.
* **Design:**  
  A Phase 2, randomized, double-blind, placebo-controlled, multi-center study enrolling 200 patients.
* **Endpoints:**
  + **Primary Endpoint:** Percentage change in LDL cholesterol from baseline at Week 24.
  + **Secondary Endpoints:** Changes in total cholesterol, HDL, triglycerides, and safety assessments including liver enzymes and muscle toxicity markers.
* **Study Duration:**  
  March 2, 2024 – September 22, 2024

**6. Risk/Benefit Assessment and Safety Monitoring**

* **Risk Assessment:**  
  Based on comprehensive preclinical and Phase 1 data, the risk associated with Novostatin is minimal. Ongoing monitoring will focus on hepatic and muscular parameters to preempt any adverse effects.
* **Benefit Analysis:**  
  The ability to achieve significant lipid lowering at low dosages offers a considerable advantage, potentially reducing the incidence of adverse side effects commonly seen with higher-dose statin therapies.
* **Safety Monitoring:**  
  An independent Data Monitoring Committee (DMC) will regularly review safety data. Interim analyses at Week 12 will further ensure patient safety throughout the trial.

**7. Conclusions and Next Steps**

Preclinical studies and Phase 1 clinical data for Novostatin (Novitor) have demonstrated a favorable safety and efficacy profile. The ability to administer the drug at low dosages with minimal side effects, coupled with significant LDL cholesterol reduction, supports the progression to Phase 2 clinical trials. Given the positive outcomes observed during the Phase 2 study (March 2, 2024 – September 22, 2024), the results strongly advocate for moving forward to Phase 3 trials to confirm these findings in a larger patient population and to further evaluate long-term safety and cardiovascular outcomes.

**8. Appendices**

* **Appendix A:** Detailed Preclinical Study Reports
* **Appendix B:** Full Phase 1 Clinical Study Protocol and Data Summaries
* **Appendix C:** Investigator Contact List and Site Information
* **Appendix D:** Regulatory Correspondence and Approvals