**Pharmacokinetic and Pharmacodynamic Comparability of B12019, a Proposed Pegfilgrastim Biosimilar**

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**Introduction**

• Neutropenia is a common complication in patients receiving myelosuppressive chemotherapy.
• Filgrastim is a recombinant human granulocyte colony-stimulating factor (G-CSF) that acts in the same manner as the endogenous G-CSF protein to stimulate the production of neutrophils and the release of mature neutrophils from the bone marrow into the peripheral blood.
• Neulasta® is a pegylated formulation of filgrastim.
• Pegfilgrastim is a pegylated filgrastim with prolonged activity compared to the non-pegylated form due to increased resistance to proteolytic degradation.
• Neulasta® is approved for the prevention of chemotherapy-induced neutropenia in patients with non-Hodgkin's lymphoma or breast cancer receiving myelosuppressive chemotherapy and for the treatment of chemotherapy-induced neutropenia in patients 65 years of age and older receiving myelosuppressive chemotherapy.

**Objectives of the clinical program**

• To determine pharmacokinetic (PK) comparability of B12019 to Neulasta®.
• To demonstrate pharmacodynamic (PD) comparability of B12019 to Neulasta®.
• To assess the immunogenicity and safety of B12019 compared to Neulasta®.

**Methods**

**Study designs**

- **B12019-101**: Randomized, double-blind, two-sequence, two-period, two-stage, cross-over design. Subjects were allocated at random to sequentially receive B12019-B12019-Neulasta® or Neulasta®-B12019.
- **B12019-102**: Randomized, double-blind, two-sequence, three-period, multi-dose design. Subjects were allocated at random to sequentially receive B12019-Neulasta® or Neulasta®-B12019.

**Eligibility criteria**

- Eligible subjects were male or female patients, aged 18-55 years, with a body mass index (BMI) range of 18-30 kg/m².
- Subjects were required to have a normal medical history and no history of significant disease.
- Subjects were required to have normal laboratory values at screening.

**Study parameters**

- **PK parameters**: Area under the curve (AUC) and maximum concentration (Cmax).
- **PD parameters**: ANC (absolute neutrophil count) and CD34+ cell count.
- **Immunogenicity**: Presence of anti-drug antibodies (ADA) was assessed using a validated ELISA assay.

**Study protocol**

- Subjects were dosed with B12019 and Neulasta® at doses of 6 mg and 3 mg, respectively.
- Blood samples were collected pre-dose and at multiple time points post-dose.
- Serum samples were analyzed for pegfilgrastim concentration using a validated ELISA assay.

**Safety**

- Safety was assessed by monitoring for adverse events (AEs) and laboratory parameters.

**Safety endpoints**

- **Primary safety parameters**: All-cause AEs and laboratory parameters.

**Immunogenicity**

- **Primary immunogenicity parameter**: Area under the curve (AUC) of an ADA-positive sample.

**Pharmacokinetic and Pharmacodynamic Comparability**

- **PK comparability**: The AUC and Cmax of B12019 and Neulasta® were compared using a two-way ANOVA model.
- **PD comparability**: The ANC and CD34+ cell count were compared using a two-way ANOVA model.

**Immunogenicity**

- **Immunogenicity parameter**: Area under the curve (AUC) of ADA-positive samples.

**Results**

**Pharmacokinetics**

- The geometric mean ratio of AUC of B12019 and Neulasta® was 100.20% with 95% confidence interval (CI) [98.26; 102.26].

**Pharmacodynamics**

- The geometric mean ratio of ANC of B12019 and Neulasta® was 101.59% with 95% CI [99.58; 103.63].

**Safety**

- The number of subjects with treatment-emergent adverse events (TEAEs) was similar for both B12019 and Neulasta®.
- No serious adverse events were reported.

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